AHRQ Healthcare Horizon Scanning System – Status Updates

Horizon Scanning Status Update: September 2015

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

A novel intervention may not appear in this report simply because the System has not yet detected it. The list of novel interventions in the Horizon Scanning Status Update Report will change over time as new information is collected. This should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual target technology reports are developed for those that appear to be closer to diffusion into practice in the United States.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in the horizon scanning, assessing the leads or topics, or provide opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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http://www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of emerging technologies that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

This edition of the Status Update lists interventions that have been identified and are being monitored. The next edition will be published in 2–3 months. We welcome comments on the list, which may be sent by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Introduction

The AHRQ Healthcare Horizon Scanning System produces reports and status updates from its activities. More than 4 years have passed since the system was initiated. The horizon time frame focuses on identifying topics anticipated to be within 3 years of possible diffusion into clinical practice. A few surrogates are used to determine this horizon, such as clinical investigation in phase III trials for interventions subject to regulatory processes of the U.S. Food and Drug Administration (FDA). Topics with FDA orphan drug, fast-track, or innovation pathway status are considered if phase II trials are ongoing. For the broad priority area of "Functional Limitations and Disability," AHRQ has designated use of the definition of disability used by the Department of Health and Human Services.

The Status Update is a summary of data elements collected in implementing the Horizon Scanning Identification and Monitoring Protocol. Status Update reports are produced five times a year, with each new report superseding the prior version. This Status Update is organized into three main topic-status sections and by priority condition within each section. The table of contents provides direct links to each section's priority condition tables. Topics that were already in the system for this tracking period are presented first as "Currently Tracked Interventions," followed by "Interventions Added Since Last Update," and then by "Interventions Tracked but Archived Since Last Update" (i.e., during the prior tracking period of 10 weeks). Each table provides information under the following column headings: Topic Title, Potential Patient Population, Intervention Description (including the Developer/Manufacturer[s] and Phase of Development), Potential Comparators, and Potential Health or Other Impacts.

Criteria for including topics in the Status Update are provided in detail in the "Horizon Scanning Protocol and Operations Manual," which is available on the Effective Health Care Web site (Protocol and Operations Manual). Briefly, broad scanning is performed for each priority condition to detect "leads" to interventions and innovations that are anticipated to be within 3 years of potential diffusion into clinical practice. Sets of questions are applied to determine whether any given intervention addresses an "unmet need" such as a large gap in effective ways to screen, diagnose, treat, monitor, manage, or provide or deliver care for a health condition or disease. Interventions might be lacking entirely, or existing options may be less than optimal. Leads that appear to address an important unmet need are assigned to horizon scanning analysts and are assessed for grouping into potential topics. Potential topics are then described according to the PICO framework: potential patient Population, Intervention, potential Comparators to the intervention, and potential Outcomes of interest for the patient population.

During topic-nomination meetings, additional criteria are applied to each topic, including questions about the potential importance of the unmet need, the likelihood of the intervention being adopted in the United States, the innovativeness of the intervention, and the potential impact of the intervention on current treatments, sites of care, disparities in care, health care processes and infrastructure, patient and population health outcomes, understanding of the disease or condition, clinician and patient training needs, and costs of care. Topics accepted during topic nomination meetings are entered into the System for tracking and appear in the Status Update report as "Currently Tracked Interventions" and "Interventions Added Since Last Update."

Topics accepted for tracking may also be designated during the meeting for further searches to collect more in-depth information about them. Such topics must be far enough along in development (typically phase III trials for drugs, phase II or III trials for devices, and pilot information for off-label use, programs, and care-delivery innovation topics) to have some

preliminary efficacy and safety data available. The horizon scanning medical librarians and analysts proceed with more in-depth and topic-specific searching for information on these topics and topic profiles are written.

Once topic profiles are developed, comments are sought from five to eight experts with a variety of perspectives and areas of expertise in health care. A topic may also be archived or retired if aggregated comments from experts suggest that an intervention is unlikely to meet an unmet need or to have impact on health outcomes or health care in the United States. Over time, a topic may be archived because development has ceased, because it no longer addresses an unmet need, is not novel, or because the intervention has diffused past early adoption and "timed out" in the horizon scanning system (i.e., 2 years after approval or initial diffusion).

Populating the horizon scanning system has been ongoing since December 2010. During that time, about 21,870 leads have been uploaded into the system and reviewed by analysts, from which about 2,390 topics have been initially identified and tracked through the system. This Status Update report contains 686 identified interventions we are tracking, which includes 91 new topics entered into the system during this reporting period. Since the last reporting period (July 31, 2015), we have archived 24 topics. The reason for archiving each topic is provided in its respective priority area table. Three reasons account for the majority of archived topics: expert commenters saw no high-impact potential at this time for the parameters of interest to AHRQ; companies halted development for lack of funding or for trials failing to meet endpoints; or topics that had been tracked met criteria for retiring from the system because they have diffused since tracking started, have shown no movement at all in more than 2 years of tracking, or are 2 years past approval by FDA.

In this update, 4 priority areas comprise 76% (523/686) of the interventions (including programs) being tracked this reporting period: the cancer priority area accounts for about 34% (232/686) of tracked topics; the functional limitations and disability priority area accounts for about 25% (174/686); the cardiovascular disease priority area accounts for about 9% (60/686); and the infectious disease priority area accounts for about 8% (57/686).

Interventions being tracked in each of the remaining 10 priority conditions (arthritis, dementia, depression and other mental illness, developmental delays, diabetes, obesity, peptic ulcer disease and dyspepsia, pregnancy and childbirth, pulmonary diseases, and substance abuse) plus an additional area we designate as cross-cutting, account for 4% or fewer (each priority area) of the total topics tracked, for a combined total of about 24% (163/686) of topics being tracked in the system.

In terms of overall types of interventions, about 93% fall into one of two general categories. Eighty-one percent of topics are pharmaceutical/biotechnology (i.e., drug, vaccine, biologic) and slightly less than 12% are devices used as implants or used externally to deliver treatments. Three percent are technologies intended to screen, diagnose, identify risk, identify blood markers or gene mutations, or monitor a disease state (i.e., diagnostic devices, assays, imaging modalities). One percent of topics are surgical and other procedures. About 1% are innovative programs, services, or care delivery practices, and another 2% predominantly involve information technology, information systems, or applications used in treating, managing, or monitoring patients. Fewer than 1% are assistive technologies (e.g., prostheses) or nanotechnology.

Section 1. Currently Tracked Interventions: 595 Interventions

Table 1. AHRQ Priority Condition: 01 Arthritis and Nontraumatic Joint Disease: 17 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Apremilast (Otezla) for treatment of ankylosing spondylitis	Patients in whom ankylosing spondylitis has been diagnosed	Investigators have not found a cure for ankylosing spondylitis. Treatments are intended to reduce inflammation and improve mobility but are not effective for all patients. Apremilast (Otezla®) purportedly inhibits phosphodiesterase type 4 (PDE-4). By inhibiting the PDE-4 enzyme, apremilast purportedly increases intracellular cAMP, which modulates multiple inflammatory mediators. When FDA approved the product for psoriatic arthritis, it became available in 10, 20, and 30 mg strengths for oral administration. In a phase III trial, patients are receiving apremilast 20 or 30 mg orally, twice daily, for 24 weeks. Celgene Corp., Summit, NJ Ongoing phase III trial failed to meet primary endpoint but was continued on recommendation from independent data monitoring committee; FDA approved Mar 2014 for treating active psoriatic arthritis in adults	Corticosteroids Disease-modifying antirheumatic drugs Nonsteroidal anti-inflammatory drugs (NSAIDs) Physical therapy Sulfasalazine (Azulfidine) Tumor necrosis factor inhibitors	Reduced signs and symptoms Improved mobility Improved quality of life
Baricitinib for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	RA is a chronic inflammatory disease causing polyarthritis with frequent progression to permanent joint damage, deformity, and functional disability. Biologic therapies are the standard of care for patients with RA that no longer responds to disease-modifying antirheumatic drugs (DMARDs). However, biologics must be administered by injection and are associated with increased incidence of serious infections, including tuberculosis. DMARDs with improved efficacy and tolerability are needed. Baricitinib (LY-3009104) is an oral Janus kinase 1 (JAK 1) and Janus kinase 2 (JAK 2) inhibitor. JAK 1 and JAK 2 are thought to be involved in mediating the activity of many cytokines involved in RA pathogenesis. Thus, inhibiting these kinases may reduce inflammation and RA symptoms. In phase III trials, patients are receiving baricitinib 4 mg, orally, once daily. Incyte Corp., Wilmington, DE, and Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing	Corticosteroids DMARDs (e.g., hydroxychloroquine, methotrexate, sulfasalazine) Nonsteroidal anti-inflammatory drugs (NSAIDs) Tocilizumab Tofacitinib Tumor necrosis factor-alpha inhibitors	Improved symptom scores as measured by American College of Rheumatology 20/50/70 (% improvement) instruments Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Brodalumab for treatment of psoriatic arthritis	Patients in whom psoriatic arthritis has been diagnosed	In a subset of patients with psoriatic arthritis, the disease can progress to severe and painful symptoms that, without effective treatment, can lead to deformity and disability of the hands and fingers. Available treatments, such as disease-modifying antirheumatic drugs (DMARDs), can be suboptimal. T-helper 17 cells secrete tumor necrosis factor (TNF), interleukin-17 (IL-17), and other proinflammatory cytokines that are thought to play a key role in psoriatic arthritis pathogenesis. Standard of care focuses on inhibiting TNF; however, many patients' symptoms do not respond to TNF therapy. Brodalumab is a monoclonal antibody that purportedly blocks the IL-17 receptor, inhibiting receptor-mediated signaling and improving symptoms. In phase III trials, patients are receiving brodalumab 140 or 210 mg, subcutaneously, every 2 weeks for 16 weeks. AstraZeneca, plc, London, UK, Valeant Pharmaceuticals International, Inc., Quebec, Canada Phase III trials ongoing; May 2015, Amgen, Inc., withdrew from its partnership with AstraZeneca for psoriatic arthritis and ankylosing spondylitis indications because of concerns about adverse events (depression, suicidal ideation) in completed phase III trials; Sept 2015, AstraZeneca licensed development and commercialization rights to Valeant Pharmaceuticals International, Inc.	Apremilast Corticosteroids DMARDS (e.g., methotrexate, sulfasalazine) Immunosuppressants (e.g., azathioprine, cyclosporine, leflunomide) Nonsteroidal anti-inflammatory drugs (NSAIDs) TNF-alpha inhibitors Ustekinumab	Improved symptom scores as measured by the American College of Rheumatology 20/50/70 (% improvement) instruments Improved scores on disability measures Improved quality of life
Condoliase for treatment of lumbar disc herniation	Patients in whom lumbar disc herniation has been diagnosed	About 3 million people in the U.S. are affected by lumbar disc herniation; males aged 20–49 years have a particularly high incidence. Pharmacologic treatments focus primarily on reducing pain; no pharmacologic treatments exist for treating the disease. Disc herniation occurs when a partial protrusion of the nucleus pulposus, located in the center of each intervertebral disc, emerges from the anulus fibrosus (outer layer of the disc). Herniated discs exert pressure on the spinal nerve root causing pain and numbness. Condoliase (SI-6603) is an enzyme therapy purported to degrade glycosaminoglycans, which are the main components of the nucleus pulposus. Some clinical researchers assume that degrading glycosaminoglycans reduces pressure on the nerves by shrinking the nucleus pulposus. Condoliase purportedly does not break down proteins, leaving surrounding tissues intact, including blood vessels and nerves. In phase III trials, patients are receiving condoliase 1.25 U, as a single intradiscal injection. Seikagaku Corp., Tokyo, Japan Phase III trials ongoing	Lumbar disc replacement surgery Physical therapy	Improved leg pain

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fasinumab for treatment of osteoarthritis pain	Patients in whom osteoarthritis (OA) has been diagnosed	No regenerative treatments are FDA approved for patients with OA who experience musculoskeletal pain. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, or narcotics generally does not provide long-term relief. New therapies are needed. Fasinumab (REGN475/SAR164877) is a humanized monoclonal antibody specific for nerve growth factor (NGF). It is intended to inhibit pain signaling, reducing pain in patients with OA. In a phase III trial, patients are receiving 1 of 4 unspecified fasinumab regimens. Regeneron Pharmaceuticals, Inc., Tarrytown, NY Sanofi, Paris, France Phase III trial re-initiated in May 2015 after FDA lifted a clinical hold from 2012 that had been put in place to examine possible adverse effects (related to peripheral nervous system) associated with use of NGF antagonists for treating OA pain	Analgesics Autologous conditioned serum Corticosteroids Lifestyle modification Mesenchymal stem cells NSAIDs Physical therapy Platelet-rich plasma Topical pain relievers Viscosupplementation (hyaluronan injections)	Reduced pain Increased range of motion Improved quality of life
Fulranumab for treatment of osteoarthritis pain	Patients with osteoarthritis (OA) who have moderate to severe pain, particularly in the knee or hip	No regenerative treatments are FDA approved for patients with OA who experience musculoskeletal pain. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, or narcotics generally does not provide long-term relief. New therapies are needed. Fulranumab is a humanized monoclonal antibody specific for nerve growth factor (NGF). It is intended to inhibit pain signaling, reducing pain in patients with OA. In phase III trials, patients are receiving 1 or 3 mg, injected subcutaneously, once every 4 weeks for up to 16 weeks. Janssen Research & Development unit of Johnson & Johnson, New Brunswick, NJ Phase III trials re re-initiated in Mar 2015 after FDA lifted a clinical hold from 2012 that had been put in place to examine possible side effects (related to the peripheral nervous system) associated with use of NGF antagonists for treating OA pain	Analgesics Autologous conditioned serum Corticosteroids Lifestyle modification Mesenchymal stem cells NSAIDs Physical therapy Platelet-rich plasma Topical pain relievers Viscosupplementation (hyaluronan injections)	Reduced pain Increased range of motion Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ixekizumab for treatment of psoriatic arthritis	Patients in whom active psoriatic arthritis has been diagnosed	In a subset of patients with psoriatic arthritis, the disease can progress to severe and painful symptoms that, without effective treatment, can lead to deformity and disability of the hands and fingers. Available treatments, such as disease-modifying antirheumatic drugs (DMARDs), can be suboptimal. Ixekizumab is a monoclonal antibody that purportedly blocks the activity of interleukin 17A, which is thought to contribute to psoriatic arthritis pathogenesis. In an ongoing trial, patients are receiving ixekizumab subcutaneously in two 80 mg injections at week 0, followed by weekly 80 mg injections until week 12. Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing	Apremilast Corticosteroids DMARDS (e.g., methotrexate, sulfasalazine) Immunosuppressants (e.g., azathioprine, cyclosporine, leflunomide) Nonsteroidal anti-inflammatory drugs (NSAIDs) Tumor necrosis factor–alpha inhibitors Ustekinumab	Improved symptom scores as measured by the American College of Rheumatology 20/50/70 (% improvement) instruments Improved disability measures Improved quality of life
Joint-sparing knee implant (KineSpring System) for treatment of knee osteoarthritis	Patients in whom knee osteoarthritis (OA) has been diagnosed	Younger, more active patients are often poor candidates for traditional joint replacement surgery because a prosthesis may not last for the rest of their lives. The KineSpring® System purportedly fills an unmet need in knee OA treatment by providing a minimally invasive option between conservative care and joint-modifying surgery for patients with primarily unicompartmental medial knee osteoarthritis. The system is intended to treat pain and restore knee function by supplementing natural joint structures and reducing joint overload. The device consists of an articulated absorber (spring) anchored with bone screws to the femoral and tibial cortices using standard surgical techniques. The absorber is designed to bear up to 30 lb (13.6 kg) of body weight per step, reducing the load on the joint; 2 ball-and-socket joints at the ends of the spring purportedly match natural knee motion. The absorber is implanted in the extracapsular space along the medial side of the joint through 2 incisions. The procedure purportedly spares the joint and is reversible; the device is extracapsular and extra-articular; no bone, ligament, or cartilage is removed. Moximed, Inc., Hayward, CA Pivotal investigational device exemption trial ongoing in U.S.	High tibial osteotomy Joint distraction Mesenchymal stem-cell therapy Nonsteroidal anti-inflammatory drugs (NSAIDs) Physical therapy Platelet-rich plasma Special orthotic devices Unloading braces Weight loss (if patient is overweight)	Reduced pain Improved mobility Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout	Patients in whom hyperuricemia has been diagnosed and thus are at high risk of developing acute gout	Hyperuricemia is believed to be the most important risk factor for developing gout. About half of patients with gout do not achieve target goals for serum uric acid levels with the standard of care, allopurinol or febuxostat. Lesinurad (RDEA594) is a selective urate transporter inhibitor. This inhibition leads to uric acid excretion, reducing uric acid and crystal formation and potentially alleviating symptoms of acute gout or preventing gout flares. Lesinurad can be used as monotherapy or in combination with allopurinol or febuxostat. In phase III trials, patients are receiving lesinurad 200 mg, orally, twice daily, or 400 mg, orally, once daily. AstraZeneca, London, UK Phase III trials ongoing	Allopurinol Colchicine Febuxostat Nonsteroidal anti-inflammatory drugs (NSAIDs) Probenecid Steroids	Reduced uric acid accumulation and crystal formation Fewer acute flares
Masitinib for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	RA is a chronic inflammatory disease causing polyarthritis with frequent progression to permanent joint damage, deformity, and functional disability. Biologic therapies have become standard of care for patients with RA that no longer responds to disease-modifying antirheumatic drugs (DMARDs). However, biologics must be administered by injection and are associated with increased incidence of serious infections, including tuberculosis. DMARDs with improved efficacy, tolerability, and convenient dosing are needed. Masitinib is a tyrosine kinase inhibitor that purportedly targets the activity of mast cells, which are involved in mediating inflammation in the synovium. Masitinib purportedly targets mast cells through selectively inhibiting KIT, platelet-derived growth factor receptor, Lyn, and to a lesser extent, fibroblast growth factor receptor 3. In a phase II/III trial, patients are receiving masitinib, 3 or 4.5 mg/kg, orally, twice daily. AB Science S.A., Paris, France Phase II/III trial ongoing; also under investigation for treating various cancers and other diseases, including amyotrophic lateral sclerosis, Alzheimer's disease, and severe asthma	Biologics (e.g., tocilizumab, adalimumab, abatacept) Corticosteroids DMARDs (e.g., hydroxychloroquine, methotrexate, sulfasalazine) Nonsteroidal anti-inflammatory drugs Tofacitinib Tumor necrosis factor-alpha inhibitors	Improved symptom scores as measured by American College of Rheumatology 20/50/70 (% improvement) instruments Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Piclidenoson for treatment of rheumatoid arthritis	Patients in whom methotrexate-resistant rheumatoid arthritis (RA) has been diagnosed	Available RA therapies are not effective in some patients and can lead to immunosuppression and poor tolerability. Improved therapies are needed. Piclidenoson (CF101) is a small-molecule antagonist of the adenosine 3A receptor (A3AR), which researchers postulate modulates several key inflammatory signaling proteins, such as PI3K, PKA, PKB/Akt, IKK, and NF-kappaB, resulting in inhibition of inflammatory cytokine production. Modulation of cytokine production might improve treatment outcomes for patients with RA. In phase II trials, patients received piclidenoson 1 mg, orally, every 12 hours. Can-Fite BioPharma, Ltd., Petah-Tikva, Israel Phase II trials completed	Corticosteroids Disease-modifying antirheumatic drugs (DMARDS; e.g., hydroxychloroquine, methotrexate, sulfasalazine) Nonsteroidal anti-inflammatory drugs (NSAIDs) Tocilizumab Tofacitinib Tumor necrosis factor-alpha inhibitors	Reduced inflammation Improved symptoms Improved activities of daily living Improved quality of life
Secukinumab (Cosentyx) for treatment of ankylosing spondylitis	Patients in whom ankylosing spondylitis has been diagnosed	Ankylosing spondylitis is an inflammatory disease, a form of arthritis that primarily affects the spine and can cause vertebrae to fuse together; investigators have not found a cure. Treatments focus on reducing inflammation, improving mobility, and decreasing pain, but are not effective for all patients. Effective treatments are needed. Secukinumab is purportedly a monoclonal antibody antagonist for interleukin-17 (IL-17). IL-17 purportedly is involved in developing delayed-type hypersensitivity reactions by increasing chemokine production, which promotes the recruitment of inflammatory cells such as monocytes and neutrophils to the local area. By blocking the effects of IL-17–localized autoimmune reactions, ankylosing spondylitis pathology could be blocked while minimizing the systemic immunosuppression associated with tumor necrosis factor (TNF) blockers, which are often used in treatment. In phase III trials, patients are receiving secukinumab subcutaneously, 75 or 150 mg, monthly. Novartis International AG, Basel, Switzerland Phase III trials ongoing	Corticosteroids Disease-modifying antirheumatic drugs Nonsteroidal anti-inflammatory drugs (NSAIDs) Physical therapy Sulfasalazine (Azulfidine) TNF inhibitors	Improved mobility Reduced pain and other symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Secukinumab (Cosentyx) for treatment of psoriatic arthritis	Patients in whom psoriatic arthritis has been diagnosed	In a subset of patients with psoriatic arthritis, the disease can progress to severe and painful symptoms that, without effective treatment, can lead to deformity and disability of the hands and fingers. Some patients do not have an adequate response to disease-modifying antirheumatic drugs (DMARDs), and other effective treatments are needed. Secukinumab (Cosentyx™) is a monoclonal antibody antagonist for interleukin-17 (IL-17), which purportedly is involved in developing delayed-type hypersensitivity reactions by increasing chemokine production, thus recruiting inflammatory cells such as monocytes and neutrophils to the local area. By blocking these effects, psoriatic arthritis pathology could be obstructed while minimizing the systemic immunosuppression associated with the tumor necrosis factor (TNF) blockers that are often used in treatment. In phase III trials, patients are receiving secukinumab 150 mg, subcutaneously, monthly. Novartis International AG, Basel, Switzerland Phase III trials ongoing; FDA approved Jan 2015 for treating moderate-to-severe plaque psoriasis	Apremilast Corticosteroids DMARDS (e.g., methotrexate, sulfasalazine) Immunosuppressants (e.g., azathioprine, cyclosporine, leflunomide) Nonsteroidal anti-inflammatory drugs (NSAIDs) TNF-alpha inhibitors Ustekinumab	Improved symptom scores as measured by the American College of Rheumatology 20/50/70 (% improvement) instruments Improved scores on disability measures Improved quality of life
Secukinumab (Cosentyx) for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	RA is a chronic inflammatory disease causing polyarthritis with frequent progression to permanent joint damage, deformity, and functional disability. Biologic therapies have become standard of care for patients with RA that no longer responds to disease-modifying antirheumatic drugs (DMARDs). However, biologics must be administered by injection and are associated with increased incidence of serious infections, including tuberculosis. DMARDs with improved efficacy and tolerability are needed. Secukinumab (Cosentyx™) is a monoclonal antibody antagonist for interleukin-17 (IL-17), which purportedly is involved in developing delayed-type hypersensitivity reactions by increasing chemokine production, thus recruiting inflammatory cells such as monocytes and neutrophils to the local area. By blocking these effects, RA pathology could be blocked while minimizing the systemic immunosuppression associated with tumor necrosis factor (TNF) blockers, which are often used in treatment. In phase III trials, patients are receiving secukinumab 75 or 150 mg, subcutaneously, monthly, with a 10 mg/kg loading dose. Novartis International AG, Basel, Switzerland Phase III trials ongoing; FDA approved Jan 2015 for treating moderate-to-severe plaque psoriasis	Biologics (e.g., abatacept, adalimumab, tocilizumab) Corticosteroids DMARDs (e.g., hydroxychloroquine, methotrexate, sulfasalazine) Nonsteroidal anti-inflammatory drugs (NSAIDs) Tofacitinib Tumor necrosis factor-alpha inhibitors	Improved symptom scores as measured by American College of Rheumatology 20/50/70 (% improvement) instruments Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tanezumab for treatment of osteoarthritis pain	Patients with osteoarthritis (OA) who have moderate to severe pain, particularly in the knee or hip	No regenerative treatments are approved by FDA for patients with OA who suffer from musculoskeletal pain. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, or narcotics generally does not provide long-term relief. New therapies providing long-term relief of symptoms could improve quality of life for many patients with OA. Tanezumab is a humanized monoclonal antibody against nerve growth factor (NGF). Tanezumab is intended to inhibit pain signaling and reduce pain in patients with OA. In a phase III trial, patients are receiving tanezumab 5 or 10 mg as a subcutaneous infusion once every 8 weeks. Pfizer Inc., New York, NY, Eli Lilly and Co., Indianapolis, IN Phase III trial ongoing; Mar 2015, FDA lifted a clinical hold from 2012 that was put in place to examine possible adverse effects (rapidly progressing osteoarthritis, osteonecrosis) associated with use of NGF antagonists for treating osteoarthritic pain	Analgesics Autologous conditioned serum Corticosteroids Lifestyle modification Mesenchymal stem cells NSAIDs Physical therapy Platelet-rich plasma Viscosupplementation	Reduced pain Increased range of motion Increased tissue regeneration Improved quality of life
TissueGene-C (Invossa) allogeneic chondrocyte implantation for treatment of knee osteoarthritis	Patients in whom grade 3 degenerative chronic knee osteoarthritis (OA) has been diagnosed	Current knee OA chondrocyte treatments require a multistep process to harvest autologous chondrocytes from the patient, culture them, and reimplant them in the knee. This process can lead to deposit of fibrocartilage in the patient rather than the normally endogenous hyaline cartilage (microfracture surgery). Developer asserts a novel method for inserting therapeutic growth-factor gene into allogeneic chondrocyte cells, culturing and stabilizing them, and injecting them into the injured site in the knee. The intent is to secrete growth-factor proteins to potentially regenerate and repair tissue. TissueGene-C (Invossa™) chondrocytes have been genetically modified to express transforming growth factor-beta, which is intended as a permanent repair and purported to be applicable to major (full-thickness) cartilage defects, rather than just minor (partial-thickness) defects. The biologic can also be mass produced and used off the shelf. TissueGene, Inc., Rockville, MD Phase III trial ongoing	Microfracture surgery Autologous chondrocyte implantation (Carticel®) Osteochondral autograft transfer Knee replacement	Decreased knee pain Improved knee function Delayed or avoided knee replacement surgery

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tofacitinib (Xeljanz) for treatment of juvenile idiopathic arthritis	Patients in whom juvenile idiopathic arthritis (JIA) has been diagnosed	Available treatments for JIA only partially mitigate symptoms and do not prevent the disease's long-term damage. Additionally, prolonged use of steroids used in treatment can slow growth and delay puberty. Improved treatments to prevent joint deformity and reduce complications are needed. Tofacitinib (Xeljanz) is a tyrosine kinase inhibitor and targeted disease-modifying antirheumatic drug (DMARD) intended for treating JIA. Tofacitinib inhibits the Janus kinase (JAK 3) signaling pathway believed to mediate several processes involved in chronic inflammatory diseases, such as antibody production by B cells, production of rheumatic factor, and activation of T cells. By inhibiting the JAK 3 pathway, tofacitinib may suppress the inflammatory reactions that are the basis of JIA. As an orally administered biologic, it might provide better adherence to treatment recommendations and improve symptom control compared with current injectables, nonsteroidal anti-inflammatory drugs (NSAIDs), or methotrexate. Approved dosage in adults is tofacitinib, 5 mg, orally, twice daily. Lower doses would be given to patients weighing less than 40 kg. Pfizer, Inc., New York, NY Phase III trial ongoing; FDA approved Nov 2012 for treating adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate	Anakinra Canakinumab Corticosteroids Methotrexate NSAIDs Tocilizumab	Improved adapted ACR pediatric 30/50/70/90/100 disability criteria Improved CHAQ (Child Health Assessment Questionnaire) clinical response Decreased CHQ (Child Health Questionnaire) pain intensity as assessed on a 100 mm visual analog scale Improved quality of life

Table 2. AHRQ Priority Condition: 02 Cancer: 207 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
5-aminolevulinic acid fluorescence guidance for identifying clear surgical margins in glioma	Patients undergoing surgery for glioma	Complete surgical resection of glioma improves outcomes in patients who are eligible for surgery; however, the highly invasive nature of glioma and the high degree of similarity between glioma tumors and surrounding healthy brain tissue make complete surgical resection and identification of clear surgical margins difficult. 5-aminolevulinic acid (5-ALA) is a small-molecule prodrug that is converted to protoporphyrin IX (PIX) in neoplastic cells, but not in normal cells. Illuminating PIX with ultraviolet light induces fluorescence in the visible light spectrum, potentially serving as a marker for glioma tissue. Researchers postulate that surgical resection guided by the pattern of PIX fluorescence could increase the percentage of glioma tissue removed, thereby improving outcomes. 5-ALA is administered as an oral medication about 3–5 hours before surgery at a dose of 20 mg/kg. Medac GmbH, Hamburg, Germany (developer) NX Development Corp., Louisville, KY, optioned development rights in North America Phase III trial (MC-ALS.3/GLI) completed, phase III trial (BALANCE) ongoing; commercially available as Gliolan® in Europe; FDA granted orphan drug status	Standard surgical resection without fluorescence assistance	Increased overall survival Increased progression-free survival Improved quality of life
^{90}Y-clivatuzumab tetraxetan for treatment-refractory pancreatic cancer	Patients with metastatic pancreatic cancer who have received at least 2 therapies, including at least 1 gemcitabine-containing regimen	Only about 5% of patients with pancreatic cancer have disease that responds to the current standard of care (gemcitabine chemotherapy), and the prognosis for these patients is poor. ^{90}Y-clivatuzumab tetraxetan is a novel radiopharmaceutical under investigation for treating pancreatic cancer. Clivatuzumab is a humanized monoclonal antibody that binds a mucin antigen expressed by most pancreatic cancer cells but is minimally expressed in pancreatitis or by normal pancreatic cells. Clivatuzumab is conjugated to the radioisotope yttrium-90 using the chelator tetraxetan. In clinical trials, ^{90}Y-clivatuzumab tetraxetan is administered once weekly for 3 weeks of each 4-week cycle, in combination with weekly, low-dose gemcitabine (200 mg/m^2, intravenously). Immunomedics, Inc., Morris Plains, NJ Phase III trial (PANCRIT®-1) ongoing; FDA granted orphan drug and fast-track statuses	Chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) Folic acid derivatives (e.g., leucovorin) Multikinase inhibitors (e.g., erlotinib) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
^{177}Lutetium-octreotate (Lutathera) for treatment of advanced refractory neuroendocrine tumors	Patients with neuroendocrine tumors (NETs) whose disease is refractory to somatostatin analogues or systemic therapy	Most cases of NETs are advanced at diagnosis and cannot be surgically resected. NETs are usually slow growing and treatment with somatostatin analogues can reduce hormonal overproduction and decrease symptoms, but in most cases, NETs become resistant. Because of a lack of effective treatments, these tumors are associated with poor outcomes. A need exists for treatments that can prevent NET recurrence. [^{177}Lu]-DOTA-Tyr3-Octreotate (Lutathera®) is a ^{177}lutetium-labeled somatostatin analogue with high affinity for the somatostatin receptor subtype sst 2 receptor. [^{177}Lu]-DOTA-Tyr3-Octreotate is a highly sensitive and very specific method to detect NETs by single photon emission computed tomography (SPECT). Additionally, [^{177}Lu]-DOTA-Tyr3-Octreotate also emits beta particles, which are high-energy electrons capable of destroying tumor cell DNA and preventing resistance. In a phase III clinical trial, patients are given 4 administrations of 7.4 GBq (200 mCi) [^{177}Lu]-DOTA-Tyr3-Octreotate at 8-week plus or minus 1-week intervals to enable acute, treatment-related toxicity issues to resolve between treatments. Advanced Accelerator Applications, S.A., Saint-Genis-Pouilly, France Phase III trial (NETTER-1) ongoing; Jan 2009, FDA granted orphan drug and fast-track statuses	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., streptozotocin) Anthracyclines (e.g., doxorubicin, etoposide) Antimetabolites (e.g., 5-fluorouracil) Platinum-based drugs (e.g., cisplatin) mTOR inhibitors (e.g., everolimus) Multikinase inhibitors (e.g., sunitinib) Somatostatin analogues (e.g., octreotate)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Abemaciclib for treatment of estrogen receptor–positive breast cancer	Patients& with estrogen receptor–positive, HER2-negative breast cancer in whom locally advanced disease is not amenable to treatment by surgery or who have metastatic disease	Although endocrine therapies (e.g., estrogen receptor antagonists, aromatase inhibitors) are often effective in treating patients who have estrogen receptor–positive breast cancer, the response duration is typically limited to about 1 year. Abemaciclib (LY2835219) is a dual inhibitor of cyclin-dependent kinase (CDK) 4 and CDK 6, kinases involved in controlling cell-cycle progression. CDK 4 and CDK 6 regulate a cell-cycle checkpoint controlling initiation of DNA synthesis; therefore, their inhibition may limit tumor growth mediated by cell proliferation. Preclinical studies have demonstrated that estrogen receptor–positive breast cancer may be highly sensitive to CDK 4/6 inhibition and that this inhibition may be synergistic with endocrine therapies. Abemaciclib is being studied for use in combination with fulvestrant in various treatment settings for advanced disease. In clinical trials, it is given orally at a dose of 200 mg, once every 12 hours, in 28-day cycles. Abemaciclib is also being tested in advanced nonsmall cell lung cancer Eli Lilly and Co., Indianapolis, IN Phase III trials (MONARCH 2 and MONARCH 3) ongoing	Chemotherapy with 1 or more of the following: Anabolic steroids (e.g., fluoxymesterone) Aromatase inhibitors (e.g., anastrozole, exemestane, letrozole) CDK4/6 inhibitors (e.g., palbociclib [LEE011; in development]) Estrogen inhibitors (e.g., tamoxifen, toremifene) Estrogen receptor inhibitors (e.g., fulvestrant) Protein kinase inhibitors (e.g., everolimus) Synthetic progestogens (e.g., progestin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Adenosine receptor agonist (CF102) for treatment-refractory hepatocellular carcinoma	Patients with treatment-refractory or metastatic hepatocellular carcinoma (HCC)	Patients with HCC that cannot be surgically resected have few treatment options and a poor prognosis; no 2nd-line therapy is available after sorafenib. CF102 is a highly specific and selective agonist of the A3 adenosine receptor (A3AR), which can downregulate the NF-kappaB and the Wnt signal transduction pathways and promote apoptosis of tumor cells. In clinical trials, CF102 is administered to patients orally, 25 mg, twice daily, in 28-day cycles. Can-Fite BioPharma, Ltd., Petah-Tikva, Israel Phase II trial (CF102-201HCC) ongoing; FDA granted orphan drug and fast-track statuses	Radiofrequency ablation Surgical resection Locoregional treatment with 1 of the following: Transarterial embolization Transcatheter arterial chemoembolization Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Multikinase inhibitors (e.g., regorafenib, sorafenib) Platinum-based agents (e.g., cisplatin, oxaliplatin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Afatinib (Gilotrif) for treatment of advanced head and neck cancer	Patients in whom advanced head and neck cancer has been diagnosed	Patients with advanced head and neck cancer have a poor prognosis and high recurrence rate, suggesting the need for novel treatment options. Afatinib (Gilotrif™) is a small-molecule, irreversible ErbB-family inhibitor. It inhibits both epidermal growth factor receptor (EGFR; HER1) and HER2 receptor tyrosine kinases. Targeted EGFR-like receptor inhibition using the anti-EGFR monoclonal antibody cetuximab has demonstrated efficacy. Although multiple receptor tyrosine kinase inhibitors are available, none are approved for use in treating head and neck cancer. In clinical trials, afatinib is being tested as 1st-line treatment, 2nd-line treatment after a platinum-based regimen, and maintenance therapy. Afatinib is administered orally, 40–50 mg, once daily. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials (Lux-Head & Neck 1, 2, 3, and 4) ongoing	Chemoradiation Surgical resection Chemotherapy with 1 or more of the following: Alkylating agents (e.g., ifosfamide) Antimetabolites (e.g., 5-fluorouracil, gemcitabine, methotrexate) Cytoprotective agents (e.g., bleomycin) EGFR inhibitor (e.g., cetuximab) Immunotherapy (e.g., durvalumab, nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g., cisplatin) Oncolytic virus (e.g., Reolysin® [in development]) Taxanes (e.g., docetaxel, paclitaxel) Tyrosine kinase inhibitors (e.g., lenvatinib, sorafenib) Vinca alkaloids (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Akt inhibitor (MK-2206) for treatment of recurrent ovarian cancer	Patients with recurrent platinum-resistant ovarian, fallopian tube, or peritoneal cancer	Ovarian, fallopian tube, or primary peritoneal cancer frequently recurs after initial treatment, and recurrence is associated with poor outcomes. In some types of cancer, including ovarian, the PI3K/Akt signaling pathway is deregulated and is frequently associated with tumorigenesis that is resistant to various anticancer agents. MK-2206 is a small-molecule inhibitor of Akt (protein kinase B) that binds to an allosteric site to prevent the enzyme's serine/threonine kinase activity. MK-2206–mediated inhibition of Akt purportedly stops cancer cells from growing and has potential to improve survival in patients with ovarian cancer, who have limited 2nd-line treatment options. In a phase II clinical trial, patients are treated with an unspecified dose of MK-2206 that is taken orally, once a week in 4-week cycles, until disease progression or unacceptable toxicity. National Cancer Institute, Bethesda, MD in collaboration with Merck & Co., Inc., Whitehouse Station, NJ Phase II trial completed; Sept 2009, FDA granted orphan drug status	Combination or single agent chemotherapy with 1 of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if *BRCA*1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Aldoxorubicin for treatment of unresectable, advanced soft tissue sarcoma	Patients with unresectable or metastatic soft tissue sarcoma who have undergone at least 1 systemic therapy	Patients with soft tissue sarcoma have few treatment options and a poor prognosis. Aldoxorubicin is a novel formulation of doxorubicin, a chemotherapy compound approved for use in treating soft tissue sarcoma, intended to provide targeted delivery of the compound to tumors. In this formulation, doxorubicin is coupled to albumin via an acid-sensitive linker. Circulating albumin preferentially accumulates in tumor tissues, which also generate acidic microenvironments. In these acidic conditions, the linker is cleaved, potentially releasing active doxorubicin locally at the site of the tumor. Aldoxorubicin is administered at a dosage of 350 mg/m^2, intravenously, once every 3 weeks, for up to 6 cycles. CytRx Corp., Los Angeles, CA Phase III trial ongoing under an FDA special protocol assessment; FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, ifosfamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., gemcitabine, methotrexate) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, paclitaxel) Tyrosine kinase inhibitors (e.g., imatinib, pazopanib) Vinca alkaloids (e.g., vincristine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Alectinib for treatment of nonsmall cell lung cancer	Patients with nonsmall cell lung cancer (NSCLC) harboring a genetic rearrangement that leads to constitutive activation of anaplastic lymphoma kinase (ALK)	The 5-year survival rate for patients with advanced NSCLC is less than 15% with current treatments. ALK is an oncogenic tyrosine kinase that was identified in gene fusions that caused activation of ALK in lymphoblastoma. The ALK inhibitor crizotinib (Xalkori®) has been successful in treating ALK mutation–positive NSCLC, but acquired drug resistance is a major issue. Alectinib (RG7853, RO5424802) is a next-generation ALK inhibitor with purported clinical activity in patients with ALK mutation–positive NSCLC whose disease has become resistant to crizotinib. In a phase II clinical trial, alectinib is administered orally in a range of doses. In the ALEX trial the dosage was 600 mg given twice daily. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase II trials ongoing; phase III trials (ALEX and expanded access) ongoing; FDA granted breakthrough therapy status; Sept 2015, FDA accepted new drug application and granted priority review	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Algenpantucel-L (HyperAcute-Pancreas) immunotherapy for pancreatic cancer	Patients in whom nonmetastatic adenocarcinoma of the pancreas has been diagnosed	Patients with pancreatic cancer have a 5-year survival rate of about 5%; effective treatment options are needed. Algenpantucel-L immunotherapy is intended to stimulate an immune response against the patient's pancreatic cancer cells. HyperAcute®-Pancreas therapy consists of 2 allogeneic pancreatic cancer cell lines that have been genetically engineered to express the enzyme alpha (1,3) galactosyl transferase, which marks the cells with a nonhuman carbohydrate that elicits a strong antibody immune response. Antibody binding to the cell lines leads to complement-mediated cell lysis, potentially leading to the uptake of pancreatic cancer antigens and a systemic immune response against the patient's cancer. Clinical trials are testing this intervention in surgically resected and unresectable/borderline resectable pancreatic cancers; it is being administered by injection in combination with the standard of care, chemoradiation. HyperAcute-Pancreas is administered at a dose of 300 million immunotherapy cells, via intradermal injection, biweekly, for up to 18 doses. NewLink Genetics Corp., Ames, IA Phase III trials (IMPRESS and PILLAR) ongoing under FDA special protocol assessment; trials examining use in surgically resected and unresectable disease; FDA granted fast-track and orphan drug statuses	Chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) Folic acid derivatives (e.g., leucovorin) Multikinase inhibitors (e.g., erlotinib) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life
Alvocidib for treatment of acute myeloid leukemia	Patients in whom acute myeloid leukemia (AML) has been diagnosed	Only about 25% of patients in whom AML is diagnosed will survive for 5 years after diagnosis. Alvocidib inhibits cyclin-dependent kinases (CDKs), which are key regulators of cell-cycle progression. Deregulation of CDK activity purportedly contributes to uncontrolled cell division and growth of cancer cells. Besides alvocidib's inhibitory activity towards cell cycle-regulating CDKs (i.e., CDK 4/6), alvocidib also has activity against CDK9, a CDK involved in regulating gene transcription. Researchers purport that CDK9 is involved in increasing expression of multiple cancer-related genes and, therefore, its inhibition may have therapeutic benefit. Alvocidib is administered intravenously in combination with standard multiagent chemotherapy regimens. In a recent clinical trial, alvocidib is being dosed as a 30 mg/kg bolus (30-minute infusion) followed by a 60 mg/kg infused over 4 hours. Tolero Pharmaceuticals, Inc., Lehi, UT Phase II trials complete; FDA granted orphan drug status	Cladribine, cytarabine, and granulocyte colony stimulating factor (G-CSF) plus or minus mitoxantrone or idarubicin Fludarabine, cytarabine, and G-CSF plus or minus idarubicin High-dose cytarabine and anthracycline Mitoxantrone, etoposide, and cytarabine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anamorelin for treatment of cancer-related cachexia/anorexia	Patients with nonsmall cell lung cancer in whom cancer-related cachexia/anorexia (CRCA) has been diagnosed	CRCA is caused by metabolic and neurochemical alterations in the body that lead to the loss of the desire to eat (anorexia) and the wasting of skeletal muscle mass (cachexia). The condition can limit patients' tolerance of further treatment, directly affecting survival. Although a number of treatments have been applied to CRCA, many patients do not respond. Ghrelin, through its activity on the growth hormone secretagogue receptor, may increase appetite and inhibit leptin and proinflammatory cytokine expression. Anamorelin (ONO-7643) is a ghrelin receptor agonist that can potentially address both the appetite and metabolic (e.g., proinflammatory) aspects of CRCA. In clinical trials, it is being administered at a dosage of 100 mg, orally, daily. Helsinn Healthcare S.A., Lugano/Pazzallo, Switzerland Phase III trials (ROMANA 1 and ROMANA 2) ongoing	Anticytokine antibodies Appetite stimulants (e.g., cannabinoids, corticosteroids, cyproheptadine) Dietary counseling Melanocortin antagonists Metabolic disturbance modulators (e.g., pentoxifylline, thalidomide) Progesterone derivatives	Improved lean body mass Improved muscle strength Increased body weight Increased overall survival Improved quality of life
Anti-CD19 monoclonal antibody (MOR208) for treatment of diffuse large B-cell lymphoma	Patients in whom diffuse large B-cell lymphoma (DLBCL) has been diagnosed	Although the majority of patients with DLBCL respond to standard 1st-line chemotherapy, some patients' disease is resistant to this therapy and a significant number of patients experience relapse after an initial response. MOR208 is an Fc-optimized, humanized monoclonal antibody specific for CD19, a protein expressed by cells of the B-cell lineage including malignant DLBCL cells. MOR208 purportedly leads to antibody-dependent, cell-mediated cytotoxicity (ADCC) of DLBCL cells, and the Fc region of the antibody has been modified to optimize the ADCC activity of the antibody. In clinical trials, MOR208 is administered intravenously in 8 weekly doses of 12 mg/kg. Morphosys AG, Planegg-Martinsried, Germany Phase II trial ongoing; FDA granted fast-track status	Various combination chemotherapy regimens with or without rituximab	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Antigen-specific immunotherapy (TG01) for treatment of pancreatic cancer	Patients with resectable pancreatic cancer who have undergone surgery to remove the tumor	Only about 5% of patients with pancreatic cancer respond to the standard of care (gemcitabine chemotherapy), and the prognosis for these patients is poor. An unmet need exists for interventions that can serve as adjuvant therapy after pancreatic cancer surgery. About 80% to 90% of all pancreatic cancers are caused by mutations that constitutively activate RAS; therefore, TG01 is designed to activate cytotoxic T cells that will target cells bearing RAS mutations. TG01 is a series of peptides that contain pancreatic cancer-specific RAS mutations, can be processed by antigen-presenting cells (APCs), and promiscuously bind to HLA class II for presentation to T cells. TG01 purportedly activates an immune response against pancreatic cancer cells that will increase the time to relapse. It is injected subcutaneously and is taken up by APCs, which present the antigen via HLA class II to cytotoxic T cells. The T cells target and kill cancer cells that present mutant RAS peptides in the HLA class I. In clinical trials, patients are inoculated with TG01 after surgery on days 1, 3, 5, 8, and 15 and then every 2 weeks until the end of treatment with gemcitabine, which will be administered on days 1, 8, and 15 of a 4-week cycle for up to 6 cycles. Targovax AS, Lysaker, Norway Phase I/II trial (TG01-01) ongoing; Jun 2011, FDA granted orphan drug status	Chemotherapy with 1 of the following: Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) Folic acid derivatives (e.g., leucovorin) Multikinase inhibitors (e.g., erlotinib) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life
Apaziquone (EOquin) for treatment of nonmuscle-invasive bladder cancer	Patients with nonmuscle-invasive bladder cancer who have undergone transurethral resection of bladder tumor (TURBT)	Nonmuscle-invasive bladder cancer has a 5-year survival rate of 85% if detected and treated early. Unfortunately, surgically resected bladder cancers have a 5-year recurrence rate of 80% and can progress to an advanced stage; in patients with lymph node–positive and/or metastatic disease, the survival rate decreases to 14%. A need exists for interventions that can prevent the recurrence of bladder cancer after it has been surgically resected. Apaziquone (EOquin®) is an inactive bioreductive agent that is activated into a cytotoxic alkylating agent by reductase enzymes (e.g., DT-diaphorase) overexpressed in bladder tumor cells. In clinical trials, apaziquone is instilled directly into patients' bladders, in a 40 mL dose containing 4 mg apaziquone. Studies are comparing the safety and efficacy of single vs. multiple instillations. Spectrum Pharmaceuticals, Inc., Henderson, NV Phase III trials (SPI-1011 and SPI-1012) ongoing	Surgery (cystectomy) Radiotherapy combined with chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Platinum-based agents (e.g., cisplatin) Taxanes (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Apocept for treatment-refractory glioblastoma	Patients in whom temozolomide-resistant glioblastoma has been diagnosed	Patients with temozolomide-resistant glioblastoma have few treatment options and a poor prognosis. APG101 is a novel fusion protein that links the CD95 ligand (CD95L) to the Fc region of human immunoglobulin. APG101 (Apocept™) purportedly blocks the interaction between CD95L and CD95. In glioblastoma cells, stimulation of CD95 by CD95L is purported to drive tumor invasiveness and cell growth; therefore, blocking this interaction has the potential to improve patient outcomes. APG101 is administered as a once-weekly intravenous infusion. Apogenix GmbH, Heidelberg, Germany Phase II trial ongoing; FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., carmustine, cyclophosphamide, lomustine, nitrosourea, procarbazine, temozolomide) Angiogenesis inhibitors (e.g., bevacizumab) Immunotherapeutics (e.g., DCVax-L, HSPPC-95, ICT-107, rindopepimut, SL-701 [in development]) mTOR inhibitors (e.g., everolimus) PD-1 antibodies (e.g., nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin) Radiation therapy Vinca alkaloids (e.g., vincristine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Archexin for treatment of metastatic renal cell carcinoma	Patients with metastatic renal cell carcinoma (mRCC) whose disease has progressed after treatment with VEGFR-targeting tyrosine kinase inhibitor	Since 2005, FDA has approved 6 targeted interventions for treating mRCC. Although patient outcomes have substantially improved with these therapies, new interventions are needed to complement or replace standard treatment to further improve patient outcomes. Archexin (RX-0201) is an antisense oligonucleotide (RNA) that complements a sequence of the Akt-1 mRNA, which promotes its degradation and prevents the synthesis of the Akt-1 protein. Akt-1 is involved in the phosphorylation of proteins in pathways that control cell proliferation, growth, and survival, and it has been shown to be upregulated in different types of cancer. Archexin-mediated downregulation of Akt-1 purportedly prevents uncontrolled growth and proliferation of cancer cells. Because it has a distinct mechanism of action, archexin could be paired with approved therapies to extend disease-free survival in patients. In clinical trials, archexin is being tested in combination with everolimus; archexin is administered to patients in a dose up to 250 mg/m^2 as a daily intravenous infusion for 14 days of a 21-day cycle for up to 8 cycles, while everolimus is taken daily, orally, at a dose 10 mg for up to 8 cycles. Rexahn Pharmaceuticals, Inc., Rockville, MD Phase IIa trial (RX-0201-P2-A-09) ongoing; a liposomal formulation of archexin (RX-0201-nano) is also under development to enhance cell delivery; Dec 2004, FDA granted orphan drug status	Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab [under development]) Cytokines (e.g., interferon, interleukin-2) mTOR inhibitors (e.g., temsirolimus) PD-1 inhibitors (e.g., nivolumab [in development]) Tyrosine kinase inhibitors (e.g., everolimus, pazopanib, sorafenib, sunitinib)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Astuprotimut-r for treatment of advanced melanoma	Patients with resectable stage IIIB or IIIC cutaneous melanoma that expresses melanoma antigenic epitope (MAGE)-A3 antigen	Patients with advanced melanoma frequently experience disease recurrence after surgical resection of the primary tumor. Current immunotherapies used in the adjuvant setting have shown little effect on the duration of overall survival in this patient population. Astuprotimut-r (GSK2132231A) is a peptide-based therapeutic vaccine directed at the cancer-specific antigen MAGE-A3, which is expressed by a significant proportion of melanomas. It is being tested in the adjuvant setting for treating melanoma. In a multicenter, international phase III trial of 1,349 patients, GSK2132231A is being administered as a course of 13 injections over 27 months. GlaxoSmithKline, Middlesex, UK Phase III trial (DERMA) ongoing; Sept 2013, company announced phase III trial failed to meet 1st co-primary endpoint (increased disease-free survival); trial continues to assess overall survival	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, temozolomide) B-RAF inhibitors (e.g., dabrafenib, vemurafenib) Immunotherapy (e.g., ipilimumab, nivolumab, pembrolizumab) MEK inhibitors (e.g., trametinib [cobimetinib; in development]) Platinum-based agents (e.g., carboplatin) Taxane agents (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life
Atezolizumab for treatment of advanced non-small cell lung cancer	Patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC) that has progressed	Patients with advanced NSCLC whose disease has progressed after 1st-line platinum-based chemotherapy have few treatment options and a poor prognosis. A hallmark of cancer is its ability to evade an immune response. Atezolizumab (MPDL3280A) is a novel therapeutic that is intended to prevent immune tolerance of tumor cells. The drug's target is the programmed death-1 receptor ligand (PD-1L), which is frequently expressed in tumor microenvironments and purportedly leads to downregulation of T-cell activity via activation of the programmed death-1 immune checkpoint. Atezolizumab is a monoclonal antibody specific for PD-1L and is intended to prevent an interaction between the ligand and its receptor, potentially limiting activation of the immune checkpoint. In trials, atezolizumab is administered as a 1,200 mg intravenous infusion on day 1 of a 21-day cycle. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trial ongoing; FDA granted breakthrough therapy status	Docetaxel Erlotinib Pemetrexed	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Atezolizumab for treatment of urothelial bladder cancer	Patients with locally advanced or metastatic urothelial bladder cancer (UBC) whose disease has progressed after treatment with platinum-based chemotherapy	UBC includes disease of the ureters, urinary bladder, and urethra. About 90% of urothelial cancers begin in the bladder and have a 5-year survival rate of 85% when detected early. In contrast, the survival rate of advanced urothelial cancer is 14% for patients with lymph node–positive and metastatic disease. A hallmark of cancer is its ability to evade an immune response. Atezolizumab (MPDL3280A) is a novel therapeutic that is intended to prevent immune tolerance of tumor cells. The drug's target is the programmed death-1 receptor ligand (PD-1L), which is frequently expressed in tumor microenvironments and purportedly downregulates T-cell activity by activating the programmed death-1 immune checkpoint. Atezolizumab is a monoclonal antibody specific for PD-1L and is intended to prevent an interaction between the ligand and its receptor, potentially limiting activation of the immune checkpoint. In clinical trials, atezolizumab is administered as a 1,200 mg intravenous infusion on day 1 of each 21-day cycle. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials (GO29294 and IMvigor 010) ongoing; May 2014, FDA granted breakthrough therapy status	Surgery (cystectomy) Radiotherapy combined with chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Platinum-based agents (e.g., cisplatin) Taxanes (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Aurora A/angiogenic kinase inhibitor (ENMD-2076) for treatment of fibrolamellar hepatocellular carcinoma	Patients with advanced fibrolamellar hepatocellular carcinoma (FLHCC) whose disease has not been treated with locoregional therapy or has recurred after surgical resection	FLHCC is a rare form of liver cancer that affects about 200 people each year. Although patients respond well to surgery, the disease usually recurs and the lack of treatment options leads to a poor prognosis. ENMD-2076 is a small-molecule kinase inhibitor that targets the mitotic kinase Aurora A as well as VEGFR, Flt-3, and FGFR3 kinases, which are involved in cell-cycle regulation, cell survival, angiogenesis, and cell proliferation. ENMD-2076 purportedly improves patient outcomes by inhibiting the activity of these pathways, which are deregulated in FLHCC. In a phase I pharmacokinetic and pharmacodynamic study, patients were treated daily with oral ENMD-2076 at a dose ranging from 60 to 200 mg/m^2. CASI Pharmaceuticals, Inc., Rockville, MD Phase II trial ongoing; FDA granted orphan drug status	Radiofrequency ablation Surgical resection Locoregional treatment with 1 of the following: Transarterial embolization Transcatheter arterial chemoembolization Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Multikinase inhibitors (e.g., regorafenib, sorafenib) Platinum-based agents (e.g., cisplatin, oxaliplatin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous dendritic cell immunotherapy (AGS-003) for renal cell carcinoma	Patients in whom advanced or metastatic renal cell carcinoma (RCC) has been diagnosed	About 14,000 deaths are attributed to kidney cancer in the U.S. each year. AGS-003 is a personalized immunotherapy in which dendritic cells (antigen-presenting cells of the immune system) are removed from the patient, loaded with messenger RNA isolated from the patient's tumor, then re-administered to the patient. In clinical trials, AGS-003 is being used in combination with sunitinib in patients with newly diagnosed advanced/metastatic RCC who have undergone unilateral or partial nephrectomy. AGS-003 is administered by intradermal injection. A full treatment course consists of 8 injections in year 1 followed by quarterly booster injections. Argos Therapeutics, Inc., Durham, NC Phase III trial (ADAPT) ongoing	Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab [in development]) Cytokines (e.g., interferon-alfa, interleukin-2) mTOR inhibitors (e.g., temsirolimus) PD-1 inhibitors (e.g., nivolumab [in development]) Tyrosine kinase inhibitors (e.g., axitinib, everolimus, pazopanib, sorafenib, sunitinib)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous dendritic cell immunotherapy (DCVax-L) for glioblastoma multiforme	Patients in whom unilateral glioblastoma multiforme (GBM) has been diagnosed	GBM is difficult to treat and associated with a very poor prognosis. New therapies that slow disease progression and improve survival are needed. DCVax®-L is an autologous dendritic cell vaccine intended to promote an immune response against a patient's glioblastoma. To prepare DCVax-L, both a tumor isolate and a blood draw to obtain immune cells are required. Dendritic cells (antigen-presenting cells of the immune system) are expanded from the patient's isolated immune cells and exposed to tumor lysate. These activated dendritic cells are then injected back into the patient intradermally every 2–6 months for up to 3 years. Northwest Biotherapeutics, Inc., Bethesda, MD Phase III trial (GBM) ongoing; Nov 2014, DCVax-L was approved in Germany and the UK through early approval programs	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., carmustine, cyclophosphamide, lomustine, nitrosourea, procarbazine, temozolomide) Angiogenesis inhibitors (e.g., bevacizumab) Immunotherapeutics (e.g., HSPPC-95, ICT-107, rindopepimut, SL-701 [in development]) mTOR inhibitors (e.g., everolimus) PD-1 antibodies (e.g., nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin) Radiation therapy Vinca alkaloids (e.g., vincristine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous dendritic cell immunotherapy (ICT-107) for glioblastoma multiforme	Patients with glioblastoma multiforme (GBM) who have undergone surgical debulking treatment	GBM is difficult to treat and associated with a very poor prognosis. New therapies that can improve survival and slow disease progression are needed. Personalized dendritic cell vaccine (ICT-107) is an autologous-derived therapeutic vaccine targeting 6 tumor-associated antigens: AIM2, HER2, gp-100, melanoma antigenic epitope-1, TRP-2, and interleukin-13Ra2. ICT-107 is under investigation in newly diagnosed GBM. It is administered as an adjuvant to surgical resection and chemoradiation therapy; 4 induction doses are followed by a maintenance regimen that continues until disease progression. ImmunoCellular Therapeutics, Ltd., Woodland Hills, CA Phase IIb trial ongoing; phase III trial to start before end of 2015; Sept 2014, company received suggestions from FDA on phase III protocol; FDA granted orphan drug status in 2010	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., carmustine, cyclophosphamide, lomustine, nitrosourea, procarbazine, temozolomide) Angiogenesis inhibitors (e.g., bevacizumab) Immunotherapeutics (e.g., DCVax-L, HSPPC-96, rindopepimut, SL-701 [in development]) mTOR inhibitors (e.g., everolimus) PD-1 antibodies (e.g., nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin) Radiation therapy Vinca alkaloids (e.g., vincristine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous tumor cell vaccine (FANG) for treatment of ovarian cancer	Patients with stage III or IV high-grade serous/endometrioid ovarian, fallopian tube, or primary peritoneal cancer who have undergone debulking surgery and between 5 and 6 cycles of chemotherapy	Ovarian, fallopian tube, or primary peritoneal cancer frequently recurs after initial treatment and recurrence is associated with poor outcomes. The autologous tumor cell FANG™ vaccine is manufactured from a fragment of the patient's tumor obtained during debulking surgery. The cells are electroporated to introduce a plasmid expressing rhGMCSF and the bifunctional RNAi effector, bi-shRNAfurin. The GMCSF protein is a potent stimulator of the immune system, recruiting and activating antigen-presenting cells at the site of intradermal injection, thereby promoting antigen presentation. The furin bifunctional shRNA blocks furin protein production via mRNA degradation and translational inhibition. Furin is a protease responsible for cleaving the TGF-beta precursor into the active TGF-beta 1 and 2 isoforms, which have an inhibitory effect on GMCSF-mediated immune activation. Inoculation of patients with FANG purportedly enhances an immune response against ovarian cancer cells and prevents cancer recurrence. In clinical trials, patients receive at least 4 and up to 12 monthly intradermal injections of the FANG vaccine ($1x10^7$ cells). Gradalis, Inc., Dallas, TX Phase III trial (VITAL) ongoing; Apr 2011 FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if *BRCA*1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bavituximab for treatment of advanced nonsmall cell lung cancer	Patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC) that has progressed after 1st-line chemotherapy	Advanced NSCLC has a poor prognosis with few therapeutic options, and new treatments are needed for patients whose disease has progressed after 1st-line, platinum-based doublet chemotherapy. Bavituximab is a monoclonal antibody directed against phosphatidylserine (PS) exposed on the surface of cancer cells; PS expression is believed to be immunosuppressive. Bavituximab is thought to bind to PS and block the immunosuppressive signals to improve immune responses to the tumor; also, because chemotherapy increases the exposure of PS on tumor blood vessels, bavituximab combined with chemotherapy may hold potential for synergistic therapeutic effects. Administered intravenously 3 mg/kg, weekly, in combination with docetaxel for 2nd-line treatment of NSCLC. Peregrine Pharmaceuticals Inc., Tustin, CA Phase III trial (SUNRISE) ongoing; FDA granted fast-track status; bavituximab is also under study for treating advanced HER2- breast cancer	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Binimetinib for treatment of metastatic melanoma	Patients in whom advanced melanoma has been diagnosed	Patients with metastatic melanoma have a poor prognosis. About 15% of melanoma cases harbor the *NR*AS Q61 mutation; *NRAS* mutations are associated with higher mitotic rates and thicker tumors. Currently, no targeted therapies have been effective in *NRAS* mutation–positive melanomas. Binimetinib (MEK162) is a MEK1/2 inhibitor that effectively treated about 20% of *BRAF*- and *NRAS*-mutated melanomas in phase II trials. Binimetinib is also under investigation in combination with RAF inhibitors for treating *BRAF*-mutated melanoma. In a phase III trial in patients with NRAS-mutated melanoma, binimetinib is administered as a once-daily, oral dose of 45 mg (three 15 mg tablets). Array BioPharma, Inc., Boulder, CO Phase II and III trials (COLUMBUS and NEMO) ongoing; Nov 2013, FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, temozolomide) *BRAF* inhibitors (e.g., dabrafenib, vemurafenib) Immunotherapy (e.g., ipilimumab, nivolumab, pembrolizumab) MEK inhibitors (e.g., trametinib [cobimetinib; in development]) Platinum-based agents (e.g., carboplatin) Taxane agents (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Binimetinib for treatment of serous ovarian, fallopian tube, and peritoneal cancer	Patients in whom low-grade serous ovarian, fallopian tube, or peritoneal cancer has been diagnosed	Few effective treatment options exist for recurrent or persistent primary ovarian, peritoneal, or fallopian tube cancer. MEK162 is a MEK1/2 inhibitor that targets the RAS/RAF/MEK/ERK pathway, which signals cancer cell proliferation and survival. A global, randomized phase III trial is evaluating MEK162 versus physician's choice of standard cytotoxic chemotherapy in 300 patients with recurrent or persistent low-grade serous ovarian cancer after at least 1 platinum-based chemotherapy and no more than 3 lines of chemotherapy. MEK162 is administered as a once-daily, oral dose of 45 mg (three 15 mg tablets). Array BioPharma, Inc., Boulder, CO Phase III trial (MILO) ongoing	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if *BRCA*1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Blinatumomab (Blincyto) for treatment of acute lymphoblastic leukemia	Patients in whom Philadelphia chromosome–negative, B-cell lineage acute lymphoblastic leukemia (ALL) has been diagnosed	No new treatments for Philadelphia chromosome–negative recurrent/refractory ALL have been developed in 30 years; 5-year survival for this patient population is only 7%. Blinatumomab (Blincyto™) is a molecule that is furthest in development in a novel class of antibody-based compounds intended to link tumor cells to cytotoxic T cells. The molecule consists of 2 separate antibody-antigen binding domains: (1) the domain specific for CD19, an antigen expressed by the immature lymphocytes expanded in ALL, and (2) the domain specific for CD3, a molecule expressed on the surface of cytotoxic T cells. Blinatumomab purportedly leads to leukemic cell apoptosis by bridging an interaction between leukemic cells and T cells. Blinatumomab is administered by intravenous infusion and is being studied in patients in whom the disease is newly diagnosed, has recurred, or is refractory to other treatment. Patients typically receive blinatumomab in 6-week cycles consisting of 4 weeks of continuous infusion followed by 2 weeks off treatment. After a loading dose of 9 mcg per day for week 1 of the 1st treatment cycle, patients receive blinatumomab at a dose of 28 mcg/day. Amgen, Inc., Thousand Oaks, CA Phase III trials ongoing as adjunct to standard chemotherapy for newly diagnosed disease and as monotherapy for recurrent/refractory disease; Dec 2014, FDA granted accelerated approval for treating patients who have “Philadelphia chromosome-negative recurrent or refractory B-cell precursor acute lymphoblastic leukemia”	Newly diagnosed ALL: CALGB 8811 Larson regimen Linker 4-drug regimen Hyper-CVAD with or without rituximab MRC UKALLXII/ECOG2993 regimen Recurrent/refractory ALL: Anthracyclines Asparaginase Cyclophosphamide Cytarabine (ara-C) Epipodophyllotoxins Vincristine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Brigatinib for treatment of advanced nonsmall cell lung cancer	Patients with *ALK* translocation–positive advanced nonsmall cell lung cancer (NSCLC)	Although crizotinib, an *ALK* kinase inhibitor, has improved outcomes for the small subset of patients in whom *ALK* translocation–positive NSCLC has been confirmed, many patients' disease that initially responds to available *ALK* inhibitors develops resistance to the therapy. Studies have identified multiple resistance mechanisms, including mutations to the *ALK* kinase domain and activation of the EGFR signaling pathway. Brigatinib (AP26113) is a novel kinase inhibitor that has the potential to address both of these resistance mechanisms. Brigatinib has activity against both resistant forms of the *ALK* kinase and activated forms of the EGFR kinase. The 90 mg tablet is being administered orally, once daily continuously in a 28-day cycle or orally once daily for a 7 days followed by a 180 mg tablet once daily, continuously in a 28-day cycle. ARIAD Pharmaceuticals, Inc., Cambridge, MA Phase I/II and phase II (ALTA) trials ongoing; FDA granted breakthrough therapy status	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Buparlisib for treatment-refractory metastatic estrogen receptor–positive breast cancer	Patients with aromatase inhibitor or mTOR inhibitor–refractory, hormone receptor–positive, HER2-negative metastatic breast cancer	Patients with hormone receptor–positive breast cancer typically develop resistance to 1st-line therapy with estrogen receptor–targeted therapies. The phosphoinositide 3 kinase (PI3K)/mTOR pathway is a cell signaling pathway that is activated in a wide range of cancers and, in particular, may underlie tumor resistance to estrogen receptor–targeted therapies. Buparlisib (BKM120) is an orally administered pan-PI3K inhibitor (i.e., an inhibitor of all PI3K isoforms) that is intended to block the PI3K/mTOR pathway. In clinical trials, buparlisib is administered orally, 100 mg per day, in combination with the anti-estrogen drug fulvestrant. Novartis International AG, Basel, Switzerland Phase III trials (BELLE-2, -3 and -4) ongoing; also under study for treating endometrial cancer, glioblastoma, HER2-positive breast cancer, melanoma, nonsmall cell lung cancer, prostate cancer, and urothelial cancer	Anabolic steroids (e.g., fluoxymesterone) Aromatase inhibitors (e.g., anastrozole, exemestane, letrozole) CDK4/6 inhibitors (e.g., palbociclib [abemaciclib, LEE001; in development]) Estrogen inhibitors (e.g., tamoxifen, toremifene) Estrogen receptor inhibitors (e.g., fulvestrant) Protein kinase inhibitors (e.g., everolimus) Synthetic progestogens (e.g., progestin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cabozantinib (Cometriq) for treatment of advanced or recurrent hepatocellular carcinoma	Patients in whom advanced or recurrent hepatocellular carcinoma has been diagnosed	Few treatment options exist for advanced hepatocellular carcinoma and none of them target MET, which may be responsible for drug resistance in patients treated with available receptor tyrosine kinase (RTK) inhibitors. Cabozantinib (Cometriq™) is a small-molecule, RTK inhibitor that targets MET and VEGFR2; MET plays key roles in proliferation, migration, invasion, and angiogenesis; overexpression of the hepatocyte growth factor (HGF) ligand of MET and activation of the MET pathway supports tumors. VEGFR-2 and MET allow tumors to overcome hypoxia and stimulate angiogenesis. VEGF and MET also appear to stimulate osteoclasts and osteoblasts, thus showing potential for treating bone metastases. Selective anti-VEGF therapies do not inhibit MET, which may be responsible for tumor evasiveness and drug resistance in patients who receive VEGF tyrosine kinase inhibitors, making MET/VEGF co-inhibition an emerging target in cancer therapy. Administered 100 mg, orally, once daily, in trials. Exelixis, South San Francisco, CA Phase III trial (CELESTIA) ongoing	Radiofrequency ablation Surgical resection Locoregional treatment with 1 of the following: Transarterial embolization Transcatheter arterial chemoembolization Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Multikinase inhibitors (e.g., regorafenib, sorafenib) Platinum-based agents (e.g., cisplatin, oxaliplatin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cabozantinib (Cometriq) for treatment of renal cell carcinoma	Patients with advanced renal cell carcinoma (RCC) who have received treatment with a vascular endothelial growth factor receptor (VEGFR)-targeting tyrosine kinase inhibitor (e.g., sorafenib, sunitinib, axitinib, pazopanib, tivozanib)	Patients whose RCC has progressed after targeted therapy (e.g., VEGF or mTOR inhibitors) have limited treatment options and a poor prognosis. Cabozantinib (Cometriq™) is a small-molecule receptor tyrosine kinase inhibitor that targets MET and vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2). MET plays key roles in cell proliferation, migration, invasion, and angiogenesis. Overexpression of the hepatocyte growth factor ligand of MET and activation of the MET pathway supports tumors. Additionally, VEGFR2 and MET allow tumors to overcome hypoxia and stimulate angiogenesis. Selective anti-VEGF therapies do not inhibit MET, which may be responsible for tumor evasiveness and drug resistance in patients who receive VEGF tyrosine kinase inhibitors, making MET/VEGF co-inhibition an emerging target in cancer therapy. In clinical trials, cabozantinib is being tested in the 2nd-line setting after VEGFR-targeted tyrosine kinase inhibitor therapy. The recommended dose on the labeling approved by FDA in another indication—for treating medullary thyroid cancer—is a once-daily, oral dose of 140 mg. Exelixis, Inc., South San Francisco, CA Phase III trial (METEOR) ongoing; Aug 2015, FDA granted breakthrough therapy status; Apr 2015, FDA granted fast-track status; FDA approved Nov 2012 for treating progressive metastatic medullary thyroid cancer; labeling carries a black box warning for risk of gastrointestinal perforations, fistulas, and hemorrhage	Angiogenesis inhibitors (e.g., bevacizumab [ramucirumab; in development]) Cytokines (e.g., interferon-alpha, interleukin-2) mTOR inhibitors (e.g., temsirolimus) PD-1 inhibitors (e.g., nivolumab [in development]) Tyrosine kinase inhibitors (e.g., axitinib, everolimus, pazopanib, sorafenib, sunitinib)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cancer cell stemness inhibitor (BBI608) for treatment of advanced gastric cancer	Patients with unresectable advanced gastric cancer or gastroesophageal junction cancer whose disease has progressed after platinum-based chemotherapy	Patients with locally advanced or metastatic gastric cancer or gastroesophageal junction cancer have a poor prognosis with available treatment options. Cancer stem cells (CSCs) are specialized cells in the tumor thought to be responsible for tumor growth, therapy resistance, and metastatic spread. Although standard therapies that target non-CSCs reduce tumor size, they do not affect CSCs, and this may cause the cancer to recur. BBI608 is a small molecule purported to target and kill CSCs within the tumor. In clinical trials, BBI608 is administered orally, at a dose of 460 mg, twice daily, in combination with intravenous paclitaxel. Boston Biomedical subsidiary of Sumitomo Dainippon Pharma Co., Ltd., Osaka, Japan Phase III trial (BRIGHTER) ongoing; also under study in treating colorectal cancer	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., ramucirumab) Anthracyclines (e.g., doxorubicin, epirubicin, irinotecan) Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) DCF (docetaxel, cisplatin, 5-fluorouracil) ECF (epirubicin, cisplatin, 5-fluorouracil) HER2 antibodies if HER2-positive (e.g., trastuzumab) PD-1 antibodies (e.g., pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cancer cell stemness inhibitor (BBI608) for treatment of advanced, unresectable colorectal cancer	Patients with pretreated, unresectable, advanced colorectal cancer (CRC) who have received treatment with a thymidylate synthase inhibitor and whose disease is refractory to irinotecan- and oxaliplatin-containing regimens	Current 2nd- and 3rd-line treatments for metastatic CRC are of limited efficacy, and the median overall survival of these patients is less than 1 year. BBI608 is a novel, 1st-in-class agent that targets cancer stem cells (CSCs). CSCs are self-replicating cells that differentiate into heterogeneous cancer cells and contribute to tumor growth, recurrence, and chemotherapy resistance. Although the exact mechanism of action is unknown, BBI608 is thought to inhibit multiple signaling pathways involved in CSC stemness (i.e., self-renewal and pluripotency), preventing these malignant processes. In clinical trials, BBI608 is administered as a twice-daily, oral dose of 480 mg, given as monotherapy (phase III trial) or in combination with best supportive care (phase II trial). Boston Biomedical subsidiary of Sumitomo Dainippon Pharma Co., Ltd., Osaka, Japan Phase III trial (CO23) ongoing	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab [ramucirumab; in development]) Antimetabolites (e.g., 5-fluorouracil, capecitabine) EGFR antibodies (e.g., cetuximab, panitumumab) FOLFIRI (leucovorin, 5-fluorouracil, irinotecan) FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin) Multikinase inhibitors (e.g., regorafenib) Platinum-based agents (e.g., oxaliplatin) Topoisomerase inhibitors (e.g., irinotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Chimeric antigen receptor T-cell therapy (CTL019) for chronic lymphocytic leukemia	Patients in whom recurrent or refractory chronic lymphocytic leukemia (CLL) has been diagnosed	CLL can typically be controlled for many years with current chemotherapy options; however, these treatments are not curative and disease typically recurs. A treatment option under study is a chimeric antigen receptor T-cell (CAR-T) therapy, in which autologous T lymphocytes are genetically modified to promote T-cell activation, T-cell proliferation, and immune memory. To generate CTL019, a lentiviral vector is used to transfect autologous T cells with a CAR transgene that consists of 4 parts: (1) an extracellular domain consisting of an antibody variable chain specific for CD19 (a cell surface marker expressed by CLLs); (2) a hinge region; (3) a costimulatory domain (in this case a portion of CD137); and (4) CD3-zeta (a signal transduction component of the T-cell receptor). Extracellular binging of this recombinant protein to CD19 on target cells activates pathways typically downstream of major histocompatibility complex activation and CD137 stimulation, eliciting a persistent immune response against CD19. Novartis International AG, Basel, Switzerland, in collaboration with University of Pennsylvania, Philadelphia Phase II trial ongoing; FDA granted orphan drug status	Various chemotherapy regimens	Increased progression-free survival Increased overall survival Improved quality of life
Chimeric antigen receptor T-cell therapy (CTL019) for recurrent or refractory acute lymphoblastic leukemia	Patients in whom recurrent or refractory acute lymphoblastic leukemia (ALL) has been diagnosed	5-year survival for patients with recurrent or refractory ALL is about 7%. A treatment option under study is chimeric antigen receptor T-cell (CAR-T) therapy, in which autologous T lymphocytes are genetically modified to promote T-cell activation, T-cell proliferation, and immune memory. CTL019 is produced by using a viral vector to transfect autologous T cells with a CAR transgene that encodes a protein consisting of 4 parts: (1) an extracellular domain consisting of an antibody variable chain specific for CD19 (a cell surface marker expressed by ALLs); (2) a hinge region; (3) a costimulatory domain (in this case, a portion of CD137); and (4) CD3-zeta (a signal transduction component of the T-cell receptor). Binding of the extracellular domain of this recombinant protein to CD19 on target cells activates the pathways, typically downstream of major histocompatibility complex activation and CD137 stimulation, purportedly activating a persistent immune response against CD19. CTL019 T cells are administered by intravenous infusion. Novartis International AG, Basel, Switzerland Phase II trials ongoing; FDA granted breakthrough therapy status	Various cytotoxic chemotherapy regimens	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Chimeric antigen receptor T-cell therapy (JCAR015) for acute lymphoblastic leukemia	Patients with CD19-positive, B-cell acute lymphoblastic leukemia (ALL) who have recurrent/refractory disease or residual disease after treatment with allogeneic hematopoietic progenitor cell transplantation	5-year survival for patients with recurrent or refractory ALL is about 7%, pointing to a need for new therapies. A treatment option under study is chimeric antigen receptor T-cell (CAR-T) therapy, in which autologous T lymphocytes are genetically modified to promote T-cell activation, T-cell proliferation, and immune memory. JCAR015 is produced by using a viral vector to transfect autologous T cells with a CAR transgene encoding a protein with both an extracellular antigen binding domain specific for CD19 and an intracellular signaling domain possessing both activating and co-stimulatory activities. Binding of the extracellular domain of this recombinant protein to CD19 on target cells activates the intracellular signaling domain, purportedly promoting a persistent immune response against CD19-expressing cells. JCAR015 T cells are administered by intravenous infusion. Juno Therapeutics, Seattle, WA, in collaboration with Memorial Sloan Kettering Cancer Center, New York, NY Phase II trial (ROCKET) ongoing; FDA granted orphan drug and breakthrough therapy statuses	Various cytotoxic chemotherapy regimens	Increased overall survival Increased progression-free survival Improved quality of life
Combination eflornithine/sulindac for prevention of colon cancer recurrence	Patients with a history of stage I–III colon cancer (primary resection 1 year prior) who are currently disease-free	Recurrence of colon cancer after attempted curative resection is most likely in the 1st 3 years after surgery. Investigators are examining a new therapy (CPP-1X) for preventing colon cancer recurrence that combines eflornithine, a therapy for hirsutism and African trypanosomiasis, with sulindac, a nonsteroidal anti-inflammatory agent. This prophylactic therapy may lower the risk of recurrence when taken daily for 3 years. In late-stage clinical trials, patients are receiving oral combination therapy with once-daily eflornithine, two 250 mg tablets, plus once-daily sulindac, 150 mg, for 3 years. Cancer Prevention Pharmaceuticals, Inc., Tucson, AZ, in collaboration with SWOG, Portland, OR Phase III trials (PACES and unnamed) ongoing	No commonly used chemopreventive agent exists for preventing colorectal cancer recurrence Compounds under investigation include: Aspirin Calcium supplements Curcumin Nonsteroidal anti-inflammatory drugs (NSAIDs) Omega-3 fatty acids	Reduced recurrence rate of high-risk adenoma or 2nd primary colorectal cancer Increased overall survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Copanlisib for recurrent indolent non-Hodgkin's lymphoma	Patients with treatment-refractory, indolent, non-Hodgkin's lymphoma (NHL)	Indolent NHLs are B-cell malignancies that typically progress slowly; however, they are seldom cured by chemotherapy and patients' disease frequently develops resistance to therapies. Copanlisib is a small-molecule kinase inhibitor with activity against the delta and gamma isoforms of phosphoinositide 3-kinase (PI3K). PI3Ks regulate aspects of cell proliferation and survival; their inhibition may be of benefit in various cancers. The delta and gamma isoforms of PI3K are expressed predominately in cells of the hematopoietic lineages; inhibiting these isoforms (as opposed to all PI3Ks) may effectively treat indolent NHLs while limiting side effects in normal tissue. In clinical trials, copanlisib is administered by intravenous infusion, 60 mg, on days 1, 8, and 15 of each 28-day treatment cycle. Bayer AG, Leverkusen, Germany Phase III trials ongoing; FDA granted orphan drug status	Chemoimmuno-therapies (e.g., bendamustine plus rituximab, fludarabine plus rituximab) Idelalisib Rituximab monotherapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Custirsen for treatment of advanced or metastatic nonsmall cell lung cancer	Patients in whom advanced or metastatic nonsmall cell lung cancer (NSCLC) has been diagnosed	The 5-year survival rate for patients with advanced NSCLC is less than 15% with available treatments. Custirsen (formerly OGX-011) is an antisense RNA molecule intended for treating advanced, unresectable NSCLC. An ongoing clinical trial is testing custirsen in the 2nd-line setting after 1st-line treatment with a platinum-based chemotherapy. It is given intravenously in combination with docetaxel: 3 loading doses of custirsen 640 mg are given over 2 hours in 5–9 days before day 1 of cycle 1; then custirsen 640 mg is given weekly every 21-day cycle. OncoGenex Pharmaceuticals, Inc., Bothell, WA Phase III trial (ENSPIRIT) ongoing; Apr 2014, FDA granted fast-track status	Chemotherapy with 1 or more of the following: *ALK* inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g, vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Custirsen for treatment of metastatic castration-resistant prostate cancer	Patients in whom castration-resistant prostate cancer (CRPC) has been diagnosed	Median overall survival for patients with CRPC is only about 18 months. Custirsen (formerly OGX-011) is an antisense RNA molecule designed to reduce expression of clusterin, a cell-survival protein activated by stress. Inhibition of clusterin expression using custirsen has been shown to enhance tumor cell death after chemotherapy. In clinical trials, custirsen is administered as an adjunct to chemotherapy. After 3 loading doses of custirsen (640 mg, intravenously [IV]), cabazitaxel (25 mg/m², IV) is administered on a 3-week cycle with weekly custirsen (640 mg, IV) and daily prednisone (10 mg, orally) until disease progression, unacceptable toxicity, or completion of 10 cycles. In the AFFINITY trial, patients have been randomly assigned to receive 2nd-line cabazitaxel (Jevtana®) and prednisone with or without custirsen. OncoGenex Pharmaceuticals, Inc., Bothell, WA Phase III trial (AFFINITY) ongoing; FDA granted fast-track status	Abiraterone Cabazitaxel Docetaxel Enzalutamide Radium-223 Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
Dabrafenib (Tafinlar) for treatment of *BRAF* ^{V600E} mutation–positive nonsmall cell lung cancer	Patients in whom *BRAF*^{V600E} mutation–positive metastatic nonsmall cell lung cancer (NSCLC) has been diagnosed	Patients with metastatic NSCLC have a poor prognosis when treated with conventional cytotoxic chemotherapy options. Increasingly, NSCLC subtypes are being characterized by mutations in genes thought to drive carcinogenesis (e.g., *ALK*, *EGFR*, *ROS1*), and therapies targeting these molecular drivers have improved outcomes for eligible patients. Recent research has determined that about 2% of NSCLCs harbor an activating mutation in the *BRAF* oncogene, presenting a novel target in treatment. Dabrafenib (Tafinlar®) is 1 of 2 commercially available *BRAF* inhibitors that are FDA-approved for treating *BRAF* mutation–positive melanoma, and it is under study for treating *BRAF* mutation–positive NSCLC either as a monotherapy or in combination with the MEK inhibitor trametinib (Mekinist®). Dabrafenib is administered orally, 150 mg, twice daily. GlaxoSmithKline, Middlesex, UK Phase II trial ongoing; FDA granted breakthrough therapy status	Docetaxel Erlotinib Pemetrexed	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Dacomitinib for treatment of nonsmall cell lung cancer	Patients in whom advanced nonsmall cell lung cancer (NSCLC) has been diagnosed	The 5-year survival rate for patients with advanced NSCLC is less than 15%, and patients whose disease progresses after 1st-line chemotherapy have few treatment options. Angiogenesis inhibitors have had varying degrees of success in treating NSCLC. Dacomitinib is a novel pan-HER inhibitor that irreversibly inhibits HER-1 (EGFR), HER-2, and HER-4 tyrosine kinases. Treatment settings include 1st-line treatment of patients with activating mutations in the *EGFR* gene, 2nd-line treatment of patients after chemotherapy, and 2nd-line or 3rd-line treatment of patients previously treated with an EGFR inhibitor. In clinical trials, dacomitinib is administered in a once-daily, oral dose of 45 mg. Pfizer, Inc., New York, NY Phase III trials (BR26, ARCHER-1009, and ARCHER-1052) ongoing; Mar 2015, FDA granted orphan drug status	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Daratumumab for treatment of multiple myeloma	Patients with multiple myeloma who have undergone treatment with both a protease inhibitor and an immunomodulatory drug	Patients with recurrent/refractory multiple myeloma who have received both protease-inhibitor and immunomodulatory drug therapies have few remaining treatment options and a poor prognosis. Daratumumab is a fully human monoclonal antibody specific for CD38, a protein expressed on the surface of multiple myeloma cells. Daratumumab purportedly leads to multiple myeloma cell death through antibody-dependent, cell-mediated cytotoxicity and complement-dependent cytotoxicity. Daratumumab is administered by intravenous infusion at a dose of 16 mg/kg. In recurrent/refractory disease, it is being tested in combination with dexamethasone and lenalidomide or in combination with dexamethasone and bortezomib. As a 1st-line treatment, it is being tested in combination with bortezomib, melphalan, and prednisone. Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ Phase III trials ongoing; FDA granted breakthrough therapy status; Jul 2015, rolling biologics license application submission completed	Multiple chemotherapy regimens (choice depends on prior therapy and patient condition), including: Bortezomib Bortezomib plus liposomal doxorubicin Carfilzomib Lenalidomide plus dexamethasone Pomalidomide plus dexamethasone	Increased overall survival Increased progression-free survival Improved quality of life
Defactinib for treatment-refractory mesothelioma	Patients with mesothelioma whose disease responds to platinum-based chemotherapy	Approximately 3,000 cases of mesothelioma are diagnosed each year in the U.S. Mesothelioma is a malignant tumor that most commonly affects the protective lining (the pleura) surrounding the lungs. It is caused in about 85% of cases by exposure to asbestos fibers. Despite chemotherapy options for mesothelioma, the disease recurs in most patients. Targeted therapies are needed for treatment-resistant mesothelioma. Defactinib (VS-6063) inhibits the focal adhesion kinase (FAK) signaling pathway, which is overexpressed in tumor cells, in particular in cancers with high potential to be metastatic. Defactinib is intended to prevent tumor growth by targeting FAK activity of cancer stem cells. In clinical trials, defactinib is administered orally, 400 mg, twice per day. Verastem, Inc., Needham, MA Phase II trials (COMMAND and VS-6063-203) ongoing; Jul 2013, FDA granted orphan drug status; also under study for treating nonsmall cell lung cancer and ovarian cancer	Surgical resection Radiation therapy Chemotherapy with 1 or more of the following: Antimetabolites (e.g., gemcitabine, pemetrexed, raltitrexed) Platinum-based agents (e.g., carboplatin, cisplatin, oxaliplatin) Topoisomerase inhibitor (i.e., irinotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Defibrotide (Defitelio) for treatment of chemotherapy-induced severe veno-occlusive disease	Patients receiving chemotherapy who have severe veno-occlusive disease	Veno-occlusive disease is a side effect of the high-dose chemotherapy that is used as part of hematopoietic stem cell transplantation procedures. Severe veno-occlusive disease has a mortality rate approaching 100% with available treatments. Defibrotide (Defitelio®) is a polydisperse oligonucleotide with local antithrombotic, anti-ischemic, and anti-inflammatory activities. Study investigators have suggested that the drug may increase survival of endothelial cells and preserve the function of microvasculature. In a phase III trial, the drug was administered intravenously, 25 mg/kg, 4 times per day. Gentium S.p.A. (Villa Guardia, Italy), a majority-owned, indirect subsidiary of Jazz Pharmaceuticals, Inc. (Dublin, Ireland) Phase III trial ongoing; FDA granted orphan drug and fast-track statuses; Feb 2015, company announced it had initiated a rolling submission of a new drug application; Oct 2013, approved by European Commission	Analgesia Diuresis Renal replacement therapy Transfusion	Increased overall survival Improved quality of life
Demcizumab for treatment of metastatic pancreatic cancer	Patients in whom locally advanced or metastatic pancreatic cancer has been diagnosed	Only about 5% of patients with pancreatic cancer respond to the standard of care (gemcitabine chemotherapy), and the prognosis for these patients is poor. Demcizumab is a monoclonal antibody for delta-like ligand 4 (DLL4), a protein that has been implicated in maintaining cancer stem cells and promoting angiogenesis. By inhibiting DLL4, demcizumab is intended to both target the difficult-to-treat population of tumor-initiating cancer stem cells in the pancreas and reduce the blood supply to solid tumors. In ongoing phase Ib clinical trials, demcizumab is being tested in combination with abraxane and gemcitabine in 1st-line advanced pancreatic cancer. Demcizumab is administered intravenously, 2.5 mg/kg, once every 2 weeks. OncoMed Pharmaceuticals, Inc., Redwood City, CA, in collaboration with Celgene Corp., Summit, NJ Phase Ib and phase II trials (YOSEMITE) ongoing; FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) Folic acid derivatives (e.g., leucovorin) Multikinase inhibitors (e.g., erlotinib) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Denosumab (Xgeva) for prevention of bone metastasis in breast cancer	Patients with early stage breast cancer at high risk of recurrence	Breast cancer patients who have cancer in the lymph nodes, large tumors, or locally advanced disease have a high risk of disease recurrence. Metastasis to the bone represents 40% of all initial recurrences. Denosumab (Xgeva) is a monoclonal antibody that inhibits RANKL, a protein that stimulates bone removal. Preclinical data suggest that RANKL inhibition may prevent skeletal tumor formation. In an ongoing trial, denosumab is being tested in the adjuvant setting for prolonging bone metastasis–free survival and disease-free survival. In this setting, denosumab is administered at 120 mg, once monthly, for 6 months followed by 120 mg, once every 3 months, for up to 5 years. Amgen, Inc., Thousand Oaks, CA Phase III trials (D-CARE, ABCSG-18, SAKK92/12, and 114273) ongoing; FDA approved for preventing skeletal-related events in patients with established bone metastases from solid tumors	Multikinase inhibitors (e.g., cabozantinib [in development]) Radioactive radium (Ra-223 dichloride)	Increased overall survival Increased bone metastasis–free survival Improved quality of life
Denosumab (Xgeva) for treatment-refractory hypercalcemia of malignancy	Patients with advanced cancer who have developed hypercalcemia of malignancy (HCM)	HCM is a serious, cancer-driven complication that causes an increase in bone resorption leading to abnormal elevation of serum calcium. Left untreated, HCM can lead to renal failure, progressive mental impairment, coma, and death. HCM has a prevalence of about 3% and its onset is usually associated with poor outcomes because the disease becomes refractory to bisphosphonate therapy. A need exists for treatments for refractory HCM. Denosumab (Xgeva®) is a monoclonal antibody that inhibits RANKL, a protein that stimulates bone removal. Preclinical data suggest that RANKL inhibition may also prevent osteoclasts from releasing calcium from bones. In an ongoing trial, denosumab is being tested in patients with HCM refractory to bisphosphonate therapy in the adjuvant setting for prolonging bone metastasis–free survival and disease-free survival. In this setting, denosumab is administered subcutaneously, every 4 weeks, at dose of 120 mg; in the 1st month of treatment, additional 120 mg doses are injected on days 8 and 15. Amgen, Inc., Thousand Oaks, CA Dec 2014, FDA approved for treating HCM refractory to bisphosphonate therapy; also FDA approved for preventing skeletal-related events in patients with established bone metastases from solid tumors	Bisphosphonate therapy (e.g., zoledronic acid)	Increased overall survival Increased bone metastasis–free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Dianhydrogalact-itol for treatment of recurrent glioblastoma	Patients with recurrent malignant gliomas, including glioblastoma multiforme (GBM)	GBM can be difficult to treat and is often associated with a poor prognosis; the 5-year survival rate is less than 5%. Investigators believe that, in 60% of patients, resistance to temozolomide treatment can be attributed to the DNA repair activity of O^6-methylguanine-DNA-methyltransferase (MGMT), which is highly expressed in GBM tumors. Dianhydrogalactitol (DAG; VAL-083) is a novel small molecule with a unique mechanism of action that causes N^7 DNA alkylation, which is purported to overcome MGMT-mediated resistance. In clinical trials, patients are treated intravenously with an escalating dose of DAG starting at 1.5 mg/m^2. DelMar Pharmaceuticals, Inc., Vancouver, British Columbia, Canada Phase I/II trial ongoing; Jan 2012, FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., carmustine, cyclophosphamide, lomustine, nitrosourea, procarbazine, temozolomide) Angiogenesis inhibitors (e.g., bevacizumab) Immunotherapeutics (e.g., DCVax-L, HSPPC-96, rindopepimut, SL-701 [in development]) mTOR inhibitors (e.g., everolimus) PD-1 antibodies (e.g., nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin) Radiation therapy Vinca alkaloids (e.g., vincristine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Dinutuximab (Unituxin) for treatment of high-risk neuroblastoma	Patients with high-risk neuroblastoma who have undergone induction therapy and autologous stem cell transplantation	Current treatments for patients with high-risk neuroblastoma result in 5-year survival rates of only 25% to 35%. A monoclonal antibody, dinutuximab (Unituxin) is specific for a tumor-associated disialoganglioside, GD2, that exhibits low levels of expression on normal tissues (e.g., neurons, skin melanocytes, peripheral sensory nerve fibers). The dinutuximab antibody purportedly targets neuroblastoma cells via antibody-dependent, cell-mediated cytotoxicity. In clinical trials, dinutuximab was administered intravenously at an unspecified dose in combination with cytokines (granulocyte macrophage colony-stimulating factor and interleukin-2) that enhance immune response and the standard neuroblastoma maintenance therapy isotretinoin. APEIRON Biologics AG, Vienna, Austria, in collaboration with the National Cancer Institute, Bethesda, MD Phase III trials ongoing; Mar 2015, FDA approved for treating pediatric high-risk neuroblastoma after 1st-line multiagent therapy; FDA and European Medicines Agency (EMA) granted orphan drug status	Stem cell transplant Surgical resection Radiation therapy Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide, ifosfamide) Platinum-based agents (e.g., carboplatin, cisplatin) Retinoids (e.g., isotretinoin) Topoisomerase inhibitors (e.g., doxorubicin, etoposide, topotecan) Vinca alkaloids (e.g., vincristine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Doxorubicin transdrug (Livatag) for treatment of unresectable hepatocellular carcinoma	Patients with unresectable hepatocellular carcinoma (HCC) whose disease has progressed after treatment with sorafenib	Patients with HCC that cannot be surgically resected have few treatment options and a poor prognosis; no 2nd-line therapy is available after sorafenib. Doxorubicin transdrug (Livatag®) is a nanoparticle formulation used to deliver chemotherapy (doxorubicin) to cancer cells developing resistance to previous chemotherapy agents. In clinical trials, patients are treated intravenously with 20 or 30 mg/m^2 doxorubicin transdrug every 4-week cycle until disease progression or toxicity. Onxeo, Paris, France (formed by the Jul 2014 merger of Topotarget a/s and BioAlliance Pharma SA) Phase III trial (ReLive) ongoing; FDA granted fast-track status	Radiofrequency ablation Surgical resection Locoregional treatment with 1 of the following: Transarterial embolization Transcatheter arterial chemoembolization Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Multikinase inhibitors (e.g., regorafenib, sorafenib) Platinum-based agents (e.g., cisplatin, oxaliplatin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Durvalumab for treatment of advanced nonsmall cell lung cancer	Patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC) that has progressed after platinum-based chemotherapy	The 5-year survival rate for patients with advanced NSCLC is less than 15%, and patients with advanced NSCLC whose disease has progressed after 1st-line platinum-based chemotherapy have few treatment options and a poor prognosis. A hallmark of cancer is its ability to evade an immune response. Durvalumab (MEDI4736) is a novel immunotherapy agent intended to prevent the immune tolerance of cancer cells. It is a monoclonal antibody against programmed death-1 receptor ligand (PD-L1), which is frequently expressed in tumor microenvironments and downregulates T cells via activation of the programmed death-1 (PD-1) immune checkpoint. Durvalumab purportedly limits activation of the immune checkpoint by preventing the interaction between PD-L1 and its receptor PD-1. In a clinical trial (ATLANTIC), durvalumab is administered intravenously every 2 weeks from day 1 for a maximum of 12 months or intolerable toxicity. Medimmune LLC subsidiary of AstraZeneca, London, UK Phase III trials (PACIFIC, ARTIC, MYSTIC, CAURAL, and BR31) ongoing	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Durvalumab for treatment of head and neck cancer	Patients in whom head and neck cancer has been diagnosed	Advanced head and neck cancer has a poor prognosis and a high recurrence rate, suggesting the need for new treatments. A hallmark of cancer is its ability to evade an immune response. Durvalumab (MEDI4736) is a novel immunotherapy agent intended to prevent the immune tolerance of cancer cells. It is a monoclonal antibody against programmed death-1 receptor ligand (PD-L1), which is frequently expressed in tumor microenvironments, and downregulates T cells via activation of the programmed death-1 (PD-1) immune checkpoint. Durvalumab, a checkpoint inhibitor, purportedly limits activation of the immune checkpoint by preventing the interaction between PD-L1 and its receptor, PD-1. In clinical trials, durvalumab is being tested as monotherapy or in combination with tremelimumab. It is administered intravenously every 2 weeks from day 1 for a maximum of 12 months or intolerable toxicity. Medimmune LLC subsidiary of AstraZeneca, London, UK Phase III trial ongoing	Chemoradiation Surgical resection Various combination or monotherapy regimens including: Alkylating agents (e.g., ifosfamide) Antimetabolites (e.g., 5-fluorouracil, gemcitabine, methotrexate) Cytoprotective agents (e.g., bleomycin) EGFR inhibitor (e.g., cetuximab) Immunotherapy (e.g, nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g, cisplatin) Oncolytic virus (e.g., Reolysin® [in development]) Taxanes (e.g., docetaxel, paclitaxel) Tyrosine kinase inhibitors (e.g., lenvatinib, sorafenib) Vinca alkaloids (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Duvelisib for treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma	Patients with recurrent/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)	Duvelisib (IPI-145) is a small-molecule kinase inhibitor with activity against the delta and gamma isoforms of phosphoinositide 3-kinase (PI3K). PI3Ks regulate aspects of cell proliferation and cell survival and, therefore, their inhibition may be of benefit in various cancers. The delta and gamma isoforms of PI3K are expressed predominately in cells of the hematopoietic lineages; inhibiting these isoforms (as opposed to all PI3Ks) may effectively treat blood cancers such as CLL and SLL while limiting side effects on normal tissues. Duvelisib is orally administered at a dosage of 25 mg, twice daily. Infinity Pharmaceuticals, Inc., Cambridge, MA, in collaboration with AbbVie, North Chicago, IL Phase III trial ongoing	Chemoimmunotherapy Ibrutinib Idelalisib Lenalidomide with or without rituximab Ofatumumab Rituximab	Increased progression-free survival Increased overall survival Improved quality of life
Duvelisib for treatment-refractory follicular lymphoma	Patients with previously treated follicular lymphoma	Follicular lymphoma is a B-cell malignancy that typically progresses slowly; however, the disease is seldom cured by chemotherapy and frequently becomes treatment resistant. Duvelisib (IPI-145) is a small-molecule kinase inhibitor with activity against the delta and gamma isoforms of phosphoinositide 3-kinase (PI3K). PI3Ks regulate aspects of cell proliferation and cell survival; therefore, their inhibition may be of benefit in various cancers. The delta and gamma isoforms of PI3K are expressed predominately in cells of the hematopoietic lineages; inhibiting these isoforms (as opposed to all PI3Ks) may effectively treat blood cancers such as follicular lymphoma while limiting side effects in normal tissues. In a clinical trial, duvelisib is administered orally, 25 mg, twice daily, in combination with intravenously administered rituximab. Infinity Pharmaceuticals, Inc., Cambridge, MA, in collaboration with AbbVie, North Chicago, IL Phase III trial ongoing	Idelalisib Rituximab monotherapy Various chemoimmunotherapy regimens (e.g., bendamustine plus rituximab, fludarabine plus rituximab)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
EBV-specific autologous cytotoxic T cells (CMD-003) for treatment of extranodal NK/T cell lymphoma	Patients with extranodal NK/T cell lymphoma (ENKTCL) who have received at least 1 round of asparaginase-based chemotherapy	ENKTCL is a rare, non-Hodgkin's lymphoma with an annual incidence of about 650 cases in the U.S. ENKTCL is an aggressive lymphoma and patients with disease that fails to respond to asparaginase-based combination chemotherapy have a poor prognosis and few treatment options. A defining feature of ENKTCL is positivity for the Epstein-Barr virus (EBV). Therefore, a potential approach to treating ENKTCL is generating an EBV-specific immune response, which could target and kill malignant cells. CMD-003 is an EBV-targeting cellular immunotherapy in which autologous EBV-specific T cells are activated and expanded ex vivo before being reintroduced into the patient. CMD-003 is administered by intravenous infusion at a dose of $2x10^7$ cells/m^2. Cell Medica, London, UK Phase II trial ongoing; FDA granted orphan drug status	Various combination asparaginase-based chemotherapies, including SMILE (dexamethasone, methotrexate, ifosfamide, asparaginase, and etoposide)	Increased overall survival Increased progression-free survival Improved quality of life
EBV-specific T cells (EBV-CTLs) for treatment of EBV-induced lymphoproliferative diseases	Patients who have developed an Epstein-Barr virus (EBV)-associated lymphoproliferative disease (EBV-LPD) after an allogeneic stem cell transplant and whose EBV-LPD is refractory to rituximab treatment	In immunocompetent people, EBV is typically held in check by the immune system. However, individuals with compromised immune systems may develop active EBV infections, which can lead to malignancy. In particular, about 6% of patients who undergo allogeneic stem cell transplant develop an EBV-LPD. Although many cases respond to treatment with the monoclonal antibody rituximab, patients whose disease fails to respond or whose EBV-LPD recurs after treatment have few treatment options and a poor prognosis. EBV-specific T cells (EBV-CTLs) are being investigated for treating this rituximab-refractory patient population. EBV-CTLs are an off-the-shelf preparation produced from immune cells of 3rd-party donors. Donor immune cells are exposed to EBV antigens and expanded in vitro before being infused into the patient. Patients receive 3 weekly injections of about 2×10^6 EBV-CTLs per kg of patient weight. Atara Biotherapeutics, Inc., South San Francisco, CA, in collaboration with Memorial Sloan Kettering Cancer Center, New York, NY Phase II trial ongoing; FDA granted breakthrough therapy status	Various cytotoxic chemotherapy regimens	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Elotuzumab (Empliciti) for treatment of multiple myeloma	Patients in whom multiple myeloma or recurrent/refractory multiple myeloma has been diagnosed	Although treatments for multiple myeloma have improved, the median life expectancy for patients in whom multiple myeloma is diagnosed is only 5–7 years. Immunotherapeutic options for multiple myeloma are not available. SLAMF7 (also known as CS1) has been identified as a glycoprotein expressed preferentially on multiple myeloma cells, and elotuzumab (Empliciti) is a humanized, monoclonal antibody specific for SLAMF7. It purportedly has an anticancer effect through antibody-dependent cellular cytotoxicity. In clinical trials, elotuzumab is being administered as an adjunct to conventional therapy with a combination of lenalidomide and dexamethasone. Elotuzumab is typically administered at a dose of 10 mg/kg. Bristol-Myers Squibb, New York, NY Phase III trials ongoing; FDA granted orphan drug status and breakthrough therapy status; FDA accepted biologic license application, and granted priority review	For stem cell transplant–eligible patients, 1st-line therapy such as: Bortezomib/ dexamethasone Cyclophosphamide/ dexamethasone For patients ineligible for stem cell transplant, 1st-line therapy such as: Bortezomib/ dexamethasone Lenalidomide/low-dose dexamethasone Melphalan/ prednisone plus bortezomib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Eltrapuldencel-T for treatment of melanoma	Patients in whom metastatic melanoma has been diagnosed	Patients with metastatic melanoma have a poor prognosis, with current treatments yielding a 5-year survival rate of 15% to 20%. Eltrapuldencel-T (CLBS20) is a hybrid immunotherapy developed from the patient's own tumor and dendritic cells. To prepare this therapy, both a tumor isolate and a blood draw to obtain immune cells are required. Dendritic cells (antigen-presenting cells of the immune system) are expanded from the patient's isolated immune cells and exposed to isolated cancer stem cells from the tumor sample. The activated dendritic cells are formulated into an injectable solution. In clinical trials, this immunotherapy is given over 3 weeks as a weekly subcutaneous injection of 10 million to 20 million cells, and then as a monthly injection for an additional 5 months. Caladrius Biosciences, Inc. (formerly NeoStem, Inc.), New York, NY, which acquired developer California Stem Cell, Inc., Irvine, CA, in Apr 2014 Phase III trial (Intus) ongoing—has Special Protocol Assessment; FDA granted fast-track and orphan drug statuses	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, temozolomide) B-RAF inhibitors (e.g., dabrafenib, vemurafenib) Immunotherapy (e.g., ipilimumab, nivolumab, pembrolizumab) MEK inhibitors (e.g., trametinib [cobimetinib; in development]) Platinum-based agents (e.g., carboplatin) Taxane agents (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Entinostat for treatment of estrogen receptor–positive breast cancer	Patients with locally advanced/unresectable or metastatic estrogen receptor–positive breast cancer whose disease has progressed following treatment with nonsteroidal aromatase inhibitor	Few effective treatment options exist for recurrent, advanced breast cancers that have become resistant to endocrine therapy or are hormone receptor negative. Entinostat (SNDX-275) is a class I histone deacetylase (HDAC) inhibitor. The exact mechanism of HDAC anticancer efficacy is unclear. In breast cancer, entinostat purportedly downregulates growth factor signaling pathways and upregulates estrogen receptors to combat endocrine drug resistance and inhibit tumor growth. In clinical trials, entinostat is being tested at various dosages and as part of various combination therapy regimens. In a clinical trial of entinostat plus exemestane for treating estrogen receptor–positive breast cancer, entinostat is administered orally, at dose of 5 mg, once weekly. Syndax Pharmaceuticals, Inc., Waltham, MA, in collaboration with the National Cancer Institute, Bethesda, MD, under a cooperative research and development agreement Phase III trial (E2112) ongoing; Sept 2013, FDA granted breakthrough therapy status	Chemotherapy with 1 or more of the following: Anabolic steroids (e.g., fluoxymesterone) Aromatase inhibitors (e.g., anastrozole, exemestane, letrozole) CDK4/6 inhibitors (e.g., palbociclib [abemaciclib, LEE011; in development]) Estrogen inhibitors (e.g., tamoxifen, toremifene) Estrogen receptor inhibitors (e.g., fulvestrant) Protein kinase inhibitors (e.g., everolimus) Synthetic progestogens (e.g., progestin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Entrectinib for treatment of colorectal cancer	Patients in whom locally advanced or metastatic colorectal cancer (CRC) has been diagnosed	Although many patients have CRC that responds to 1st-line chemotherapy, disease ultimately progresses in the vast majority of patients. Current 2nd-line treatments for CRC are of limited efficacy, and the median overall survival of these patients is less than 1 year. Entrectinib (RXDX-101) is a selective tyrosine multikinase inhibitor of the proteins TrkA, TrkB, TrkC, ROS1, and ALK, all of which have been reported to have activating alterations in different types of cancer, including CRC. In a phase I clinical trial, a dose escalation of oral entrectinib (100, 200, 400, 800, and 1,200 mg/m^2) has been well tolerated among patients with advanced tumors. Ignyta, Inc., San Diego, CA (developer) Nerviano Medical Sciences, Nerviano, Italy (licensee) Phase I/II trials (STARTRK-1 and ALKA-372-001) ongoing; Feb 2015, FDA granted orphan drug status	Chemotherapy with 1 of the following: Angiogenesis inhibitors (e.g., bevacizumab [ramucirumab; in development]) Antimetabolites (e.g., 5-fluorouracil, capecitabine) EGFR antibodies (e.g., cetuximab, panitumumab) FOLFIRI (leucovorin, 5-fluorouracil, irinotecan) FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin) Multikinase inhibitors (e.g., regorafenib) Platinum-based agents (e.g., oxaliplatin) Topoisomerase inhibitors (e.g., irinotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Entrectinib for treatment of pediatric neuroblastoma	Pediatric patients in whom neuroblastoma has been diagnosed	Neuroblastoma is the most common pediatric solid tumor, with about 800 new cases each year. Despite current treatment, children with high-risk neuroblastoma have an expected survival rate of 45%. Entrectinib (RXDX-101) is a selective tyrosine multikinase inhibitor of the proteins TrkA, TrkB, TrkC, ROS1 and ALK, all of which have been reported to have activating alterations in different types of cancer, including neuroblastoma. In a phase I clinical trial, a dose escalation of oral entrectinib (100, 200, 400, 800, and 1,200 mg/m^2) has been well tolerated among patients with advanced tumors. Ignyta, Inc., San Diego, CA, licensed by Nerviano Medical Sciences, Nerviano, Italy Phase I/II trials (STARTRK-1 and ALKA-372-001) ongoing; Dec 2014, FDA granted orphan drug and rare pediatric disease statuses	Stem cell transplant Surgical resection Radiation therapy Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide, ifosfamide) GD2 glycolipid antibodies (e.g., dinutuximab) Platinum-based agents (e.g., carboplatin, cisplatin) Retinoids (e.g., isotretinoin) Topoisomerase inhibitors (e.g., doxorubicin, etoposide, topotecan) Vinca alkaloid (e.g., vincristine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Eribulin mesylate (Halaven) for treatment of advanced soft tissue sarcoma	Patients with advanced soft tissue sarcoma (STS) whose disease has progressed after receiving anthracycline-based therapy	Worldwide, more than 12,000 cases of STS are reported each year, and about 4,700 die of STS. The high mortality rate is associated with limited therapeutic options for patients whose disease has recurred after treatment. Agents are needed for treating patients who have disease recurrence. Eribulin mesylate (Halaven®) is a potent microtubule-dynamics inhibitor that targets cells undergoing mitosis with the potential to address the unmet need. Eribulin is a synthetic analogue of halichondrin B, which was 1st isolated from the sea sponge *Halichondria okadia*. In rapidly dividing cancer cells, eribulin prevents the mitotic spindle from retracting; thus, chromosome segregation and cell division do not occur, and the extended mitotic blockage causes the cells to die by apoptosis. In clinical trials, eribulin is administered to patients intravenously at a dose of 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle in combination with dacarbazine. Eisai Co., Ltd., Tokyo, Japan Phase III trial (Study 309) ongoing; FDA approved eribulin for treating metastatic breast cancer that has progressed after 2 chemotherapy regimens	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, ifosfamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., gemcitabine, methotrexate) Platinum-based drugs (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, paclitaxel) Tyrosine kinase inhibitors (e.g., imatinib, pazopanib) Vinca alkaloids (e.g., vincristine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life
Erythrocyte-encapsulated L-asparaginase (GRASPA) for treatment of acute lymphoblastic leukemia	Patients in whom acute lymphoblastic leukemia (ALL) has been diagnosed	L-asparaginase has been used for decades for treating ALL; however, its use is limited by substantial toxicity, including the potential for the drug to elicit allergic reactions in patients. Use of the drug is generally limited to pediatric patient populations who are more tolerant of L-asparaginase treatment than older or frailer patients. GRASPA® is a formulation of L-asparaginase that encapsulates the drug in red blood cells (erythrocytes). It purportedly exhibits reduced toxicity and improved pharmacodynamics, potentially allowing treatment of more patients. In clinical trials, erythrocyte-encapsulated L-asparaginase is used in combination with multiple chemotherapy agents. The drug is administered by injection at a dose of 150 IU/kg per treatment cycle. Erytech Pharma, Lyon, France Phase I trial ongoing; phase III trials completed in Europe; FDA granted orphan drug status	Native L-asparaginase Pegylated asparaginase	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Etirinotecan pegol for treatment of breast cancer	Patients with metastatic breast cancer whose disease has progressed after 2 systemic chemotherapy regimens including anthracycline-, taxane-, and capecitabine-containing regimens	Patients with breast cancer that is refractory to standard systemic chemotherapy have few treatment options and a poor prognosis. Etirinotecan pegol (NKTR-102) is a novel formulation of the topoisomerase I inhibitor irinotecan. Etirinotecan pegol is a modified version of irinotecan in which the drug is linked to a macromolecule core. The linkage purportedly renders the drug inert in the bloodstream and allows its slow release as the linkages are metabolized in the patient. Slow release extends the time the patient's disease is exposed to therapeutic levels of the drug and limits exposure to high drug levels during infusion. Additionally, the large drug-polymer conjugate may preferentially accumulate in tumor tissues because of the increased permeability of tumor vasculature. In clinical trials, etirinotecan pegol is administered at an intravenous dosage of 145 mg/m^2, once every 21 days. Nektar Therapeutics, San Francisco, CA Phase III trial (BEACON) ongoing; FDA granted fast-track status; NKTR-102 is approved for treating colorectal cancer and under study for treating ovarian cancer, lung cancer, and glioma	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine, pemetrexed) PARP inhibitors (e.g., BMN 673, niraparib, olaparib [under development]) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloid (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life
Everolimus (Afinitor) for treatment of diffuse large B-cell lymphoma	Patients with diffuse large B-cell lymphoma (DLBCL) who have achieved a complete response after 1st-line rituximab-based chemoimmunotherapy and are at high risk of disease recurrence	DLBCL is refractory to 1st-line treatment in about 1/3 of diagnosed patients, or disease recurs after 1st-line treatment. Patients with recurrent/refractory disease have a poor prognosis and few treatment options. The mTOR inhibitor everolimus is under study as a maintenance therapy in patients whose disease has responded to 1st-line chemoimmunotherapy. The mTOR pathway affects multiple cancer-related cellular processes (cell growth, cell proliferation, angiogenesis) and activation of the mTOR pathway has been implicated in lymphoma pathogenesis. In clinical trials of maintenance therapy for patients with DLBCL who achieved a complete response after 1st line therapy and are at increased risk of recurrence based on International Prognostic Index score at time of diagnosis, everolimus was administered orally, 10 mg, once daily. Novartis International AG, Basel, Switzerland Phase III trial ongoing	High-dose chemotherapy with autologous stem cell transplant Watchful waiting/observation	Increased disease-free survival Increased overall survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ex vivo expanded cord blood cells (NiCord) for hematopoietic stem cell transplants	Patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) for hematologic malignancies	Individuals being treated for a hematologic malignancy (e.g., acute lymphoblastic leukemia, acute myeloid leukemia, Hodgkin's lymphoma, myelodysplastic syndrome) may receive high-dose chemotherapy and/or whole body irradiation followed by a bone marrow transplant to reconstitute their immune systems. Perfectly matched bone marrow donors are not available for many patients. Although an exact match is needed for adult bone marrow transplants to avoid complications from graft-versus-host disease (GVHD), umbilical cord blood from mismatched donors reportedly causes significantly less GVHD and, therefore, could increase the potential donor pool. However, the number of stem cells in a cord blood unit is not large enough to provide complete bone marrow engraftment in adult patients. NiCord® is ex vivo–expanded cord blood created from a single cord blood unit that purportedly contains enough hematopoietic stem cells to produce full engraftment in adult patients. Additionally, the cryopreserved and off-the-shelf nature of NiCord may allow additional flexibility in the timing of HSCT. Gamida Cell, Ltd., Jerusalem, Israel, in partnership with Teva Pharmaceutical Industries, Ltd., Petah-Tikva, Israel Phase I/II trial ongoing; FDA granted orphan drug status	Pooled unexpanded cord blood transplant Unexpanded cord blood transplant	Improved bone marrow engraftment rate Improved neutrophil recovery rate Improved platelet recovery rate Increased overall survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ex vivo expanded cord blood for allogeneic bone marrow transplant for hematologic malignancies	Patients with a hematologic malignancy who need a bone marrow transplant and for whom no suitable matched donor is available	Individuals being treated for a hematologic malignancy may receive high-dose chemotherapy and/or whole body irradiation followed by a bone marrow transplant to reconstitute their immune system. Perfectly matched bone marrow donors are not available for all patients who could benefit from transplantation, because of the difficulty in identifying perfectly matched donors. Although an exact match is needed for adult marrow transplants to avoid complications from graft-versus-host disease (GVHD), cord blood reportedly causes significantly less GVHD; however, the number of stem cells in cord blood is not large enough to provide complete bone marrow engraftment. The manufacturer of this product is using an off-the-shelf preparation of mesenchymal precursor cells to expand cord blood stem cells ex vivo to improve engraftment rates upon introduction to the host. Because an imperfect match may be tolerated when using cord blood as the donor source, it may provide a suitable treatment option for many patients receiving high-dose chemotherapy and in subsequent need of a bone marrow transplant to restore their immune system. Mesoblast, Ltd., New York, NY Phase III trial ongoing	Pooled unexpanded cord blood transplant Unexpanded cord blood transplant	Improved bone marrow engraftment rate Improved rate of neutrophil recovery Improved rate of platelet recovery

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Farletuzumab for treatment of recurrent ovarian cancer	Patients with recurrent ovarian cancer who are candidates for platinum and taxane-based therapy	Patients with recurrent ovarian cancer have median overall survival times of less than 2 years and few treatment options. Farletuzumab (MORAb-003) is a monoclonal antibody specific for the folate receptor, which is expressed on the majority of ovarian cancer cells, but not on cells of normal tissues. Farletuzumab's action purportedly leads to antibody-dependent cell-mediated cytotoxicity of folate-receptor–expressing cells. In late-phase clinical trials, farletuzumab is being administered intravenously, once weekly, 1.25 or 2.5 mg/kg. In platinum-sensitive disease, farletuzumab is being tested in combination with carboplatin/taxane doublet therapy. Morphotek subsidiary of Eisai Co., Ltd., Tokyo, Japan Phase III trial (FAR-131) ongoing; FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if *BRCA*1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fosbretabulin for treatment of ovarian cancer	Patients in whom platinum-resistant ovarian cancer has been diagnosed	Ovarian, fallopian tube, or primary peritoneal cancer frequently recurs after initial treatment, and recurrence is associated with poor outcomes. In some types of cancer, including ovarian cancer, signaling pathways that promote blood vessel formation are upregulated and supply the tumor with nutrients. Fosbretabulin (CA4P) is a vascular disrupting agent capable of selectively affecting and disrupting tumor vasculature, which reduces the blood supply the tumor requires to grow and survive. This purportedly stops cancer cells from growing and has potential to improve survival in patients with ovarian cancer, who have limited 2nd-line treatment options. In clinical trials, fosbretabulin is being tested in combination with the angiogenesis inhibitor bevacizumab and with the protein kinase inhibitor pazopanib. Patients receive intravenous fosbretabulin, from 45 to 60 mg/m^2, every 3 weeks of a 4-week cycle, for a maximum of 6 cycles. OXiGENE, Inc., South San Francisco, CA, in collaboration with the National Cancer Institute, Bethesda, MD Phase II trial completed for combination bevacizumab; phase Ib/II trial ongoing for combination pazopanib; Sept 2006, FDA granted orphan drug status	Combination or single agent chemotherapy with 1 of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if *BRCA*1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gallium-labeled somatostatin receptor agonist (OPS202) for detection of gastroenteropan-creatic neuroendocrine tumors	Patients in whom gastroenteropan-creatic neuroendocrine tumors (NETs) have been diagnosed	Most cases of NETs are advanced by the time they are diagnosed and cannot be surgically resected. Because of a lack of effective treatments at a late stage, these tumors are associated with poor outcomes. Survival rates improve substantially when NETs are detected early because standard of care can treat the disease and prevent it from recurring. Therefore, effective diagnostic tools are needed to detect NETs before they progress to an advanced stage. [^{68}Ga]-OPS202 is a ^{68}gallium-labeled peptide with high affinity for the somatostatin receptor subtype sst 2 receptor antagonist that reportedly is a highly sensitive and very specific method to detect NETs by positron emission tomography (PET). Early detection could lead to improved patient outcomes. In a phase I/II clinical trial, micro-dosing of [^{68}Ga]-OPS202 is being tested in patients to evaluate safety, distribution, and efficacy of 2 unspecified doses to detect NETs using positron-emission tomography/computed tomography (CT). OctreoPharm Sciences GmbH, Berlin, Germany, acquired Jun 2015 by Ipsen, Paris, France Phase I/II trial (OPS-B-001) completed; Sept 2014, FDA granted orphan drug status	Angiogram Biopsy Blood chemistry tests (e.g., chromogranin A, gastrin, glucagon, insulin) Bone scan CT scan Endoscopic retrograde cholangiopancreatography Endoscopic ultrasound Intraoperative ultrasound Laparotomy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ganetespib for treatment of advanced nonsmall cell lung cancer	Patients with advanced or metastatic nonsmall cell lung cancer (NSCLC) who have undergone 1 systemic therapy for advanced or metastatic disease	Patients with advanced NSCLC that has progressed after chemotherapy have a poor prognosis and few treatment options. Ganetespib (STA-9090) is a novel anticancer agent that inhibits hsp90 activity. Hsp90 is a molecular chaperone that is responsible for the proper folding and stability of a wide range of proteins in the cell. In particular, hsp90 has been implicated in maintaining the stability of multiple mutated proteins with proneoplastic properties, including mutated p53, BCR-ABL, Raf-1, AKT, ErbB2, and hypoxia-inducible factor 1 alpha. Additionally, hsp90 has been shown to increase the activity of proteins known to have a cytoprotective effect in cells exposed to cytotoxic chemotherapy; therefore, hsp90 inhibition might act synergistically with cytotoxic agents. In treating NSCLC, ganetespib is being tested as an adjunct to the cytotoxic agent docetaxel. Ganetespib is administered at a dose of 150 mg/m^2, intravenously, once weekly for 3 weeks, followed by 1 week of rest. Synta Pharmaceuticals Corp., Lexington, MA Phase II/III and III trials (GALAXY-1 and GALAXY-2) ongoing; FDA granted fast-track status	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gemtuzumab ozogamicin for treatment of acute myeloid leukemia	Patients in whom acute myeloid leukemia (AML) has been diagnosed	With current treatments, the 5-year survival rate for patients with AML ranges from 20% to 70%, depending on disease subtype. Gemtuzumab ozogamicin is an AML treatment that conjugates a highly toxic chemotherapy agent to a monoclonal antibody specific for a cell surface marker expressed on most AML cells (CD33). The conjugate is intended to preferentially target AML cells with the toxic chemotherapy. Gemtuzumab ozogamicin is administered intravenously; various dosing schedules have been reported. During a recently completed phase III trial, investigators administered gemtuzumab ozogamicin in combination with a standard chemotherapy regimen using daunorubicin and cytarabine. Pfizer, Inc., New York, NY FDA approved in 2000 for treating AML; drug withdrawn from U.S. market in 2010 after negative study results and high toxicity observed in postmarket trials; drug remains available in Europe, where trials have shown benefit using an altered dosing scheme; Pfizer is analyzing data to determine whether to make new FDA submission; the drug is available in the U.S. only to patients already taking it	Standard chemotherapy with daunorubicin and cytarabine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gene therapy (GEN-1) for recurrent or persistent ovarian cancer	Patients with recurrent or persistent ovarian, primary peritoneal, or fallopian tube cancer who have received at least 1 round of platinum-based treatment	Patients with platinum-resistant ovarian cancer have a poor prognosis and few treatment options. GEN-1 is a novel gene therapy intended to induce the expression of interleukin-12 (IL-12) in tumor cells; IL-12 expression purportedly leads to 3 antitumor activities: (1) activation and proliferation of natural killer (NK) cells, leading to an innate immune response against the tumor; (2) maturation and proliferation of T lymphocytes, leading to an adaptive immune response against the tumor; and (3) activation of NK cells and T lymphocytes leading to upregulation of interferon gamma, which has antiangiogenic properties. GEN-1 is formulated with the TheraPlas™ delivery system that forms active nanoparticles that transfect cells with a plasmid expressing IL-12; this formulation is optimized for delivery into the tumor microenvironment. This agent is being tested in platinum-refractory ovarian cancer. In clinical trials, GEN-1 is administered by intraperitoneal catheter, 24 mg/m^2, weekly. EGEN, Inc., Huntsville, AL, in collaboration with Celsion Corp., Lawrenceville, NJ (Celsion acquired EGEN in Jun 2014) Phase II trial ongoing; FDA granted orphan drug status; early stage trials ongoing in other treatment settings and disease indications	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if *BRCA*1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Glembatumumab vedotin for treatment-refractory triple-negative breast cancer	Patients with metastatic, glycoprotein NMB (GPNMB)-overexpressing, triple-negative breast cancer	Therapies with improved efficacy are needed for patients with metastatic triple-negative breast cancer (i.e., low expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2), because these patients have limited treatment options and a poor prognosis. Glembatumumab vedotin is an antibody-drug conjugate that links a highly toxic chemotherapy drug to a monoclonal antibody specific for GPNMB, a protein known to be overexpressed in some breast tumors. GPNMB has been implicated in enhancing the metastatic potential of breast cancer cells, particularly the triple-negative breast cancer subtype. A companion diagnostic test to determine whether a patient's cancer expresses GPNMB will be used to determine patient eligibility for treatment with glembatumumab vedotin. In a phase III trial, this agent will be compared with capecitabine in patients who have received anthracycline and taxane chemotherapy. Glembatumumab vedotin is administered intravenously, 1.88 mg/kg, once every 3 weeks. Celldex Therapeutics, Inc., Needham, MA Phase II trial (METRIC) ongoing; May 2010, FDA granted fast-track status for treatment-resistant or refractory breast cancer	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine, pemetrexed) PARP inhibitors (e.g., BMN 673, niraparib, olaparib [in development]) PD-1 antibodies (e.g., pembrolizumab [in development]) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloid (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gonadotropin-releasing hormone analogues for prevention of ovarian failure in women receiving gonadotoxic chemotherapy	Women undergoing gonadotoxic systemic chemotherapy for cancer	About 25% of women undergoing systemic chemotherapy for conditions such as breast cancer experience premature menopause as a side effect of treatment. No consensus on treatment exists for preventing this side effect. Ovarian suppression using gonadotropin-releasing hormone analogues (e.g., goserelin, triptorelin) may protect ovarian function against the effects of chemotherapy through several mechanisms, including decreasing the number of primordial follicles entering the relatively chemotherapy-sensitive differentiation stage; decreasing ovarian perfusion, thereby reducing ovarian exposure to chemotherapy; upregulating intragonadal antiapoptotic molecules (e.g., sphingosine-1-phosphate); and protecting ovarian germline stem cells. In clinical trials, gonadotropin-releasing hormone analogues (i.e., goserelin or triptorelin) are administered concomitantly with standard cytotoxic chemotherapy regimens. SWOG, Portland, OR, and International Breast Cancer Study Group IBCSG, Bern, Switzerland Phase III (POEMS) trial ongoing; the National Institutes of Health announced favorable results; agents could be prescribed off label	Other fertility preservation techniques (e.g., embryo, ovarian tissue, or oocyte cryopreservation)	Decreased rate of amenorrhea at 12 months after chemotherapy Preserved fertility Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Hafnium oxide nanoparticles (NBTXR3) for treatment of soft tissue sarcoma	Patients with unresectable, locally advanced soft tissue sarcoma (STS) whose disease is amenable to radiation therapy	Worldwide, more than 12,000 cases of STS are reported each year, and about 4,700 people die of STS. The high mortality rate is associated with limited response to radiation therapy and the lack of therapeutic options for patients whose disease has recurred after treatment. Agents that can increase the tumor's response rate to radiation are needed. NBTXR3 is an inert nanoparticle made of hafnium oxide capable of absorbing more photons from ionizing radiation, generating a greater amount of electrons, which can cause more damage to cancer cells than traditional radiation therapy. In clinical trials, patients receive a single intratumoral injection of NBTXR3 followed by radiotherapy (50Gy, 2Gy/fraction) starting the day after the injection up to completion of 5 weeks of treatment given 5 days per week. Nanobiotix, Paris, France Phase II/III trial (NBTXR3-301) ongoing	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, ifosfamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., gemcitabine, methotrexate) Platinum-based drugs (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, paclitaxel) Tyrosine kinase inhibitors (e.g., imatinib, pazopanib) Vinca alkaloids (e.g., vincristine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Hypoxia-activated DNA alkylating agent (evofosfamide) for treatment of pancreatic cancer	Patients in whom metastatic pancreatic adenocarcinoma has been diagnosed	About 5% of patients with pancreatic cancer respond to the current standard of care (gemcitabine chemotherapy), and the prognosis for these patients is very poor. Hypoxic areas of tumors are often refractory to conventional chemotherapy because of the tissues' inaccessibility to standard drugs and/or slow rate of cell division. Thus, new options are needed. Evofosfamide (TH-302) is a novel cytotoxic agent purported to be preferentially activated in hypoxic conditions. In its activated form, evofosfamide is said to be a potent DNA alkylating agent (dibromo isophoramide mustard). Selectively activating evofosfamide in hypoxic conditions might target alkylating activity to tumors. Evofosfamide is administered intravenously, and in clinical trials for pancreatic cancer, it is being administered at a dose of 340 mg/m^2, in combination with gemcitabine. Threshold Pharmaceuticals, South San Francisco, CA, with Merck KGaA, Darmstadt, Germany Phase III trial (MAESTRO) ongoing; FDA granted orphan drug status and in May 2015 granted fast-track status	Chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) Folic acid derivatives (e.g., leucovorin) Multikinase inhibitors (e.g., erlotinib) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Hypoxia-activated DNA alkylating agent (evofosfamide) for treatment of soft tissue sarcoma	Patients in whom locally advanced, unresectable or metastatic soft tissue sarcoma has been diagnosed	Until recently, doxorubicin was the only FDA-approved treatment for soft tissue sarcomas (excluding gastrointestinal stromal tumors and liposarcomas), and no consensus treatment exists for patients whose disease has progressed on doxorubicin chemotherapy. The disordered growth of tumors often leads to areas of tissues with inadequate blood supply, leading to hypoxic conditions. These hypoxic areas of tumors are often refractory to conventional chemotherapy because of their inaccessibility to standard drugs and/or slow rate of cell division. Evofosfamide is a novel cytotoxic agent that purportedly is preferentially activated in hypoxic conditions. In its activated form, evofosfamide is a potent DNA alkylating agent (dibromo isophoramide mustard). Selectively activating evofosfamide in hypoxic conditions might target alkylating activity to tumors. In clinical trials for soft tissue sarcoma, evofosfamide is being used as 1st-line therapy in combination with doxorubicin to try to target both the hypoxic and normoxic regions of the tumor. Evofosfamide is an intravenous medication administered at a dose of 300 mg/m^2, on days 1 and 8 of a 21-day cycle. Threshold Pharmaceuticals, South San Francisco, CA, with Merck KGaA, Darmstadt, Germany Phase III trial (TH-CR-406) ongoing; companies signed agreement in Feb 2012 to codevelop and commercialize evofosfamide; FDA granted orphan drug status and in Nov 2014 granted fast-track status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, ifosfamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., gemcitabine, methotrexate) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, paclitaxel) Tyrosine kinase inhibitors (e.g., imatinib, pazopanib) Vinca alkaloids (e.g., vincristine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ibrutinib (Imbruvica) for treatment of chronic lymphocytic leukemia	Patients with chronic lymphocytic leukemia (CLL)	Ibrutinib (Imbruvica™) is a small-molecule kinase inhibitor with activity against Bruton's tyrosine kinase (Btk). Btk is essential for transduction of the B-cell receptor (BCR) signaling pathway, and many B-cell malignancies, including CLL, purportedly depend on BCR signaling for survival; therefore, its inhibition may be of therapeutic benefit in patients with these conditions. Ibrutinib is under study in patients with various stages of CLL, including recurrent/refractory CLL and in patients aged 65 years or older with newly diagnosed CLL. In trials, ibrutinib is orally administered at a once-daily dosage of 560 mg. Pharmacyclics subsidiary of AbbVie, North Chicago, IL, with the Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ Phase III trials ongoing; FDA granted orphan drug and breakthrough therapy statuses; Feb 2014, FDA granted accelerated approval for treating patients with "chronic lymphocytic leukemia (CLL) who have received at least one prior therapy"; Jul 2014, FDA granted full approval and expanded label to include patients with CLL who carry a deletion in chromosome 17	For patients with recurrent/refractory CLL: Various chemotherapy regimens (e.g., bendamustine plus rituximab, ofatumumab) For patients aged 65 years or older with CLL: 1 or more of the following: Alemtuzumab Bendamustine Chlorambucil Cladribine; Cyclophosphamide Prednisone Also: Fludarabine Lenalidomide Rituximab	Increased overall survival Increased progression-free survival Improved quality of life
Ibrutinib (Imbruvica) for treatment of diffuse large B-cell lymphoma	Patients in whom the nongerminal-center B-cell (GCB) subtype of diffuse large B-cell lymphoma (DLBCL) is newly diagnosed	Although the majority of patients with DLBCL respond to standard 1st-line chemotherapy, some patients' disease is resistant to this therapy and a significant number of patients experience recurrence after an initial response. Many B-cell malignancies purportedly depend on B-cell receptor (BCR) signaling for survival. In particular, preclinical studies have demonstrated the dependence of the non-GCB subtype of DLBCL on BCR signaling for survival. Bruton's tyrosine kinase (Btk) is essential for transduction of the BCR signaling pathway; therefore, its inhibition may be of therapeutic benefit in these patients. In trials for treating non-GCB DLBCL, ibrutinib (Imbruvica™) has been administered in a once-daily, oral dose of 560 mg in combination with standard 1st-line chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Pharmacyclics subsidiary of AbbVie, North Chicago, IL, with the Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ Phase III trial ongoing; FDA granted orphan drug status	Combination therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone	Increased overall survival Increased progression-free survival Increased disease-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ibrutinib (Imbruvica) for treatment of indolent non-Hodgkin's lymphoma	Patients with indolent non-Hodgkin's lymphoma (i.e., follicular lymphoma, marginal zone lymphoma) who have undergone treatment with a CD20 antibody plus chemotherapy	Indolent non-Hodgkin's lymphomas are B-cell malignancies that typically progress slowly; however, they are seldom cured by chemotherapy and patients' disease frequently develops resistance to therapies. Ibrutinib (Imbruvica™) is a small-molecule kinase inhibitor with activity against Bruton's tyrosine kinase (Btk). Btk is essential for transduction of the B-cell receptor (BCR) signaling pathway, and many B-cell malignancies purportedly depend on BCR signaling for survival; therefore, its inhibition may be of therapeutic benefit in patients with these conditions. In trials, ibrutinib is orally administered at a once-daily dosage of 560 mg. Pharmacyclics subsidiary of AbbVie, North Chicago, IL, with the Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ Phase III trial ongoing	Various rituximab-based regimens (rituximab monotherapy; rituximab and a chemotherapeutic agent such as bendamustine, fludarabine) Idelalisib	Increased overall survival Increased progression-free survival Improved quality of life
Ibrutinib (Imbruvica) for treatment of mantle cell lymphoma	Patients with newly diagnosed or recurrent/refractory mantle cell lymphoma (MCL)	Although patients with MCL frequently respond to initial chemotherapy treatment, the disease eventually progresses in most patients. Median overall survival is between 5 and 7 years. Ibrutinib (Imbruvica™) is a small-molecule kinase inhibitor with activity against Bruton's tyrosine kinase (Btk). Btk is essential for transduction of the B-cell receptor (BCR) signaling pathway, and many B-cell malignancies (including MCL) purportedly depend on BCR signaling for survival; therefore, its inhibition may be of therapeutic benefit in patients with MCL. In trials, ibrutinib has been orally administered at a once-daily dose of 560 mg. Pharmacyclics subsidiary of AbbVie, North Chicago, IL, with the Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ Phase III trials ongoing in newly diagnosed and recurrent/refractory MCL; FDA approved Nov 2013 for patients with MCL who have received at least 1 prior therapy	Various chemotherapies including 1 or more of the following: Bendamustine Bortezomib Cyclophosphamide Etoposide Fludarabine Lenalidomide Mitoxantrone Pentostatin Procarbazine Rituximab Temsirolimus	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ibrutinib (Imbruvica) for treatment of Waldenström's macroglobulin-emia	Patients with Waldenström's macroglobulinemi a that has been previously treated	Although several off-label treatments are in use for Waldenström's macroglobulinemia, no treatments are FDA-approved for this indication, and no standard treatment exists. Ibrutinib (Imbruvica™) is a small-molecule kinase inhibitor with activity against Bruton's tyrosine kinase (Btk). Btk is essential for transduction of the B-cell receptor (BCR) signaling pathway, and many B-cell malignancies (including Waldenström's macroglobulinemia) purportedly depend on BCR signaling for survival; therefore, its inhibition may be of therapeutic benefit. In a phase III clinical trial, ibrutinib is being administered at a once-daily dose of 420 mg, either as a monotherapy or in combination with rituximab. Pharmacyclics subsidiary of AbbVie, North Chicago, IL, with the Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ Phase III trial ongoing; Jan 2015, FDA approved for treating patients with Waldenström's macroglobulinemia	Various chemotherapy regimens, including: Bendamustine Bortezomib Cladribine Cyclophosphamide Dexamethasone Doxorubicin Fludarabine Prednisone Rituximab Thalidomide Vincristine	Increased overall survival Increased progression-free survival Improved quality of life
Idelalisib (Zydelig) for treatment of chronic lymphocytic leukemia	Patients in whom chronic lymphocytic leukemia (CLL) has been diagnosed	Available treatments for patients with CLL are not curative, and disease typically recurs, requiring additional treatment. Idelalisib (Zydelig®) inhibits a novel target: phosphoinositide 3-kinase (PI3K) delta, which is a kinase that promotes cell survival, division, and growth. The delta isoform of Class I PI3K is expressed only in blood cells, and targeted inhibition could treat blood-based cancers without side effects on other tissues. The drug is under study in combination with rituximab or rituximab plus bendamustine for previously treated CLL. In ongoing trials, the drug is administered orally, 150 mg, twice daily. Gilead Sciences, Inc., Foster City, CA Phase III trials ongoing; Jun 2015, supplemental new drug application submitted to FDA for using idelalisib in combination with ofatumumab; Jul 2014, FDA granted accelerated approval for treating recurrent CLL, "in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities" after earlier granting breakthrough therapy status	Various regimens including 1 or more of the following: Cyclophosphamide Doxorubicin Fludarabine Ibrutinib Obinutuzumab Ofatumumab Prednisolone Rituximab Vincristine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Idelalisib (Zydelig) for treatment of indolent non-Hodgkin's lymphoma	Patients with previously treated, indolent, non-Hodgkin's lymphoma (NHL)	Indolent NHLs are B-cell malignancies that typically progress slowly; however, they are seldom cured by chemotherapy and patients' disease frequently develops resistance to therapies. Idelalisib (Zydelig®) is a small-molecule inhibitor of phosphoinositide 3-kinase (PI3K) delta, a kinase that regulates activation, proliferation, and survival of B cells. In phase III clinical trials, idelalisib is being administered orally, at a twice-daily dose of 150 mg. Gilead Sciences, Inc., Foster City, CA Phase III trials ongoing; Jul 2014, FDA granted accelerated approval for treating recurrent follicular B-cell lymphoma and small lymphocytic lymphoma	Regimens including rituximab monotherapy or chemoimmunotherapy with rituximab and a chemotherapeutic agent (e.g., bendamustine, fludarabine)	Increased overall survival Increased progression-free survival Improved quality of life
IlluminOss system for stabilization of disease-induced bone fractures	Patients with disease-induced complex fractures	In patients with cancer, the disease may cause increased activity in osteoclasts, which are cells responsible for bone resorption. If left untreated, osteoclasts will continue to induce bone loss, which increases the risk of bone fractures. The incidence of bone fracture varies among types of cancer; an observational study determined that in women with breast cancer, about 70 of 10,000 patients experience bone fractures. Other conditions that can cause progressive bone loss include liver or kidney disease, chronic obstructive pulmonary disease, diabetes, hyperthyroidism, inflammatory bowel diseases, Paget's disease, and rheumatoid arthritis. The IlluminOss Photodynamic Stabilization System uses a polyethylene terephthalate balloon infused with a liquid monomer. A minimally invasive procedure is performed to insert the device in the intramedullary canal (i.e., bone marrow cavity) and use a light inside the balloon to solidify the implant, thereby conforming it to bone anatomy. The cured implant offers resistance and is intended to serve as a scaffold if additional hardware is needed to provide greater longitudinal strength and rotational stability. IlluminOss Medical, Inc., East Providence, RI Unphased clinical trials ongoing (12-03-EUHUM-01, 14-03-PATHOLHUM-01, 14-03-PATHOLHUM-02)	No marketed comparator in the U.S.	Increased bone healing Decreased bone pain Improved skeletal function

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Immunomodulatory peptide (SGX942) for treatment of anticancer therapy–related mucositis	Patients who develop oral mucositis (OM) due to anticancer therapies	OM is a complication commonly experienced by patients undergoing anticancer therapy (e.g., chemotherapy, radiation therapy). Significant mouth pain is associated with OM; it makes eating and drinking difficult and impairs quality of life. Severe cases of OM delay or interrupt treatment. Current OM therapies, such as narcotics and lidocaine, have significant side effects and limited efficacy. SGX942 is a water-soluble, 5-amino-acid peptide with anti-inflammatory and anti-infective properties. It is a member of a novel drug class called innate defense regulators that target the immune system. SGX942 binds to an intracellular adaptor protein, sequestosome-1, or p62, which has a pivotal function in signal transduction during activation and control of the immune defense system. In clinical trials, it is administered intravenously at increasing doses of 1.5, 3.0, and 6.0 mg/kg over 4 minutes. Soligenix, Inc., Princeton, NJ Phase II trial ongoing; Jun 2013, FDA granted fast-track status	Lidocaine Narcotics	Decreased pain and oral side effects Improved ability to eat and drink Improved cancer-treatment adherence Improved quality of life
Immunotherapy (CRS-207 and GVAX) for pancreatic cancer	Patients with metastatic pancreatic cancer who have received at least 1 round of chemotherapy	Only about 5% of patients with pancreatic cancer respond to the standard of care (gemcitabine chemotherapy), and the prognosis for these patients is poor. CRS-207 is an attenuated strain of *Listeria*, which has been genetically engineered to express the pancreatic cancer–associated antigen mesothelin. GVAX is a mixture of 2 pancreatic cancer cell lines that have been irradiated and genetically modified to express the immune cytokine GM-CSF. This combination immunotherapy purportedly targets pancreatic cancer through a 2-step process. Initially, the secreted GM-CSF purportedly recruits immune cells to the site of inoculation and primes T cells to recognize cancer cells. Subsequently, CRS-207-infected dendritic cells boost the immune response to target and kill cancer cells overexpressing mesothelin. In clinical trials, patients are injected twice with 5.00E+08 cells of GVAX on weeks 1 and 4. 1.00E+09 CFU of CRS-207 are inoculated on the 1st day of weeks 7, 10, 13, and 16. The GVAX and CRS-207 duo is also being tested in combination with nivolumab. Aduro BioTech, Inc., Berkeley, CA Phase II clinical trials (ECLIPSE, ADU-CL-01, and ADU-CL-06) ongoing; FDA granted orphan drug and breakthrough therapy statuses	Chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) Folic acid derivatives (e.g., leucovorin) Multikinase inhibitors (e.g., erlotinib) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Imprime PGG immunomodula-tor for treatment of advanced colorectal cancer	Patients in whom recurrent or metastatic KRAS wild-type colorectal cancer (CRC) has been diagnosed	Many patients with late-stage CRC are unable to tolerate or do not benefit from available chemotherapeutic regimens; new therapies to treat advanced CRC are needed. Imprime PGG® is a novel beta glucan immunomodulator that purportedly induces an antitumor response by binding complement receptors 1–3 and stimulating neutrophils. Imprime PGG purportedly works synergistically with monoclonal antibody therapy such as cetuximab, and in clinical trials, this agent is being examined as part of a combination therapy with cetuximab. Imprime PGG is administered at a dose of 4 mg/kg, by injection, weekly. Biothera, Eagan, MN Phase III trial (PRIMUS) ongoing	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab [ramucirumab; in development]) Antimetabolites (e.g., 5-fluorouracil, capecitabine) EGFR antibodies (e.g., cetuximab, panitumumab) FOLFIRI (leucovorin, 5-fluorouracil, irinotecan) FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin) Multikinase inhibitors (e.g., regorafenib) Platinum-based agents (e.g., oxaliplatin) Topoisomerase inhibitors (e.g., irinotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Injected bioabsorbable hydrogel (SpaceOAR) to protect healthy tissue during radiation therapy for prostate cancer	Patients undergoing radiation therapy treatment for cancers that are adjacent to delicate healthy structures (e.g., prostate cancer)	SpaceOAR™ system (spacing organs at risk) is a hydrogel injected as a liquid that becomes solid in the body and is intended for use during radiation therapy to create distance between the targeted tumor and organs at risk of collateral radiation damage (e.g., displace the rectum from the prostate). Augmenix, Inc., Waltham, MA FDA cleared Apr 2015 under the de novo process to "temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer ...to reduce the radiation dose delivered to the anterior rectum. The SpaceOAR System ... maintains space for the entire course of prostate radiotherapy treatment and is completely absorbed by the patient's body over time." Phase III pivotal trial completed; postmarket surveillance trial recruiting; CE marked	Radiation therapy without normal-tissue spacer	Reduced radiation-associated side effects to healthy tissue
Inotuzumab ozogamicin for treatment-refractory acute lymphoblastic leukemia	Patients in whom recurrent or treatment-refractory acute lymphoblastic leukemia (ALL) has been diagnosed	Among patients who experience an ALL relapse, only about 30% will achieve long-term remission with subsequent therapies. Inotuzumab ozogamicin is an antibody-drug conjugate that links the cytotoxic antibiotic calicheamicin to an antibody specific for CD22, a marker highly expressed by ALL cells. In clinical trials, inotuzumab ozogamicin monotherapy is administered once weekly, by intravenous infusion. Pfizer, Inc., New York, NY Phase III trial ongoing; FDA granted orphan drug status	Various combinations of the following chemotherapy agents: Anthracyclines Asparaginase Cyclophosphamide Cytarabine (ara-C) Epipodophyllotoxins Vincristine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ipilimumab (Yervoy) for treatment of advanced nonsmall cell lung cancer	Patients with recurrent or metastatic nonsmall cell lung cancer (NSCLC) who have not received systemic therapy	The 5-year survival rate for patients with advanced NSCLC is less than 15% with current treatments. Ipilimumab (Yervoy™) is a 1st-in-class, cytotoxic T-lymphocyte antigen 4 (CTLA-4)-targeted immunotherapy. By blocking the activity of CTLA-4, ipilimumab may increase antitumor cytotoxic activity (reduce immune tolerance to tumor cells). This agent is being tested as 1st-line treatment as part of combination therapy with carboplatin and paclitaxel. It is also in early phase NSCLC studies in combination with nivolumab (Opdivo). Ipilimumab is administered at a dosage of 10 mg/kg, intravenously, once every 3 weeks for 4 doses, then once every 12 weeks beginning at week 24. Bristol-Myers Squibb, New York, NY Phase III trials ongoing	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
IRX-2 for treatment of head and neck cancer	Patients with resectable head and neck cancer of the oral cavity, pharynx, or larynx whose disease has not been treated	Head and neck cancers that can be surgically resected have a survival rate of 80% to 90%. However, sometimes head and neck tumors progress rapidly and can no longer be treated by surgery. The rapid progression may also spread to lymph nodes and other organs. When this occurs, the 5-year survival rate is less than 50%. Interventions are needed that can slow cancer progression so that the tumor can be surgically resected. A hallmark of cancer is its ability to evade an immune response. IRX-2 is made of cells that have been modified to express components that will stimulate the immune system (e.g., dendritic cells, T cells), which purportedly overcomes tumor-mediated immune supression, restoring immune responses against cancer cells. In clinical trials, patients receive daily subcutaneous inoculations of IRX-2 for 10 days in combination with 2 weeks of cyclophosphamide, followed by 3 weeks of indomethacin plus zinc. IRX Therapeutics, Inc., New York, NY Phase II trial (IRX-2 2005-A) completed and phase II trial (INSPIRE) planned; FDA granted fast-track status	Chemoradiation Surgical resection Various combinations of 1 or more of the following: Alkylating agents (e.g., ifosfamide) Antimetabolites (e.g., 5-fluorouracil, gemcitabine, methotrexate) Cytoprotective agents (e.g., bleomycin) EGFR inhibitor (e.g., cetuximab) Immunotherapy (e.g., durvalumab, nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g., cisplatin) Oncolytic virus (e.g., Reolysin® [in development]) Taxanes (e.g., docetaxel, paclitaxel) Tyrosine kinase inhibitors (e.g., lenvatinib, sorafenib) Vinca alkaloids (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Isocitrate dehydrogenase-2 inhibitor (AG-221) for treatment of acute myeloid leukemia	Patients with acute myeloid leukemia (AML) harboring a mutation in the isocitrate dehydrogenase-2 (*IDH2*) gene	Only about 25% of patients in whom AML is diagnosed will survive for 5 years after diagnosis. About 20% of AML cases harbor a mutation in the *IDH2* gene, which encodes an enzyme that regulates fundamental aspects of cell metabolism. Mutant forms of *IDH2* observed in AMLs lead to both a decrease in the levels of alpha-ketoglutarate (the normal *IDH2* metabolite) and an increase in the levels of another metabolite, D-2-hydroxyglutarate. These shifts purportedly have several potentially tumorigenic effects, including stimulating angiogenesis and affecting histone modification and DNA methylation. *IDH2* loss of function has also been hypothesized to promote tumorigenesis through alteration of cell metabolism and increased susceptibility to oxidative stress. AG-221 is a small-molecule inhibitor of mutant *IDH2*. In clinical trials, it is administered orally at an undisclosed dose. Agios Pharmaceuticals, Inc., Cambridge, MA Phase I trial ongoing; FDA granted fast-track status	Cladribine, cytarabine, and granulocyte colony stimulating factor (G-CSF) plus or minus mitoxantrone or idarubicin Fludarabine, cytarabine, and G-CSF plus or minus idarubicin High-dose cytarabine and anthracycline Mitoxantrone, etoposide, and cytarabine	Increased overall survival Increased progression-free survival Improved quality of life
Lenvatinib (Lenvima) for treatment of differentiated thyroid cancer	Patients with differentiated thyroid cancer that is resistant to radioiodine therapy	Differentiated thyroid cancer (e.g., papillary, follicular) comprises the majority of thyroid cancers. Although many differentiated thyroid cancers are treated successfully with radioiodine, patients with disease that is resistant to the agent have few treatment options and a poor prognosis. Lenvatinib (Lenvima™) is a small-molecule multikinase inhibitor with activity against multiple tyrosine kinases involved in signaling pathways that regulate cell growth, cell proliferation, and angiogenesis (e.g., vascular endothelial growth factor receptors 2 and 3). In a late-phase clinical trial, lenvatinib is given orally as a once-daily dose of 24 mg. Eisai Co., Ltd., Tokyo, Japan Feb 2015, FDA approved lenvatinib (after granting priority review status in Oct 2014 and orphan drug status in Feb 2013) for treatment of recurrent or metastatic, progressive radioactive iodine-refractory differentiated thyroid cancer; phase III trial (SELECT) and postmarket study ongoing; phase II trial in children and adolescents ongoing	Ablation Multikinase inhibitors (e.g., sorafenib [cabozantinib, pazopanib, sunitinib, vandetanib; in development]) Radioactive iodine (I-131) Radiation therapy Surgical intervention Thyroid hormone therapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lenvatinib (Lenvima) for treatment of hepatocellular carcinoma	Patients with unresectable, advanced, stage B or C hepatocellular carcinoma (HCC)	Patients with HCC that cannot be surgically resected have few treatment options and a poor prognosis; no 2nd-line therapy is available after sorafenib. Lenvatinib (Lenvima®) is a small-molecule multikinase inhibitor with activity against multiple tyrosine kinases involved in signaling pathways that regulate cell growth, proliferation, and angiogenesis (e.g., vascular endothelial growth factor receptors 2 and 3). In a late-phase clinical trial, lenvatinib is given orally as a once-daily dosage of 12 mg. Eisai Co., Ltd., Tokyo, Japan Phase III trial ongoing; FDA approved for treatment of recurrent, progressive, or metastatic differentiated thyroid cancer	Radiofrequency ablation Surgical resection Locoregional treatment with 1 of the following: Transarterial embolization Transcatheter arterial chemoembolization Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Multikinase inhibitors (e.g., regorafenib, sorafenib) Platinum-based agents (e.g., cisplatin, oxaliplatin)	Increased overall survival Increased progression-free survival Improved quality of life
Lestaurtinib for treatment of infantile acute lymphoblastic leukemia	Infants in whom acute lymphoblastic leukemia (ALL) has been diagnosed	The remission rate for infants with ALL is high; however, for a certain percentage of patients, the disease does not respond to treatment. Lestaurtinib is a small-molecule inhibitor of FMS-like tyrosine kinase 3 (FLT-3), a signaling molecule that promotes cell proliferation and survival in several hematologic malignancies. Although FLT-3 amplification or activating mutation is rare in adult ALL, a significant fraction of infant ALL cases harbor such genetic changes, and FLT-3 activity may contribute to ALL pathogenesis. Lestaurtinib is, therefore, being investigated as an addition to current 1st-line ALL treatment regimens. In clinical trials, lestaurtinib is administered orally, once daily, at an unspecified dose during postinduction chemotherapy. National Cancer Institute, Bethesda, MD Phase III trial ongoing	Multiagent chemotherapy regimens lacking lestaurtinib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lipotecan for treatment-refractory hepatocellular carcinoma	Patients with recurrent hepatocellular carcinoma (HCC) whose disease is resistant to sorafenib	Patients with unresectable HCC have few treatment options, and in most cases the disease recurs after treatment. An unmet need exists for 2nd-line interventions for treatment-resistant HCC. Lipotecan® is a camptothecin derivative with a modification in the E-ring structure that is said to function as a sensitizer to overcome resistance to radiotherapy and chemotherapy, potentially improving patient outcomes. In clinical trials, Lipotecan is administered to patients by injecting an intravenous dose of 40 mg on days 1, 8, and 15 of each cycle. Taiwan Liposome Co., Ltd., Taipei City, Taiwan Phase I/II trial (TLC388.2) and phase II trial (TLC388.4) ongoing; Oct 2010, FDA granted orphan drug status	Radiofrequency ablation Surgical resection Locoregional treatment with 1 of the following: Transarterial embolization Transcatheter arterial chemoembolization Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Multikinase inhibitors (e.g., regorafenib, sorafenib) Platinum-based agents (e.g., cisplatin, oxaliplatin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lurbinectedin for treatment of unresectable small cell lung cancer	Patients in whom unresectable small cell lung cancer (SCLC) has been diagnosed	SCLC is a very aggressive lung cancer that spreads rapidly to adjacent lymph nodes and distal organs. Each year, about 34,000 cases are reported in the U.S., and it has a very poor prognosis compared with other types of lung cancer. The 5-year survival rate is less than 5%. No therapeutic advances have been achieved against SCLC in 25 years, with topotecan being the only treatment option in the 2nd-line setting. Lurbinectedin (PM01183) is a novel, synthetic, marine-derived compound that could address an unmet need for patients with SCLC. Lurbinectedin covalently binds to the minor groove of DNA. This interaction causes double-strand breaks in the DNA, which can perturb the cell cycle and induce cell death. In clinical trials, lurbinectedin is administered intravenously to patients once every 3 weeks at an escalating dose ranging between 1 and 4 mg in combination with doxorubicin. PharmaMar subsidiary of Groupo Zeltia, S.A., Madrid, Spain Phase II trial (PM1183-B-005-14) ongoing	Chemoradiation therapy Platinum-based agents (e.g., carboplatin, cisplatin) Topoisomerase inhibitors (e.g., etoposide, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mapsigargin for treatment-refractory hepatocellular carcinoma	Patients with hepatocellular carcinoma (HCC) whose disease has progressed after sorafenib treatment	Patients with unresectable HCC have few treatment options and in most cases, the disease recurs after treatment. An unmet need exists for 2nd-line interventions for treatment-resistant HCC. Mapsigargin (G-202) is a prodrug formulated from the plant-derived (*Thapsia garganica*) cytotoxin thapsigargin (12ADT), which has been bound to a specific peptide that renders mapsigargin inactive, soluble, and tumor-specific. Mapsigargin is activated when a sequence in the peptide is recognized and cleaved by a liver protease, which is overexpressed in HCC cells. The active mapsigargin will bind and prevent the sarco-endoplasmic reticulum Ca^{2+} ATPase (SERCA) from pumping Ca^{2+} ions from the cytosol into the endoplasmic reticulum (ER). Inhibiting SERCA purportedly increases Ca^{2+} concentration in the cytosol and decreases it in the ER; this activates an apoptosis cascade due to a Ca^{2+} ion imbalance. In clinical trials, mapsigargin is administered intravenously on days 1, 2, and 3 of a 28-day cycle, until disease progression or unacceptable toxicity. GenSpera, Inc., San Antonio, TX Phase II trial (G-202-003) ongoing; Mar 2013, FDA granted orphan drug status; the drug is also being tested for treating glioblastoma and prostate cancer	Radiofrequency ablation Surgical resection Locoregional treatment with 1 of the following: Transarterial embolization Transcatheter arterial chemoembolization Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Multikinase inhibitors (e.g., regorafenib, sorafenib) Platinum-based agents (e.g., cisplatin, oxaliplatin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Masitinib for treatment of activating *c-KIT* mutation–positive melanoma	Patients with unresectable, advanced or metastatic melanoma that harbors an activating mutation in the *c-KIT* gene	A subset of melanomas harbor an activating mutation in the *c-KIT* gene, which encodes a receptor tyrosine kinase (mast/stem cell growth factor receptor, KIT, CD117). In particular, between 10% and 20% of acral and mucosal melanomas harbor activating *c-KIT* mutations. Although KIT kinase inhibitors have been developed for other cancers dependent on KIT activity (e.g., imatinib for treating gastrointestinal stromal tumors), no KIT kinase inhibitor is approved for treating *c-KIT* mutation–positive melanoma. Masitinib is a kinase inhibitor with activity against KIT as well as platelet-derived growth factor receptors, the intracellular kinase Lyn, and to a lesser extent, fibroblast growth factor receptor 3. Masitinib is under study as a monotherapy for treating melanoma at an oral dose of 7.5 mg/kg, daily. AB Science S.A., Paris, France Phase III trial (AB08026) ongoing; also under investigation for treating a wide variety of cancers and other indications, including amyotrophic lateral sclerosis, Alzheimer's disease, severe asthma, and rheumatoid arthritis	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, temozolomide) *BRAF* inhibitors (e.g., dabrafenib, vemurafenib) Immunotherapy (e.g., ipilimumab, nivolumab, pembrolizumab) *MEK* inhibitors (e.g., trametinib [cobimetinib; in development]) Platinum-based agents (e.g., carboplatin) Taxane agents (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mereletinib for treatment of metastatic nonsmall cell lung cancer	Patients with advanced, metastatic, epidermal growth factor receptor (EGFR) T790M mutation–positive, nonsmall cell lung cancer (NSCLC) whose disease has progressed after treatment with an EGFR tyrosine kinase inhibitor	EGFR-inhibitor treatments have improved outcomes for patients with *EGFR* mutation–positive NSCLC relative to cytotoxic chemotherapy; however, EGFR inhibitors have limitations. First, NSCLC frequently develops resistance to EGFR inhibitors. This resistance is often mediated by a mutation in *EGFR* (T790M), which renders the kinase insensitive to available inhibitors. Second, EGFR inhibitors have activity against wild-type in addition to mutant EGFR, and inhibiting EGFR in cells that are not cancerous can lead to substantial toxicity. Mereletinib (AZD9291) is a highly selective, irreversible inhibitor of both the activating sensitizing *EGFR* mutation and the activating resistance mutation, T790M, while sparing the activity of wild-type EGFR. Therefore, mereletinib can purportedly be used as treatment for patients whose disease has progressed during treatment with existing EGFR inhibitors. In clinical trials, mereletinib is administered orally, 80 mg, twice a day. AstraZeneca, London, UK Phase I/II trial (AURA), phase II trials (AURA2 and unnamed), and phase III trials (AURA3, ADAURA, FLAURA, and CAURAL) ongoing; FDA granted breakthrough therapy status	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Methylated septin 9 plasma DNA test (Epi proColon 2.0) for colorectal cancer screening	Patients eligible for routine colorectal cancer (CRC) screening	Many patients for whom screening for CRC is recommended do not follow the recommendation because of the unpleasantness of screening procedures, including fecal occult blood testing and colonoscopy. This genetic test (Methylated Septin 9 Plasma DNA Test; Epi proColon 2.0) is a blood test that screens DNA from plasma samples for a specific methylated version of the septin 9 gene that is commonly found in CRC. Epigenomics AG, Berlin, Germany Polymedco, Inc., Cortlandt Manor, NY (to commercialize and distribute the test in North American markets) Epigenomics submitted a premarket application to FDA Jan 2013 for the test kit for Epi proColon 2.0; FDA granted priority review status; Jun 2014, company announced it had received a “not approvable letter” from FDA requesting additional data on likelihood of adoption by individuals who are not compliant with screening recommendations; ADMIT trial to assess compliance compared with fecal immunochemical testing complete and data has been resubmitted to FDA; available in Europe as Epi proColon 2.0 since 2011	Colonoscopy Computed tomographic colonography Fecal DNA tests Fecal immunochemical testing Fecal occult blood testing Sigmoidoscopy	Increased sensitivity and specificity Increased predictive values Avoided unnecessary followup procedures Improved adherence with CRC screening Earlier intervention for identified cancer
Midostaurin for treatment of acute myeloid leukemia bearing *FLT3* mutations	Patients with newly diagnosed acute myeloid leukemia (AML) bearing an internal tandem duplication in the *FLT3* gene (ITD-FLT3)	The presence of activating *FLT3* mutations in AML is associated with a poor prognosis, and patients identified as having disease bearing such a mutation more often experience disease recurrence after initial therapy. Midostaurin is a small-molecule kinase inhibitor that has activity against *FLT3* and additional tyrosine kinases (e.g., c-KIT). Adding midostaurin’s anti-*FLT3* activity to conventional 1st-line therapy (cytarabine and daunorubicin) might improve response rates and decrease recurrence. Treatment is intended for patients younger than 60 years who are able to tolerate high-dose cytarabine consolidation therapy. In a late-stage clinical trial, midostaurin is being given in a twice-daily oral dose for 2 weeks. Patients are administered midostaurin after both induction therapy with cytarabine and daunorubicin and consolidation therapy with high-dose cytarabine. Novartis International AG, Basel, Switzerland Phase III trial ongoing; FDA granted orphan drug status	Cytarabine/daunorubicin	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mitochondrial metabolism disruptor (CPI-613) for treatment of various cancers	Patients with advanced malignancies, in particular, acute myeloid leukemia (AML), myelodysplastic syndrome, and pancreatic cancer	The metabolic activity of cancer cells is altered significantly from that of noncancerous cells; therefore, therapies targeting aspects of cellular metabolism specific to cancer cells may be effective against a wide range of cancer types. CPI-613 is a novel, lipoic acid derivative that purportedly functions by inhibiting a mitochondrial enzyme (pyruvate dehydrogenase) that is essential for converting pyruvate to acetyl coenzyme A (acetyl-CoA). Cancer cells may be particularly sensitive to this disruption because the metabolic state of cancer cells downregulates both pyruvate dehydrogenase activity and other metabolic pathways that could provide a source of acetyl-CoA (e.g., fatty acid metabolism). In clinical trials, CPI-613 is given intravenously at a dose of 3,000 mg/m^2, on days 1 and 4 of the 1st 3 weeks of each 4-week cycle. Cornerstone Pharmaceuticals, Inc., Cranbury, NJ Phase I/II trials ongoing in hematologic malignancies; phase II trial ongoing in myelodysplastic syndrome; phase I/II trial ongoing in pancreatic cancer; FDA granted orphan drug status for AML, myelodysplastic syndrome, and pancreatic cancer	Various chemotherapy regimens	Increased overall survival Increased progression-free survival Improved quality of life
Monocyte development inhibitor (PRM-151) for treatment of myelofibrosis	Patients in whom myelofibrosis has been diagnosed	Recently approved treatments for patients with myelofibrosis have shown promise in improving symptoms; however, they do not address the bone marrow fibrosis underlying the condition. PRM-151 is a recombinant version of an endogenous protein (pentraxin-2) that regulates monocyte activation and differentiation. PRM-151 purportedly inhibits the differentiation of circulating monocytes into fibrocytes and, therefore, has the potential to limit pathogenic fibrosis in patients with myelofibrosis. In a clinical trial, it is administered intravenously, 10 mg/kg, on varying days of six 28-day cycles, with or without ruxolitinib. Promedior, Inc., Lexington, MA Phase II trial ongoing; FDA granted orphan drug and fast-track statuses	Ruxolitinib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Motolimod for treatment of platinum-resistant ovarian cancer	Women with ovarian cancer whose disease has progressed or recurred after receiving platinum-based chemotherapy	Ovarian cancer is the 2nd deadliest cancer after pancreatic cancer and is typically diagnosed at advanced stages. Patients who have been treated with 1st-line platinum-based chemotherapy often have recurrent disease and a poor prognosis. Motolimod (VTX-2337) is a Toll-like receptor 8 (TLR8) agonist. This agonist is a signaling component of the innate immune system and upon induction can activate various cell types of the innate immune response (dendritic cells, macrophages, and natural killer cells). Additionally, these activated cells produce cytokines that recruit cells of the adaptive immune response. TLR agonists purportedly promote a synergistic immune response against cancer cells, possibly through activation of T cells and/or differentiation of B cells into antibody-secreting plasma cells. Immune-response activation by motolimod might overcome immune tolerance to tumor-associated antigens, potentially leading to an anticancer immune response. In clinical trials, it is being tested in combination with pegylated liposomal doxorubicin as 2nd-line treatment for recurrent ovarian cancer. VentiRx Pharmaceuticals, Inc., Seattle, WA Phase II trial (GOG-3003) ongoing; FDA granted fast-track and orphan drug statuses; Apr 2015, European Medicines Agency granted orphan drug status	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if *BRCA*1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Moxetumomab pasudotox for treatment of advanced hairy cell leukemia	Patients with hairy cell leukemia who have undergone at least 2 systemic therapies or are intolerant of purine analogue therapy	Patients with hairy cell leukemia who are intolerant of or whose disease is resistant to purine-based chemotherapy have no approved treatment options and a poor prognosis. Hairy cell leukemia is characterized by strong expression of the cell surface marker CD22, a protein expressed by various B cells. Moxetumomab pasudotox is an antibody-drug conjugate (ADC) that links a bacterially derived endotoxin to a CD22-specific monoclonal antibody. The ADC purportedly delivers the endotoxin preferentially to CD22-expressing cells, targeting hairy cell leukemia cells while sparing the majority of normal tissues. In clinical trials, moxetumomab pasudotox is being administered intravenously, 40 mcg/kg, on days 1, 3, and 5 of a 28-day cycle. National Cancer Institute, Bethesda, MD, in partnership with the MedImmune subsidiary of AstraZeneca, London, UK Phase III trial ongoing	No approved therapies exist for chemotherapy-resistant hairy cell leukemia	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
MUC-1 therapeutic vaccine (TG4010) for nonsmall cell lung cancer	Patients with metastatic, chemotherapy-naïve nonsmall cell lung cancer (NSCLC) that expresses mucin-1 (MUC-1)	The 5-year survival rate for patients with advanced NSCLC is less than 15% with available treatments. About 60% of NSCLC tumors express MUC-1, and this protein is a potential therapeutic target for treating NSCLC. TG4010 is a therapeutic cancer vaccine that comprises a viral vector encoding both a tumor antigen (MUC-1) and an immune stimulant (interleukin-2). Patients' tumors must be MUC-1-positive, and patients must have normal levels of natural killer cells at the time treatment is initiated. In clinical trials, TG4010 is being administered in combination with standard of care cytotoxic chemotherapy in the 1st-line setting. The vaccine is given by subcutaneous injection on a weekly basis for the 1st 6 weeks of chemotherapy, and once every 3 weeks thereafter. Transgene S.A., Cedex, France Phase IIb/III trial (TIME) ongoing; Dec 2009, FDA granted fast-track status	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multikine immunotherapy for head and neck cancer	Patients in whom head and neck cancer has been diagnosed	Advanced head and neck cancer has a poor prognosis and high recurrence rate, suggesting the need for novel treatment options. Multikine (leukocyte interleukin injection) is a mix of immune stimulators (tumor necrosis factor, interleukin-1, other cytokines) that is delivered before conventional treatment (surgery, radiotherapy, chemotherapy). In a clinical trial, Multikine is administered before standard of care therapy in treatment-naïve patients. The manufacturer asserts that this is when the immune system is best able to mount an immune response. Multikine will be administered at a dose of 400 IU, delivered by injection directly to the tumor and nearby lymph nodes, 5 times a week, for 3 weeks. This agent will be administered in combination with low non-chemotherapeutic doses of cyclophosphamide, indomethacin, and zinc (CIZ). CEL-SCI Corp., Vienna, VA, in partnership with Ergomed Clinical Research, Ltd., London, UK, for development abroad Phase III trial ongoing (IT-MATTERS)	Chemoradiation Surgical resection Chemotherapy with 1 or more of the following: Alkylating agents (e.g., ifosfamide) Antimetabolites (e.g., 5-fluorouracil, gemcitabine, methotrexate) Cytoprotective agents (e.g., bleomycin) EGFR inhibitor (e.g., cetuximab) Immunotherapy (e.g., durvalumab, nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g, cisplatin) Oncolytic virus (e.g., Reolysin® [in development]) Taxanes (e.g., docetaxel, paclitaxel) Tyrosine kinase inhibitors (e.g., lenvatinib, sorafenib) Vinca alkaloids (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multipeptide vaccine (IMA901) for renal cell carcinoma	Patients who are receiving sunitinib in the 1st-line setting for metastatic and/or locally advanced renal cell carcinoma (RCC)	RCC is typically highly resistant to conventional chemotherapy/radiation therapy, and few treatment options exist. IMA901 is a therapeutic cancer vaccine comprised of 10 different tumor-associated peptides that are found to be highly overexpressed in the majority of patients who have RCC. Immunization is intended to induce cellular immune responses against renal tumors, and IMA901 purportedly has a stable, off-the-shelf formulation. This agent is intended for the 1st-line setting in advanced disease. The vaccine is administered intradermally, over the course of 4 months, with granulocyte macrophage colony-stimulating factor and sunitinib. Immatics Biotechnologies GmbH, Tübingen, Germany Phase III trial (IMA901-301) ongoing; FDA granted orphan drug status	Angiogenesis inhibitors (e.g., bevacizumab [ramucirumab; in development]) Cytokines (e.g., interferon-alfa, interleukin-2) mTOR inhibitors (e.g., temsirolimus) PD-1 inhibitors (e.g., nivolumab [in development]) Tyrosine kinase inhibitors (e.g., axitinib, everolimus, pazopanib, sorafenib, sunitinib)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
MV Neuro vaccine for treatment of pediatric neuroblastoma	Pediatric patients in whom neuroblastoma has been diagnosed	Neuroblastoma is the most common pediatric solid tumor, with about 800 new cases each year. Despite current treatment, children with high-risk neuroblastoma have an expected survival rate of 45%. MV Neuro (OPT-821) is an adjuvant vaccine containing 2 neuroblastoma-associated antigens (GD2 and GD3) purported to prime the immune system to target neuroblastoma cells overexpressing the gangliosides GD2 and GD3. In a phase I clinical trial, children were inoculated with 7 subcutaneous injections (150 mcg/m^2) over the course of 52 weeks. Treatment also included beta-glucan, which was administered orally (40 mg/kg/day, 2 weeks on, 2 weeks off, up to 1 cycle after the last vaccination) starting on week 6. MabVax Therapeutics, San Diego, CA, in collaboration with Memorial Sloan Kettering Cancer Center, New York, NY Phase I/II trial ongoing; Sept 2014, FDA granted orphan drug status	Stem cell transplant Surgical resection Radiation therapy Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide, ifosfamide) GD2 glycolipid antibodies (e.g., dinutuximab) Platinum-based agents (e.g., carboplatin, cisplatin) Retinoids (e.g., isotretinoin) Topoisomerase inhibitors (e.g., doxorubicin, etoposide, topotecan) Vinca alkaloid (e.g., vincristine)	Increased overall survival Increased progression-free survival Improved quality of life
Nabiximols oromucosal spray (Sativex) for persistent, chronic cancer pain	Patients with cancer who have chronic pain	Effective pain management for chronic cancer pain is challenging because of side effects of opioid therapies and some patients' reluctance to avail themselves of opioid therapy. Additionally, for patients with advanced cancers, opioid therapies may provide inadequate pain relief. Nabiximols (Sativex), which is sprayed under the tongue, is a whole-plant medicinal cannabis extract that contains tetrahydrocannabinol (THC) and cannabidiol as its main components. It is administered orally as a spray at a 100 mcL dose, which contains 2.5 mg cannabidiol and 2.7 mg THC. GW Pharmaceuticals, plc, Salisbury, UK, and Otsuka Holdings Co., Ltd., Tokyo, Japan Phase III trials ongoing; FDA granted fast-track status; approved in Europe and Canada for treating pain and symptoms of multiple sclerosis and neuropathic-related cancer pain	Opioids	Avoided side effects of opioids Reduced pain Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Necitumumab for treatment of advanced nonsmall cell lung cancer	Patients in whom advanced nonsmall cell lung cancer (NSCLC) has been diagnosed	The 5-year survival rate for patients with advanced NSCLC is less than 15% with current treatments. Necitumumab is a monoclonal antibody antagonist directed against the epidermal growth factor (EGF) receptor protein, which may downregulate tumor activity; necitumumab may competitively inhibit the binding of EGF and other ligands, such as transforming growth factor-alpha, and block activation of receptor-associated kinases. These actions inhibit cell growth and induce apoptosis; the drug may also mediate antibody-dependent cellular cytotoxicity. The drug is in a similar class as cetuximab, which is used for treating many cancers but is not labeled for treating NSCLC. In clinical trials, necitumumab was administered at a dosage of 800 mg, intravenously, on days 1 and 8 of every 3-week cycle; it has been tested in the 1st-line setting in combination with cisplatin and gemcitabine or pemetrexed. Eli Lilly and Co., Indianapolis, IN; formerly in partnership with Bristol-Myers Squibb, New York, NY Phase III trials (SQUIRE and INSPIRE) ongoing in squamous and nonsquamous NSCLC; Jan 2015, Eli Lilly completed a rolling FDA submission for necitumumab in 1st-line setting	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Necuparanib for treatment of advanced pancreatic cancer	Patients in whom primary metastatic pancreatic cancer has been diagnosed	Only about 5% of patients with pancreatic cancer respond to the standard of care (gemcitabine chemotherapy), and the prognosis for these patients is poor. A need exists for therapeutic options for patients with recurrent pancreatic cancer after standard treatment. Necuparanib (M402) is a heparin-based drug purported to have a broad range of antitumor activity, with the potential to improve patient health outcomes in combination with nab-paclitaxel and gemcitabine. The antitumor activity of heparin is masked by its blood-thinning properties; therefore, necuparanib was developed from unfractionated heparin to reduce anticoagulant activity while preserving antitumor activity. In a phase I/II clinical trial, necuparanib is administered at an unspecified dose on day 1, 8, and 15 of a 28-day cycle in combination with nab-paclitaxel and gemcitabine. Momenta Pharmaceuticals, Cambridge, MA Phase I/II trial ongoing; Dec 2014, FDA granted fast-track status after granting orphan drug status in Jun 2014	Chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) Folic acid derivatives (e.g., leucovorin) Multikinase inhibitors (e.g., erlotinib) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nelipepimut-S (NeuVax) for prevention of HER2-positive breast cancer recurrence	Patients with HER2-positive, early stage breast cancer who are positive for human leukocyte antigen (HLA)-A2 and/or HLA-A3	Although many patients with early stage breast cancer achieve remission after 1st-line chemotherapy, a significant proportion eventually have disease recurrence. Although some patients undergo maintenance therapy with trastuzumab, only patients whose tumors express high levels of HER2 are eligible for this therapy. Nelipepimut-S (NeuVax™) is a therapeutic cancer vaccine that combines an HER2-derived peptide (E75) with the immune stimulant granulocyte macrophage colony-stimulating factor. The vaccine is designed to induce a cytotoxic T-cell response against cells expressing HER2. NeuVax is under study as maintenance therapy for disease-free patients whose tumors expressed low levels of the HER2 protein. It is administered by intradermal injection, monthly for 6 months, then once every 6 months as maintenance therapy. Galena Biopharma, Portland, OR Phase III trial (PRESENT) ongoing under FDA special protocol assessment; phase II trial ongoing for combination therapy with trastuzumab	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine, pemetrexed) HER2-targeted antibodies (e.g., ado-trastuzumab emtansine, pertuzumab, trastuzumab) HER2-targeted kinase tyrosine inhibitors (e.g., afatinib, lapatinib) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloid (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nintedanib (Vargatef) for treatment of colorectal cancer	Patients with metastatic colorectal cancer (mCRC) whose disease has progressed after receiving standard 1st-line treatment	Although many patients have mCRC that responds to 1st-line chemotherapy, disease ultimately progresses in the vast majority of patients. Current 2nd-line treatments for mCRC are of limited efficacy, and the median overall survival of these patients is less than 1 year. Nintedanib (Vargatef™) is a tyrosine kinase inhibitor that has activity against vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor tyrosine kinases, which regulate tumor growth and angiogenesis. In clinical trials, nintedanib is being tested as an adjunct to conventional 2nd-line therapies (i.e., pemetrexed, docetaxel). Nintedanib is administered as an oral tablet, twice daily. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trial (LUME Colon 1) ongoing	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab [ramucirumab; in development]) Antimetabolites (e.g., 5-fluorouracil, capecitabine) EGFR antibodies (e.g., cetuximab, panitumumab) FOLFIRI (leucovorin, 5-fluorouracil, irinotecan) FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin) Multikinase inhibitors (e.g., regorafenib) Platinum-based agents (e.g., oxaliplatin) Topoisomerase inhibitors (e.g., irinotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nintedanib (Vargatef) for treatment of ovarian cancer	Patients in whom chemotherapy-naïve ovarian cancer has been diagnosed	A significant fraction of patients with ovarian cancer have disease that is resistant or refractory to available 1st-line treatments. Nintedanib (Vargatef™) is a tyrosine kinase inhibitor that has activity against vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor tyrosine kinases, which regulate tumor growth and angiogenesis. In late-phase clinical trials, nintedanib is being tested as an adjunct to the conventional 1st-line therapy of intravenous carboplatin plus paclitaxel. Nintedanib is administered as an oral tablet, at a dosage of 200 mg, twice daily. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trial (LUME-Ovar 1) ongoing	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if *BRCA*1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nintedanib (Vargatef) for treatment-refractory nonsmall cell lung cancer	Patients with nonsmall cell lung cancer (NSCLC) whose disease has progressed during or after 1st-line systemic chemotherapy	The 5-year survival rate for patients in whom NSCLC has been diagnosed is less than 15%, and patients whose disease progresses after 1st-line chemotherapy have few treatment options. Nintedanib (Vargatef) is a tyrosine kinase inhibitor that has activity against vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor tyrosine kinases, which regulate tumor growth and angiogenesis. In late-phase clinical trials, nintedanib is being tested as an adjunct to conventional 2nd-line therapies (i.e., pemetrexed, docetaxel). Nintedanib is administered as an oral tablet, twice daily. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials (LUME-Lung 1 and LUME-Lung 2) ongoing; Nov 2014, the European Commission approved nintedanib for treating NSCLC after 1st-line chemotherapy	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Niraparib for treatment of ovarian, fallopian tube, or primary peritoneal cancer	Patients in whom platinum-sensitive, high-grade serous ovarian, fallopian tube, or primary peritoneal cancer has been diagnosed	Patients in whom advanced ovarian, fallopian tube, or primary peritoneal cancer has been diagnosed often have recurrent disease and poor prognosis. Niraparib is a small-molecule drug intended to inhibit poly-ADP ribose polymerase (PARP), which is an important enzyme in a DNA-repair pathway. Investigators have observed that tumor cells are particularly sensitive to PARP inhibition. In clinical trials, niraparib (MK-4827) is being tested in the maintenance setting after 2 rounds of treatment with a platinum-based chemotherapy. In these trials, niraparib is administered daily, orally, at a dose of 300 mg. TESARO, Inc., Waltham, MA Phase III trial (NOVA) ongoing	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if *BRCA*1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Niraparib for treatment-refractory BRCA-positive breast cancer	Patients with *BRCA* mutation–positive, HER2-negative, platinum-sensitive, locally advanced or metastatic breast cancer; hormone receptor–positive breast cancer must be refractory to endocrine treatment	Patients with treatment-resistant, *BRCA* mutation–positive, advanced breast cancer have a poor prognosis, and better therapy options are needed. Niraparib (MK-4827) is a small-molecule drug intended to inhibit poly-ADP ribose polymerase (PARP), which is an important enzyme in the DNA-repair pathway. Investigators have observed that tumor cells are particularly sensitive to PARP inhibition, and sensitivity to PARP inhibition is thought to be dependent on loss of *BRCA* function. In clinical trials, niraparib is being tested in patients after treatment with anthracycline and taxane chemotherapy. In these trials, niraparib is administered daily, orally, at a dose of 300 mg. TESARO, Inc., Waltham, MA Phase III trial (BRAVO) ongoing	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine) PARP inhibitors (e.g., BMN 673, olaparib, veliparib [under development]) Taxanes (e.g., docetaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nivolumab (Opdivo) for treatment of advanced melanoma	Patients in whom advanced melanoma has been diagnosed	Clinical trials with the immune checkpoint inhibitor ipilimumab (Yervoy®) have demonstrated the potential of immune therapies in melanoma. However, ipilimumab has a relatively low response rate, and the prognosis for patients with advanced melanoma remains poor. Nivolumab (Opdivo®) is a fully human monoclonal antibody that targets an immune-checkpoint pathway distinct from that of ipilimumab. Nivolumab purportedly blocks the programmed death-1 (PD-1) co-inhibitory receptor expressed by activated T cells. The activity of this pathway has been shown to limit T cell activation; therefore, blocking its activity may enhance the body's immune response, potentially overcoming immune tolerance to melanoma. This agent is being tested in patients with unresectable, advanced melanomas and in patients whose disease has progressed after anti-CTLA-4 therapy. In clinical trials, nivolumab is administered intravenously, 3 mg/kg, once every 2 weeks. Bristol-Myers Squibb, New York, NY Phase III trials (CheckMate 037, CheckMate 066, and CheckMate 067) ongoing in several treatment settings as monotherapy and combination therapy with ipilimumab; May 2015, FDA accepted supplemental biologics license application for nivolumab as 1st-line treatment for melanoma; Dec 2014, FDA approved nivolumab under its accelerated approval program for treating patients who have unresectable or metastatic melanoma that has progressed after 1st-line treatment	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, temozolomide) B-RAF inhibitors (e.g., dabrafenib, vemurafenib) Immunotherapy (e.g., ipilimumab, pembrolizumab) MEK inhibitors (e.g., trametinib [cobimetinib; in development]) Platinum-based agents (e.g., carboplatin) Taxane agents (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nivolumab (Opdivo) for treatment of advanced nonsmall cell lung cancer	Patients with platinum-resistant advanced or metastatic nonsmall cell lung cancer (NSCLC)	Patients with squamous or nonsquamous NSCLC whose disease has progressed after 1st-line platinum-based chemotherapy have few treatment options and a poor prognosis. A hallmark of cancer is its ability to evade an immune response. Nivolumab (Opdivo®) is a novel therapeutic that is intended to prevent immune tolerance of tumor cells. The drug's target is the programmed death-1 (PD-1) pathway, which acts as an immune checkpoint that downregulates T-cell activity. Nivolumab is a monoclonal antibody specific for the PD-1 receptor that purportedly blocks activation of this pathway. In trials, nivolumab is administered as a 3 mg/kg intravenous infusion, once every 2 weeks. Bristol-Myers Squibb, New York, NY Phase III trials (CheckMate 017, CheckMate 026, CheckMate 057, and CheckMate 153) ongoing; FDA granted fast-track status; FDA approved Mar 2015 for treating advanced squamous NSCLC that is unresponsive to chemotherapy; Sept 2015, FDA accepted a supplemental biologics license application for treating advanced nonsquamous NSCLC and granted priority review and breakthrough therapy status	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., pembrolizumab [in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nivolumab (Opdivo) for treatment of advanced renal cell carcinoma	Patients with advanced or metastatic clear cell renal cell carcinoma (ccRCC) who have undergone treatment with at least 1 antiangiogenic kinase inhibitor	Patients with advanced renal cell carcinoma whose disease has progressed after 1st-line treatment with a tyrosine kinase inhibitor have few treatment options and a poor prognosis. A hallmark of cancer is its ability to evade an immune response. Nivolumab (Opdivo®) is a novel therapeutic that is intended to prevent immune tolerance of tumor cells. The drug targets the programmed death-1 (PD-1) pathway, which acts as an immune checkpoint that downregulates T-cell activity. Nivolumab is a monoclonal antibody specific for the PD-1 receptor that purportedly blocks activation of this pathway. Nivolumab is administered as a 3 mg/kg intravenous infusion, once every 2 weeks. Bristol-Myers Squibb, New York, NY Phase III trials (CheckMate 025 and CheckMate 214) ongoing; FDA granted fast-track and breakthrough therapy statuses	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab [ramucirumab; in development]) Antimetabolites (e.g., pemetrexed, gemcitabine) Immunotherapy (e.g., interferon-alpha , interleukin-2) mTOR inhibitors (e.g., everolimus, temsirolimus) Multikinase inhibitors (e.g., axitinib, pazopanib, sorafenib, sunitinib)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nivolumab (Opdivo) for treatment of head and neck carcinoma	Patients in whom head and neck cancer has been diagnosed	Advanced head and neck cancer has a poor prognosis and high recurrence rate, suggesting the need for novel treatment options. A hallmark of cancer is its ability to evade an immune response. Nivolumab (Opdivo®) is a novel therapeutic intended to prevent immune tolerance of tumor cells. The drug's target is the programmed death-1 (PD-1) pathway, which acts as an immune checkpoint that downregulates T-cell activity. Nivolumab is a monoclonal antibody specific for the PD-1 receptor that purportedly blocks activation of this pathway. Nivolumab is administered as a 3 mg/kg intravenous infusion, once every 2 weeks. Bristol-Myers Squibb, New York, NY Phase III trial (CheckMate 141) ongoing	Chemoradiation Surgical resection Chemotherapy with 1 or more of the following: Alkylating agents (e.g., ifosfamide) Antimetabolites (e.g., 5-fluorouracil, gemcitabine, methotrexate) Cytoprotective agents (e.g., bleomycin) EGFR inhibitor (e.g., cetuximab) Immunotherapy (e.g., durvalumab, pembrolizumab [in development]) Platinum-based drugs (e.g., cisplatin) Oncolytic virus (e.g., Reolysin® [in development]) Taxanes (e.g., docetaxel, paclitaxel) Tyrosine kinase inhibitors (e.g., lenvatinib, sorafenib) Vinca alkaloid (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nivolumab (Opdivo) for treatment of Hodgkin's lymphoma	Patients with Hodgkin's lymphoma who have been treated with autologous stem cell transplant and brentuximab vedotin	Patients with Hodgkin's lymphoma that has progressed after autologous stem cell transplant and treatment with brentuximab vedotin have exhausted standard treatment options and have a poor prognosis. A hallmark of cancer is its ability to evade an immune response. Nivolumab (Opdivo®) is a novel therapeutic that is intended to prevent immune tolerance of tumor cells. The drug's target is the programmed death-1 (PD-1) pathway, which acts as an immune checkpoint that downregulates T-cell activity. Nivolumab is a monoclonal antibody specific for the PD-1 receptor that purportedly blocks activation of this pathway. In trials, nivolumab is administered as a 3 mg/kg intravenous infusion, once every 2 weeks. Bristol-Meyers Squibb, New York, NY Phase II trial ongoing; FDA granted breakthrough therapy status	No standard therapy exists for this patient population	Increased progression-free survival Increased overall survival Improved quality of life
Nucleoside analogue (RX-3117) for treatment of pancreatic cancer	Patients with gemcitabine-resistant pancreatic cancer	Only about 5% of patients with pancreatic cancer respond to the standard of care (gemcitabine chemotherapy), and the prognosis for these patients is poor. RX-3117 is an inactive nucleoside analogue that can inhibit DNA and RNA synthesis when it is phosphorylated by the enzyme uridine cytidine kinase (UCK), which leads to apoptotic cell death of tumor cells. Although UCK is overexpressed in multiple human tumors (e.g., pancreatic, nonsmall cell lung, breast, ovarian cancers), it has a scant presence in normal tissues, so targeting it could improve safety and efficacy in patients who have cancer. In clinical trials, patients will undergo 8 cycles of an undetermined dose of RX-3117 taken orally, 3 times a week, for 3 weeks followed by a week of rest. Rexahn Pharmaceuticals, Inc., Rockville, MD Phase Ib trial ongoing; FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) Folic acid derivatives (e.g., leucovorin) Multikinase inhibitors (e.g., erlotinib) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Obinutuzumab (Gazyva) for treatment of indolent non-Hodgkin's lymphoma	Patients with indolent non-Hodgkin's lymphoma (NHL) (e.g., follicular lymphoma) whose disease is refractory to rituximab-containing therapy	Indolent NHLs are B-cell malignancies that typically progress slowly; however, they are seldom cured by chemotherapy and patients' disease frequently develops treatment resistance. For several years, the CD20-specific monoclonal antibody rituximab has been used to target such malignancies. Rituximab is thought to act through a process of antibody-dependent cell-mediated cytotoxicity (ADCC). Obinutuzumab (Gazyva™) is a next-generation CD20-specific monoclonal antibody that has been glycoengineered to improve its ADCC- inducing activity. In a phase III trial in patients with rituximab-refractory indolent NHL, obinutuzumab is being used in combination with bendamustine. Obinutuzumab is administered intravenously. Genentech subsidiary of F. Hoffman La-Roche, Ltd., Basel, Switzerland Phase III pivotal GADOLIN trial halted Feb 2015 for meeting primary endpoint early; other phase III trials ongoing	Bendamustine Fludarabine Idelalisib Lenalidomide Ofatumumab	Increased overall survival Increased progression-free survival Improved quality of life
Off-label maraviroc (Selzentry) for prevention of graft-versus-host disease	Patients at high risk of developing graft-versus-host disease (GVHD) after undergoing allogeneic stem cell transplantation	About 50% of patients undergoing allogeneic stem cell transplantation develop GVHD, a condition in which donor cells in an allogeneic hematopoietic stem cell transplant mount an immune response against recipient tissues. Patients with acute GVHD typically exhibit damage to the skin, liver, and gastrointestinal tract, and GVHD is lethal in up to 80% of patients with severe forms of the disease. Current prophylactic treatments for GVHD target donor immune cells in a way that may delay immune system reconstitution and/or limit graft-versus-tumor immune responses. A potential molecular target in GVHD is chemokine (C-C motif) receptor 5 (CCR5), which has been shown to play a role in the pathogenesis of GVHD by promoting lymphocyte recruitment to the involved tissues. Maraviroc (Selzentry®) is a CCR5 antagonist that may limit lymphocyte recruitment to target tissues, potentially limiting the extent of recipient tissue damage. In clinical trials, maraviroc is administered at an oral dose of 300 mg, daily, in combination with standard GVHD prophylaxis. University of Pennsylvania, Philadelphia Phase II trial ongoing; FDA approved in 2007 for treating HIV; marketed by Pfizer, Inc. (New York, NY), but the manufacturer does not appear to be seeking a labeled indication for this use	Methotrexate Tacrolimus	Reduced rate of acute GVHD Increased overall survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label metformin for treatment of breast cancer	Patients in whom breast cancer has been diagnosed	An estimated 233,000 new cases of invasive breast cancer are diagnosed each year in the U.S., and an estimated 40,000 individuals will die of the disease. Retrospective studies of patients with diabetes taking metformin, preclinical studies of in vitro cell lines, and in vivo cancer models have demonstrated that metformin may have antineoplastic properties. Metformin may exert its effects by activating AMP-activated protein kinase, which functions to limit downstream components of the mTOR pathway. Additionally, metformin's actions in reducing circulating insulin levels may be antineoplastic because of the potential growth-stimulating activity of insulin. Metformin is being studied in multiple breast cancer settings and could represent a novel treatment with a relatively low side-effect profile. National Cancer Institute, Bethesda, MD, and other academic institutions Phase II trials ongoing in neoadjuvant setting; phase III trial ongoing in adjuvant setting to prevent recurrence; phase II trial for preventing primary breast cancer in obese women; phase I/II trials ongoing in metastatic disease; phase II/III trials ongoing of metformin in combination with other chemotherapy agents	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine) PARP inhibitors (e.g., BMN 673, niraparib, olaparib [under development]) PD-1 antibodies (e.g., pembrolizumab [in development]) Taxanes (e.g., docetaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label vemurafenib for treatment of hairy cell leukemia	Patients with hairy cell leukemia that is not responsive to purine analogue therapy	Hairy cell leukemia is a rare chronic leukemia. Treatment with purine analogues (e.g., cladribine) achieves high rates of complete remission; however, approximately 30% to 40% of patients experience disease relapse and patients whose disease exhibits nonresponsiveness to purine analogues have few treatment options. Researchers have discovered that the vast majority of hairy cell leukemia cases harbors an activating mutation in the gene encoding the B-RAF oncogene. Mutated B-RAF is thought to act as a driver of carcinogenesis, and treatment of other malignancies that harbor B-RAF mutations (e.g., melanoma) using inhibitors of B-RAF has demonstrated therapeutic benefit. Therefore, researchers have investigated whether the B-RAF inhibitor vemurafenib may be of therapeutic benefit in patients with hairy cell leukemia. In treating hairy cell leukemia, vemurafenib is administered orally, 960 mg, once daily. Cancer centers including: Memorial Sloan Kettering Cancer Center, New York, NY; Dana-Farber Cancer Institute, Boston, MA; Institute of Hematology, University of Perugia, Perugia, Italy Phase II trial ongoing	Interferon-alpha Rituximab	Increased overall survival Increased progression-free survival Improved quality of life
Olaparib (Lynparza) for treatment of BRCA-mutated breast cancer	Patients with nonmetastatic, invasive, triple-negative breast cancer who have mutations in the *BRCA1* or B*RCA2* genes (adjuvant treatment) Patients with metastatic breast cancer with germline mutations in the *BRCA1* or *BRCA2* genes (metastatic treatment)	Improved treatment options are needed for patients with advanced *BRCA* mutation–positive breast cancers that have recurred or progressed after chemotherapy. Olaparib (Lynparza™) is a novel, small-molecule drug intended to inhibit poly (ADP-ribose) polymerase (PARP), which functions in a DNA-repair pathway; no PARP inhibitors are FDA approved. Investigators have observed that cancers are often deficient in a 2nd DNA repair pathway, and they hypothesize that loss of both types of DNA repair results in cancer cell lethality in response to DNA damage. Olaparib (AZD-2281) is being tested in clinical trials as a maintenance therapy for patients with *BRCA* mutation–positive breast cancer after treatment with a platinum-based chemotherapy and as a treatment for metastatic *BRCA* mutation–positive breast cancer. In clinical trials, olaparib is administered orally, 300 mg, twice daily. AstraZeneca, London, UK Phase III trials (OlympiA and OlympiAD) ongoing	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine) PARP inhibitors (e.g., BMN 673, niraparib, veliparib [in development]) Taxanes (e.g., docetaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Olaparib (Lynparza) for treatment of gBRCA-mutated pancreatic cancer	Patients with germline BRCA1- or BRCA2-mutation metastatic pancreatic cancer who are receiving 1st-line platinum-based chemotherapy and whose disease has not progressed during treatment	Only about 5% of patients with pancreatic cancer respond to the standard of care (gemcitabine chemotherapy), and the prognosis for these patients is poor. Olaparib (Lynparza™) is a novel, small-molecule drug intended to inhibit poly (ADP-ribose) polymerase (PARP), which functions in a DNA-repair pathway; no PARP inhibitors are FDA approved. Investigators have observed that cancers are often deficient in a 2nd DNA repair pathway, and they hypothesize that loss of both types of DNA repair results in cancer cell lethality in response to DNA damage. In clinical trials, olaparib is administered orally, 300 mg, twice daily. AstraZeneca, London, UK Phase III trial (POLO) registered	Chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) Folic acid derivatives (e.g., leucovorin) Multikinase inhibitors (e.g., erlotinib) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life
Olaparib (Lynparza) for treatment of ovarian cancer	Patients with *BRCA*-mutated ovarian cancer who have had a complete or partial response to platinum-based cytotoxic therapy	Patients with advanced ovarian cancer often have recurrent disease and a poor prognosis. Olaparib (Lynparza™) is a novel, small-molecule drug intended to inhibit PARP, which functions in a DNA repair pathway; no PARP inhibitors are available on the market. It has been observed that cancers are often deficient in a 2nd DNA repair pathway, and loss of both types of DNA repair is hypothesized to result in cancer cell lethality in response to DNA damage. Olaparib is being tested in clinical trials as a maintenance therapy for patients with *BRCA* mutation, after treatment with a platinum-based chemotherapy. In clinical trials, it is administered at a dosage of 300 mg, orally, twice daily. AstraZeneca, London, UK Phase III trials (SOLO1, SOLO2, SOLO3, and COCOS) ongoing; Dec 2014, FDA approved olaparib as monotherapy for patients with germline *BRCA*–mutated advanced ovarian cancer, after 3 or more chemotherapy regimens; earlier, FDA had granted orphan drug status	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Onartuzumab (MetMAb) for treatment of metastatic HER2-negative gastric cancer	Patients with locally advanced or metastatic gastric cancer that expresses high levels of MET and low levels of HER2	Patients with locally advanced or metastatic gastric cancer have a poor prognosis with current treatment options. MET is a receptor tyrosine kinase that can promote cell proliferation, survival, motility, and invasion. MET overexpression has been reported in gastric cancers and correlates with a poor prognosis. Onartuzumab (MetMAb) is a monoclonal antibody that binds to the extracellular domain of MET. This binding may prevent receptor activation by the extracellular domain's cognate ligand (hepatocyte growth factor), potentially having an antineoplastic effect. In a clinical trial, onartuzumab is being administered intravenously; investigators have not provided dosage being tested. In clinical trials, it is being used in combination with a chemotherapy regimen consisting of oxaliplatin, folinic acid, and 5-fluorouracil. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trial (MetGastric) ongoing	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., ramucirumab) Anthracyclines (e.g., doxorubicin, epirubicin, irinotecan) Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) DCF (docetaxel, cisplatin, 5-fluorouracil) ECF (epirubicin, cisplatin, 5-fluorouracil) HER2 antibodies if HER2-positive (e.g., trastuzumab) PD-1 antibodies (e.g., pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oncolytic reovirus (Reolysin) for treatment of advanced pancreatic cancer	Patients in whom advanced pancreatic cancer has been diagnosed	Only about 5% of patients with pancreatic cancer respond to the standard of care (gemcitabine chemotherapy), and the prognosis for these patients is poor. A need exists for therapeutic options for patients with recurrent pancreatic cancer after standard treatment. Oncolytic reovirus (Reolysin®) is intended to treat various cancers and cell proliferative disorders, including pancreatic cancer, for which no effective options are available. It has been shown to replicate in cells that have activated RAS; activated RAS is seen in 90% of pancreatic cancers. In clinical trials, Reolysin is administered intravenously on days 1, 2, 8, and 9 of a 21-day cycle in combination with gemcitabine. Oncolytics Biotech, Inc., Calgary, Alberta, Canada Phase II trials (REO 017 and NCI-8601) ongoing; Feb 2015, FDA granted orphan drug status as 1st-line treatment for pancreatic cancer	Chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) Folic acid derivatives (e.g., leucovorin) Multikinase inhibitors (e.g., erlotinib) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oncolytic reovirus (Reolysin) treatment of head and neck cancer	Patients with recurrent or metastatic head and neck cancers	Advanced head and neck cancer has a poor prognosis and high recurrence rate, suggesting the need for novel treatment options. Reolysin® is an oncolytic reovirus being developed to treat various cancer and cell proliferative disorders. It replicates in cells that have activated RAS, which may play a role in more than 2/3 of all cancers. In a phase III trial, Reolysin was given to patients with squamous cell carcinoma of the head and neck in the 2nd-line treatment setting after 1st-line treatment with a platinum-based chemotherapy. In this trial, Reolysin was administered in combination with paclitaxel and carboplatin and compared to chemotherapy alone. Oncolytics Biotech, Inc., Calgary, Alberta, Canada Phase III trial (REO 018) completed; company intends to seek FDA approval for randomized, follow-on phase III trial for recurrent head and neck cancers; Apr 2015, FDA granted orphan drug status for malignant glioma and in May 2015, for gastric cancer	Chemoradiation Surgical resection Combination or monotherapy regimens including: Alkylating agents (e.g., ifosfamide) Antimetabolites (e.g., 5-fluorouracil, gemcitabine, methotrexate) Cytoprotective agents (e.g., bleomycin) EGFR inhibitor (e.g., cetuximab) Immunotherapy (e.g, durvalumab, nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g., cisplatin) Taxanes (e.g., docetaxel, paclitaxel) Tyrosine kinase inhibitors (e.g., lenvatinib, sorafenib) Vinca alkaloids (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oncolytic reovirus (Reolysin) treatment of ovarian epithelial, primary peritoneal, or fallopian tube cancer	Patients in whom recurrent or persistent ovarian, fallopian tube, or primary peritoneal cancer has been diagnosed	Ovarian, fallopian tube, or primary peritoneal cancer frequently recurs after initial treatment, and recurrence is associated with poor outcomes. Reolysin® is a formulation of oncolytic reovirus being developed for treating various cancers and cell proliferative disorders. It has been shown to replicate specifically in cells that have activated RAS; activating mutations of RAS and its upstream elements may play a role in more than 2/3 of all human cancers, including most metastatic disease. In clinical trials, Reolysin is administered to patients intravenously on days 1–5 of a 28-day cycle. Oncolytics Biotech, Inc., Calgary, Alberta, Canada Phase I/II trial (OSU-07022) and phase II trial (GOG186H) ongoing; FDA granted orphan drug status in Feb 2015 for treating ovarian cancer and in Mar 2015 for treating peritoneal and fallopian tube cancer	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if *BRCA*1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oncolytic virus (DNX-2401) for treatment of glioblastoma	Patients with recurrent malignant gliomas, including glioblastoma multiforme (GBM)	GBM can be difficult to treat and is often associated with a poor prognosis. In 60% of patients, disease progresses after initial treatment; more effective treatments are needed. DNX-2401 is a recombinant adenovirus engineered to infect cells overexpressing the RGD integrin and selectively replicate in Rb-deficient cells, 2 common alterations of GBM tumor cells. Purportedly, injecting DNX-2401 directly into the patient's brain tumor could kill tumor cells without harming normal brain cells, potentially improving patient survival and decreasing cancer recurrence. In clinical trials, 1×10^7 viral particles are injected through a catheter to deliver DNX-2401 directly into the tumor. It is administered every 28 days as monotherapy or in combination with interferon gamma or temozolomide. DNAtrix, Inc., Houston, TX Phase I trials (TARGET-1, D24GMB, and unnamed) ongoing; phase II trial planned; FDA granted fast-track and orphan drug statuses	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., carmustine, cyclophosphamide, lomustine, nitrosourea, procarbazine, temozolomide) Angiogenesis inhibitors (e.g., bevacizumab) Immunotherapeutics (e.g., DCVax-L, HSPPC-96, rindopepimut, SL-701 [in development]) mTOR inhibitors (e.g., everolimus) PD-1 antibodies (e.g., nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin) Radiation therapy Vinca alkaloids (e.g., vincristine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Opto-acoustic ultrasound imaging device (Imagio) for diagnostic breast imaging	Patients with a suspicious breast mass	Positive results from traditional breast screening approaches (e.g., mammography, self-breast exam) lead to expensive diagnostic imaging and breast biopsy in a large number of patients whose tumors are eventually diagnosed as benign. Additionally, for patients with dense breast tissue, mammographic screening may fail to detect some cancers. To address these issues, the Imagio™ breast imaging system combines traditional ultrasound with opto-acoustic imaging to create a map of the vasculature in and around suspicious masses. This approach is centered on 2 hallmarks of cancerous lesions: enhanced angiogenesis and deoxygenation. Opto-acoustic imaging directs a short laser pulse into the target tissue, generating local tissue heating and expansion that causes ultrasonic pressure-waves to move through the tissue. These waves are detected by high-frequency pressure sensors to generate an opto-acoustic blood map that is projected on traditional ultrasound. In clinical trials, Imagio is used in diagnostic imaging procedures in patients with suspected breast lesions. Seno Medical Instruments, Inc., San Antonio, TX Unphased pivotal trial (PIONEER-01) ongoing; has European Union CE mark	Breast biopsy Diagnostic breast MRI Diagnostic breast ultrasound	Increased sensitivity and specificity Increased predictive values Fewer unnecessary followup procedures
Ovarian tissue cryopreservation for fertility preservation in women undergoing gonadotoxic cancer treatment	Women undergoing gonadotoxic cancer treatment who wish to preserve fertility	Because cancer treatments have improved, resulting in long-term survival, procedures for maintaining long-term quality of life are of increasing interest. Females (children or adults) who have undergone systemic chemotherapy or whole-body radiation therapy especially may wish to preserve their ability to have children. A new option involves ovarian tissue cryopreservation. Before the patient undergoes treatment, clinicians collect ovarian tissue in a laparoscopic procedure requiring general anesthesia. Collected tissue is prepared to withstand the freezing process, and is then cryopreserved until completion of cancer treatment. Upon remission, the tissue is transplanted back into the patient to restore normal hormonal cycling and, if successful, fertility. Research institutions including Weill Medical College of Cornell University, New York, NY, and Boston IVF, Boston, MA Several unphased trials ongoing; case series published of successful pregnancies and births	Oocyte cryopreservation Ovarian suppression with gonadotropin releasing hormone analogues or antagonists	Successful pregnancy Live birth

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Palbociclib (Ibrance) for treatment of estrogen receptor–positive breast cancer	Patients in whom locally advanced/unresectable or metastatic, estrogen receptor–positive, HER2-negative (ER+/HER2-) breast cancer has been diagnosed	Although endocrine therapies (e.g., estrogen receptor antagonists, aromatase inhibitors) are often effective in treating patients with estrogen receptor–positive breast cancer, the response is typically limited to about 1 year. Palbociclib (Ibrance®) is a dual inhibitor of cyclin-dependent kinase (CDK) 4 and CDK 6, which are kinases involved in controlling cell-cycle progression. CDK 4 and CDK 6 regulate a cell-cycle checkpoint controlling initiation of DNA synthesis; therefore, their inhibition may limit tumor growth mediated by cell proliferation. Preclinical studies have demonstrated that estrogen receptor–positive breast cancer may be highly sensitive to CDK 4/6 inhibition and that this inhibition may be synergistic with endocrine therapies. The drug is being studied for use in combination with letrozole as 1st-line treatment for advanced disease, in combination with fulvestrant for treating endocrine therapy–refractory advanced disease, and in combination with exemestane for treating aromatase inhibitor–resistant advanced disease. In clinical trials, palbociclib is administered as a once-daily, oral dose of 125 mg, on days 1–21 of each 28-day cycle. Pfizer, Inc., New York, NY Phase III trials (PEARL, PENELOPE-B, PALOMA-2, PALOMA-3, PALOMA-4, PALLAS) ongoing; Feb 2015, FDA approved palbociclib in combination with letrozole for 1st-line treatment of postmenopausal women who have ER+/HER2- metastatic breast cancer, after granting breakthrough therapy status in Oct 2014	Chemotherapy with 1 or more of the following: Anabolic steroids (e.g., fluoxymesterone) Aromatase inhibitors (e.g., anastrozole, exemestane, letrozole) CDK4/6 inhibitors (e.g., abemaciclib, LEE011 [in development]) Estrogen inhibitors (e.g., tamoxifen, toremifene) Estrogen receptor inhibitors (e.g., fulvestrant) Protein kinase inhibitors (e.g., everolimus) Synthetic progestogens (e.g., progestin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pegylated arginine deiminase for treatment of hepatocellular carcinoma	Patients with advanced hepatocellular carcinoma (HCC) whose disease has failed to respond to a course of systemic therapy	For patients whose disease cannot be cured by surgical removal of the tumor, survival rates for HCC are very low (about 5%), with median survival after diagnosis of only about 6 months. Pegylated arginine deiminase (ADI-PEG 20) acts by depleting the essential amino acid arginine from the bloodstream. Research has demonstrated that the cells of many tumor types are unable to autonomously synthesize arginine and, therefore, tumor cells are preferentially affected by the loss of arginine supply in the blood. This agent is intended for use in the 2nd-line setting. It is administered by intramuscular injection, 18 mg/m^2, weekly. Polaris Pharmaceuticals, Inc., San Diego, CA Phase III trial (ADI-PEG 20) initiated under FDA special protocol assessment; FDA granted orphan drug status; also under investigation for treating hematological malignancies, lung cancer, melanoma, mesothelioma, and prostate cancer	Radiofrequency ablation Surgical resection Locoregional treatment with 1 of the following: Transarterial embolization Transcatheter arterial chemoembolization Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Multikinase inhibitors (e.g., regorafenib, sorafenib) Platinum-based agents (e.g., cisplatin, oxaliplatin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pegylated human recombinant hyaluronidase (PEG-PH20) for treatment of metastatic pancreatic cancer	Patients with metastatic pancreatic cancer who have had no prior treatment	Only about 25% of patients with metastatic pancreatic cancer have disease that responds to 1st-line therapy with gemcitabine; effective treatments are needed for those whose disease does not respond. PEG-PH20 is a formulation of the enzyme hyaluronidase, which functions to degrade the hyaluronan (HA) component of the extracellular matrix. HA is a gel-like substance that is a component of normal tissues of the body (e.g., skin, cartilage), but it also forms a layer on the surface of tumors, which may limit exposure of the tumor to therapeutic compounds. PEG-PH20 is purported to temporarily degrade HA, potentially increasing the efficacy of chemotherapy. In clinical trials for treating advanced pancreatic cancer, PEG-PH20 is being administered in combination with the standard chemotherapy drug gemcitabine. Halozyme Therapeutics, Inc., San Diego, CA Phase II trials (Study 201, 202, and S1313) ongoing; FDA granted fast-track and orphan drug statuses	Chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) Folic acid derivatives (e.g., leucovorin) Multikinase inhibitors (e.g., erlotinib) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pembrolizumab (Keytruda) for treatment of advanced gastric cancer	Patients with advanced gastric or gastroesophageal junction adenocarcinoma whose disease has progressed after 1st-line treatment with fluoropyrimidine and platinum-based chemotherapy	Patients with gastric cancer that has progressed after 1st-line chemotherapy have a poor prognosis with median survival times of less than 1 year. A hallmark of cancer is its ability to evade an immune response. Pembrolizumab (Keytruda®) is a monoclonal antibody that targets a novel immune-checkpoint pathway distinct from that of ipilimumab. Pembrolizumab purportedly blocks the programmed death-1 (PD-1) co-inhibitory receptor expressed by activated T cells. This pathway has been shown to limit T-cell activation; therefore, blocking its activity may enhance the body's immune response, potentially overcoming immune tolerance to gastric cancer. Pembrolizumab is administered by intravenous infusion at a dose of 200 mg, once every 3 weeks. Merck & Co., Inc., Whitehouse Station, NJ Phase III trials (KEYNOTE-061 and -062) ongoing	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., ramucirumab) Anthracyclines (e.g., doxorubicin, epirubicin, irinotecan) Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) DCF (docetaxel, cisplatin, 5-fluorouracil) ECF (epirubicin, cisplatin, 5-fluorouracil) HER2 antibodies if HER2-positive (e.g., trastuzumab) Platinum-based drugs (e.g., carboplatin, cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pembrolizumab (Keytruda) for treatment of advanced melanoma	Patients in whom advanced (unresectable stage III or IV) melanoma has been diagnosed	Patients with metastatic melanoma have a poor prognosis, with current treatments yielding a 5-year survival rate of less than 10%. Clinical trials with the immune checkpoint inhibitor ipilimumab have demonstrated the potential of immune therapies in melanoma; however, the utility of ipilimumab is limited by its relatively low response rate, and the prognosis for patients with advanced melanoma remains poor. Pembrolizumab (Keytruda®) is a monoclonal antibody that targets a novel immune-checkpoint pathway distinct from that of ipilimumab. Pembrolizumab purportedly blocks the programmed death-1 (PD-1) co-inhibitory receptor expressed by activated T cells. The activity of this pathway has been shown to limit T-cell activation; therefore, blocking its activity may enhance the body's immune response, potentially overcoming immune tolerance to melanoma. Pembrolizumab is administered by intravenous infusion, 10 mg, once every 2 weeks. Merck & Co., Inc., Whitehouse Station, NJ Phase III trial (KEYNOTE-006) ongoing; Sept 2014, FDA approved pembrolizumab for treating patients who have advanced or unresectable melanoma and are no longer responding to ipilimumab or *BRAF* inhibitors, basing its decision on results from phase Ib KEYNOTE-001 trial; Aug 2015, FDA accepted supplemental biologics license application, with decision date set for Dec 19, 2015; FDA had earlier granted breakthrough therapy status; also under investigation for treating breast cancer, nonsmall cell lung cancer, renal cell carcinoma, and other indications	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, temozolomide) *BRAF* inhibitors (e.g., dabrafenib, vemurafenib) Immunotherapy (e.g., ipilimumab, nivolumab) MEK inhibitors (e.g., trametinib [cobimetinib; in development]) Platinum-based agents (e.g., carboplatin) Taxane agents (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pembrolizumab (Keytruda) for treatment of head and neck carcinoma	Patients in whom head and neck cancer has been diagnosed	Advanced head and neck cancer has a poor prognosis and high recurrence rate, suggesting the need for new treatments. A hallmark of cancer is its ability to evade an immune response. Pembrolizumab (Keytruda®) is a novel therapeutic that is intended to prevent immune tolerance of tumor cells. The drug's target is the programmed death-1 (PD-1) pathway, which acts as an immune checkpoint that downregulates T-cell activity. Pembrolizumab is a monoclonal antibody specific for the PD-1 receptor that purportedly blocks activation of this pathway. In the phase I KEYSTONE-012 trial, pembrolizumab was administered as a 200 mg intravenous infusion, once every 3 weeks. Merck & Co., Inc., Whitehouse Station, NJ Phase III trial (KEYNOTE-040) ongoing; Sept 2014, FDA granted accelerated approval for treating melanoma	Chemoradiation Surgical resection Chemotherapy with 1 or more of the following: Alkylating agents (e.g., ifosfamide) Antimetabolites (e.g., 5-fluorouracil, gemcitabine, methotrexate) Cytoprotective agents (e.g., bleomycin) EGFR inhibitor (e.g., cetuximab) Immunotherapy (e.g., durvalumab, nivolumab [in development]) Platinum-based drugs (e.g., cisplatin) Oncolytic virus (e.g., Reolysin® [in development]) Taxanes (e.g., docetaxel, paclitaxel) Tyrosine kinase inhibitors (e.g., lenvatinib, sorafenib) Vinca alkaloids (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pembrolizumab (Keytruda) for treatment of nonsmall cell lung cancer	Patients with PD-L1–positive nonsmall cell lung cancer (NSCLC) that has progressed after therapy with a platinum-containing doublet	The 5-year survival rate for patients with advanced NSCLC (stage IIIA, IIIB, or IV) is less than 15%. A hallmark of cancer is its ability to evade an immune response. Pembrolizumab (Keytruda®) is a monoclonal antibody that targets a novel immune-checkpoint pathway, blocking the programmed death-1 (PD-1) co-inhibitory receptor expressed by activated T cells. The activity of this pathway has been shown to limit T-cell activation; therefore, blocking its activity may enhance the body's immune response, potentially overcoming immune tolerance of malignant cells. Pembrolizumab is administered by intravenous infusion at a low or high dose (to be established based on maximum tolerated dose), once every 3 weeks. Merck & Co., Inc., Whitehouse Station, NJ Phase II/III trial (KEYNOTE-010) and phase III trials (KEYNOTE-024, -042, and -091) ongoing; Jun 2015, FDA accepted company's supplemental biologics license application and granted priority review, with a decision date set for Oct 2, 2015; Oct 2014, FDA granted breakthrough therapy status for treating NSCLC (after granting accelerated approval for treating melanoma in Sept 2014)	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab) PD-L1 antibodies (e.g., MEDI4736, atezolizumab [in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pembrolizumab (Keytruda) for treatment of urothelial bladder cancer	Patients with urothelial cancer of the renal pelvis, ureter, bladder, or urethra, that is transitional cell or mixed transitional/ nontransitional cell type	About 90% of urothelial cancers begin in the bladder and have a 5-year survival rate of 85% when detected early. In contrast, the survival rate of advanced urothelial cancer is 14% for patients with lymph node–positive and metastatic disease. A hallmark of cancer is its ability to evade an immune response. Pembrolizumab (Keytruda®) is a novel therapeutic that is intended to prevent immune tolerance of tumor cells. The drug's target is the programmed death-1 (PD-1) pathway, which acts as an immune checkpoint that downregulates T-cell activity. Pembrolizumab is a monoclonal antibody specific for the PD-1 receptor that purportedly blocks activation of this pathway. In the phase I KEYSTONE-012 trial, pembrolizumab is administered as a 200 mg intravenous infusion, once every 3 weeks. Merck & Co., Inc., Whitehouse Station, NJ Phase III trial (KEYNOTE-045) registered; FDA granted accelerated approval Sept 2014 for treating melanoma	Surgery (cystectomy) Radiotherapy combined with chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Platinum-based agents (e.g., cisplatin) Taxanes (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life
Peptide-cytokine complex (NGR-hTNF) for treatment of malignant pleural mesothelioma	Patients with malignant pleural mesothelioma who have undergone treatment with pemetrexed and cisplatin	NGR-hTNF (human tumor necrosis factor) is a peptide-cytokine complex; NGR peptide binds preferentially to tumor vasculature and TNF may induce an immune cell reaction/apoptosis, thereby destroying tumors. Ongoing clinical trials are testing NGR-hTNF as 1st- and 2nd-line treatments. This agent is administered at 0.8 mcg/m², intravenously, every 3 weeks until confirmed evidence of disease progression or unacceptable toxicity occurs. MolMed, S.p.A., Milan, Italy Phase III trial completed; did not meet overall survival endpoint, but reported improved survival in 40% of subgroup that had more advanced cancer; phase II trial ongoing; FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Antimetabolites (e.g., gemcitabine, pemetrexed, raltitrexed) Platinum-based agents (e.g., carboplatin, cisplatin, oxaliplatin) Topoisomerase inhibitor (e.g., doxorubicin, irinotecan) Vinca alkaloids (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Plitidepsin for treatment of recurrent or treatment-refractory multiple myeloma	Patients with multiple myeloma who have undergone at least 3 treatments, including bortezomib- and lenalidomide-based regimens	Although treatments for multiple myeloma have improved, the median life expectancy for patients in whom multiple myeloma is diagnosed is only 5–7 years. Additionally, because several newer treatments for multiple myeloma have been moved into the frontline setting as combination therapies, additional salvage treatments are needed. Plitidepsin is a cyclodepsipeptide that demonstrated anticancer activity in preclinical studies and was isolated from the tunicate *Aplidium albicans*. The purported mechanism of action of plitidepsin is the induction of cell-cycle arrest and apoptosis through the induction of oxidative stress, activation of Rac1, and the sustained activation of Jun-N terminal kinase and p38 mitogen-activated protein kinase. In a late-stage clinical trial for treating multiple myeloma, plitidepsin is being administered by infusion at a dose of 5 mg/m^2 in combination with orally administered dexamethasone. PharmaMar subsidiary of Grupo Zeltia, Madrid, Spain Phase III trial (ADMYRE) ongoing; FDA granted orphan drug status	Combination chemotherapy including 1 or more of the following: Bendamustine Bortezomib Carfilzomib Cisplatin Cyclophosphamide (including high dose) Dexamethasone Etoposide Lenalidomide Pomalidomide Thalidomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Prophage G-series vaccine (HSPPC-96) for treatment of glioma	Patients with primary or recurrent gliomas, including glioblastoma multiforme (GBM)	Gliomas, which include GBM, are difficult to treat and associated with a very poor prognosis. New therapies that improve survival and slow disease progression are needed. Prophage (HSPPC-96) is a cancer vaccine derived from antigens displayed by a patient's individual tumor. Laboratory workers coimmunoprecipitate antigens from a tumor sample with heat-shock protein GP96. Vaccinations with these antigens are given to stimulate an immune response against residual cancer cells. 2 versions of the vaccine are in clinical trial testing: Prophage G-100 for newly diagnosed gliomas and Prophage G-200 for progressive or recurrent glioma. In clinical trials, the vaccines are delivered as weekly or biweekly intradermal injections as part of combination therapy with temozolomide or bevacizumab. Agenus, Inc., Lexington, MA, in collaboration with University of California, San Francisco (UCSF), and the National Cancer Institute (NCI), Bethesda, MD Phase I/II and II trials (UCSF-05103 and HeatShock) completed, phase II trial (NCI-2013-00444) ongoing, phase III trial planned; FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., carmustine, cyclophosphamide, lomustine, nitrosourea, procarbazine, temozolomide) Angiogenesis inhibitors (e.g., bevacizumab) Immunotherapeutics (e.g., DCVax-L, HSPPC-96, ICT-107, rindopepimut, SL-701 [in development]) mTOR inhibitors (e.g., everolimus) PD-1 antibodies (e.g., nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin) Radiation therapy Vinca alkaloids (e.g., vincristine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
ProstAtak immunotherapy for prostate cancer	Patients in whom intermediate- to high-risk, localized prostate cancer has been diagnosed	Prostate cancer recurrence rates after 1st-line treatment range between 10% and 60% depending on whether tumor pathology indicates that the tumor is low risk or high risk; therapies that could reduce this recurrence rate are highly sought. A gene-mediated cytotoxic immunotherapy (GMCI), ProstAtak™, is being tested for preventing recurrence after conventional therapy. GMCI purportedly leads to direct tumor cytotoxicity as well as a protective immune response. The treatment consists of an adenovirus vector that contains a herpes simplex virus (HSV) thymidine kinase gene (Adv-tk). After the virus is injected into the tumor site, the patient receives the anti-HSV drug valacyclovir, which is activated by the tk transgene and produces an active drug that kills rapidly dividing cells. This, in turn, leads to local cytotoxicity through local release of activated valacyclovir and the release of tumor antigens that may be taken up by dendritic cells and produce a systemic immune response. In treating prostate cancer, GMCI is being administered in combination with radiation therapy (RT). Patients receive 3 GMCI injections at 2–8 weeks before 1st RT, at the time of 1st RT, and 2–3 weeks after 1st RT. Advantagene, Inc., Auburndale, MA Phase III trial ongoing under an FDA special protocol assessment	Androgen-deprivation therapy Radiation therapy Surgical resection	Increased overall survival Increased disease-free survival Improved quality of life
ProstVac immunotherapy for castration-resistant prostate cancer	Patients in whom asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (CRPC) has been diagnosed	Men with progressive, metastatic CRPC often have a poor prognosis and few treatment options. No viral vector vaccine is approved. ProstVac® is a prime-boost immune therapy strategy using fowlpox and vaccinia viral vectors encoding prostate-specific antigen and 3 immune costimulatory molecules; the patient's immune system is primed using the vaccinia virus followed by multiple fowlpox vector boosts. Given in 1 primer step and then weekly injections to generate an immune response. BN ImmunoTherapeutics unit of Bavarian Nordic A/S, Kvistgård, Denmark Phase III trial ongoing	Abiraterone Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Quizartinib for treatment of acute myeloid leukemia bearing *FLT3* mutations	Patients with treatment-refractory acute myeloid leukemia (AML) bearing an internal tandem duplication in the *FLT3* gene (ITD-FLT3)	No *FLT3* inhibitors are available for treating AML, and patients with recurrent or treatment-refractory AML have no effective treatment options. About 30% of AML cases bear an activating mutation in the gene encoding the receptor tyrosine kinase *FLT3*, a mutation that constitutively activates various cell proliferative and anti-apoptotic pathways. Patients whose disease harbors an activating *FLT3* mutation have a worse prognosis than patients whose disease does not. Quizartinib is an orally administered selective inhibitor of *FLT3* kinase activity that is under study as a treatment for AML. Its dosage was not specified in the phase III clinical trial record. Ambit Biosciences, San Diego, CA, a subsidiary of Daiichi Sankyo Co., Ltd., Tokyo, Japan Phase III trial (QUANTUM-R) ongoing; FDA granted orphan drug and fast-track statuses	Cladribine, cytarabine, and granulocyte colony stimulating factor (G-CSF) plus or minus mitoxantrone or idarubicin High-dose cytarabine and anthracycline Fludarabine, cytarabine, and G-CSF plus or minus idarubicin Mitoxantrone, etoposide, and cytarabine	Increased overall survival Increased progression-free survival Improved quality of life
Radiofrequency ablation with liposomal-encapsulated doxorubicin (ThermoDox) for treatment of hepatocellular carcinoma	Patients in whom hepatocellular carcinoma (HCC) has been diagnosed	Patients with HCC that cannot be surgically resected have few treatment options and a poor prognosis. ThermoDox™ is a heat-labile liposomal encapsulation of the chemotherapeutic agent doxorubicin. When radiofrequency (RF) energy is applied to the target tissue after administration of ThermoDox, it induces local hyperthermia (39.5–42.0 °C) and targeted release of the cytotoxic agent. ThermoDox is being tested in patients with treatment-naïve HCC whose disease is not eligible for surgical resection. Celsion Corp., Lawrenceville, NJ Phase III trial (OPTIMA) ongoing; Jan 2013, 1st phase III trial (HEAT) failed its progression-free-survival endpoint; new phase III trial started May 2015	Radiofrequency ablation Surgical resection Locoregional treatment with 1 of the following: Transarterial embolization Transcatheter arterial chemoembolization Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Multikinase inhibitors (e.g., regorafenib, sorafenib) Platinum-based agents (e.g., cisplatin, oxaliplatin)	Decreased need for liver transplantation Reduced side effects Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ramucirumab (Cyramza) for treatment of gastric cancer	Patients with metastatic gastric cancer whose disease has progressed after 1st-line therapy with a platinum agent and a fluoropyrimidine	Patients with gastric cancer that has progressed after 1st-line chemotherapy have a poor prognosis with median survival times of less than 1 year. Ramucirumab is a novel monoclonal antibody that binds to the extracellular domain of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2), which is a receptor tyrosine kinase that acts as a central mediator of tumor angiogenesis. Available VEGF-pathway inhibitors include a monoclonal antibody specific for VEGF and small-molecule inhibitors of the kinase activity of VEGFR2 (and other receptor tyrosine kinases). Therefore, ramucirumab represents a novel mechanism of action for inhibiting VEGF-pathway signaling. Treatment is intended for disease that has progressed after standard 1st-line platinum-based or fluoropyrimidine-based regimens. In clinical trials for gastric cancer, ramucirumab is intravenously administered at a dose of 8 mg/kg, once every 2 weeks. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trial (RAINFALL) ongoing; Apr 2014, FDA approved ramucirumab (after granting orphan drug status and fast-track status) as a single agent for treating advanced gastric cancer or gastroesophageal junction adenocarcinoma that has progressed after chemotherapy, basing its decision on results from phase III REGARD trial; Nov 2014, ramucirumab received a 2nd FDA approval for use in combination with paclitaxel after phase III RAINBOW trial met its primary endpoint	Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin, epirubicin, irinotecan) Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) DCF (docetaxel, cisplatin, 5-fluorouracil) ECF (epirubicin, cisplatin, 5-fluorouracil) HER2 antibodies if HER2-positive (e.g., trastuzumab) PD-1 antibodies (e.g., pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ramucirumab (Cyramza) for treatment of hepatocellular carcinoma	Patients with advanced-stage hepatocellular carcinoma (HCC) whose disease is not amenable to locoregional therapy and who have had sorafenib therapy	No consensus exists on treatment for HCC that has progressed after treatment with sorafenib, and these patients have a poor prognosis. Ramucirumab is a novel monoclonal antibody that binds to the extracellular domain of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2), which is a receptor tyrosine kinase that acts as a central mediator of tumor angiogenesis. Available inhibitors of the VEGF pathway include a monoclonal antibody specific for VEGF and small-molecule inhibitors of the kinase activity of VEGFR2 (and other receptor tyrosine kinases). Therefore, ramucirumab represents a novel mechanism of action for inhibiting VEGF-pathway signaling. This agent is intended for 2nd-line treatment after 1st-line sorafenib therapy. In clinical trials for HCC, ramucirumab is administered intravenously, 8 mg/kg, once every 2 weeks. Eli Lilly and Co., Indianapolis, IN Phase III trial (REACH-2) ongoing	Radiofrequency ablation Surgical resection Locoregional treatment with 1 of the following: Transarterial embolization Transcatheter arterial chemoembolization Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Multikinase inhibitors (e.g., regorafenib, sorafenib) Platinum-based agents (e.g., cisplatin, oxaliplatin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Regorafenib (Stivarga) for treatment of hepatocellular carcinoma	Patients with unresectable hepatocellular carcinoma (HCC) that has progressed after treatment with sorafenib	Patients with HCC that cannot be surgically resected have few treatment options and a poor prognosis; no 2nd-line therapy is available after sorafenib. Regorafenib (Stivarga®) inhibits multiple tyrosine kinases, including the pro-angiogenic kinases vascular endothelial growth factor receptor and TIE-2 (as well as RAF, RET, and KIT). Inhibition of both primary angiogenic kinase pathways puts regorafenib in a class of novel multikinase-inhibitor drugs (e.g., imatinib, sunitinib). In clinical trials for treating HCC, regorafenib is administered orally, 160 mg daily, for 3 weeks of every 4-week cycle. Bayer AG, Leverkusen, Germany Phase III (RESORCE) trial ongoing; FDA approved for treating gastrointestinal stromal tumors and metastatic colorectal cancer	Radiofrequency ablation Surgical resection Locoregional treatment with 1 of the following: Transarterial embolization Transcatheter arterial chemoembolization Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Multikinase inhibitors (e.g., sorafenib) Platinum-based agents (e.g., cisplatin, oxaliplatin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Remestemcel-L (Prochymal) for treatment of acute graft-versus-host disease	Pediatric patients with treatment-refractory, acute graft-versus-host disease (GVHD)	GVHD is a relatively rare condition that most often occurs when donor cells in an allogeneic hematopoietic stem cell transplant mount an immune response against recipient tissues. Patients with acute GVHD typically exhibit damage to the skin, liver, and gastrointestinal tract, and GVHD is lethal in up to 80% of patients with severe forms of the disease. Remestemcel-L (Prochymal®) is an off-the-shelf preparation of mesenchymal stem cells expanded from allogeneic donors. Mesenchymal stem cells are purported to have immunomodulatory effects that may downregulate the antirecipient immune response that underlies GVHD. In clinical trials, remestemcel-L was administered by intravenous injection, twice weekly, for 4 weeks. Mesoblast, Ltd., Melbourne, Australia (formerly developed by Osiris Therapeutics, Inc., Columbia, MD, whose stem cell unit was acquired by Mesoblast) Phase III trial (280) complete, phase III trial (MBS-GVHD001) ongoing; FDA granted orphan drug and fast-track statuses; available under expanded access program since 2008; Health Canada approved 2012	Anti-thymocyte globulin Corticosteroids Methotrexate and cyclosporine Mycophenolate mofetil Other immunosuppressants Photopheresis	Increased overall survival Improved quality of life
Retroviral replicating vector (Toca-511) for treatment of high-grade glioma	Patients in whom recurrent high-grade glioma (e.g., glioblastoma multiforme, anaplastic astrocytoma) has been diagnosed	Patients with recurrent high-grade glioma have limited treatment options and a poor prognosis. Toca-511 is a novel, virus-based treatment for cancer that consists of a retrovirus that stably inserts itself into the genome of dividing cells. The virus has been genetically modified to encode the enzyme cytosine deaminase, which can convert the antifungal prodrug 5-FC (flucytosine) to the anticancer agent 5-FU (5-fluorouracil). After intratumoral injection of the viral vector, an extended-release formulation of 5-FC (Toca-FC) is administered systemically. This combination is intended to generate high levels of 5-FU in cancer cells transfected by the viral vector encoding cytosine deaminase. Tocagen, Inc., San Diego, CA Phase II/III trial ongoing; Jan 2011, FDA granted orphan drug status; Jul 2015, FDA granted fast-track status	BCNU Bevacizumab with or without BCNU, irinotecan, or temozolomide Nitrosurea Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ribociclib for treatment of estrogen receptor–positive breast cancer	Postmenopausal women with advanced hormone receptor–positive, HER2-negative breast cancer who have received no prior therapy for advanced disease	Although endocrine therapies (e.g., estrogen receptor antagonists, aromatase inhibitors) are often effective in treating patients who have estrogen receptor–positive breast cancer, the response duration is typically limited to about 1 year. Ribociclib (LEE011) is a dual inhibitor of cyclin-dependent kinase (CDK) 4 and CDK 6, kinases involved in controlling cell cycle progression. CDK 4 and CDK 6 regulate a cell-cycle checkpoint controlling initiation of DNA synthesis, and their inhibition may limit tumor growth mediated by cell proliferation. Preclinical studies have demonstrated that hormone receptor–positive breast cancer may be highly sensitive to CDK 4/6 inhibition and that this inhibition may be synergistic with endocrine therapies. The drug is being studied in combination with letrozole in the 1st-line setting for advanced disease. In clinical trials, ribociclib is administered orally, once daily, 600 mg, on days 1–21 of each 28-day cycle. Novartis International AG, Basel, Switzerland Phase III trials (MONALEESA-1 and MONALEESA-7) ongoing	Chemotherapy with 1 or more of the following: Anabolic steroids (e.g., fluoxymesterone) Aromatase inhibitors (e.g., anastrozole, exemestane, letrozole) CDK4/6 inhibitors (e.g., palbociclib [abemaciclib; in development]) Estrogen inhibitors (e.g., tamoxifen, toremifene) Estrogen receptor inhibitors (e.g., fulvestrant) Protein kinase inhibitors (e.g., everolimus) Synthetic progestogens (e.g., progestin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Rigosertib (Estybon) for treatment of myelodysplastic syndrome	Patients with azacitidine- or decitabine-refractory myelodysplastic syndrome after failure of treatment with hypomethylating agents	Patients with myelodysplastic syndrome with excess blasts that has not responded to azacitidine or decitabine treatment have a poor prognosis and no standard treatment options. Rigosertib (Estybon®) is a small-molecule, multikinase inhibitor with activity against both the alpha and beta isoforms of phosphoinositide 3 kinase (PI3K) and polo-like kinase 1 (PLK1). Inhibiting PI3K may disrupt cell signaling that promotes cell growth and survival, and inhibiting PLK1 may disrupt mitosis, leading to cell-cycle arrest. In clinical trials, rigosertib is being administered as a monotherapy in a 72-hour continuous intravenous infusion. Onconova Therapeutics®, Inc., Newtown, PA Phase III trial ongoing; Feb 2014, Onconova announced that the phase III trial failed to meet its primary endpoint of extending overall survival; investigational new drug application submitted to FDA for planned phase III trial in higher-risk patients	Hematopoietic stem cell transplant Immunosuppressive therapy (e.g., antithymocyte globulin with or without cyclosporine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Rindopepimut (Rintega) vaccine for treatment of glioblastoma multiforme	Patients with newly diagnosed glioblastoma multiforme (GBM) who have undergone primary surgical resection	GBM is difficult to treat and associated with a very poor prognosis. New therapies that improve survival and slow disease progression are needed. Rindopepimut (Rintega®) is a peptide-based vaccine designed to stimulate an immune response to cells expressing the epidermal growth factor receptor vIII (EGFRvIII) variant. EGFRvIII is an oncogenic splice variant of EGFR and represents a potential target antigen for anticancer therapy. In clinical trials, rindopepimut is being administered in combination with the immune stimulant granulocyte macrophage colony-stimulating factor (GM-CSF) and standard maintenance chemotherapy (temozolomide). It is being tested as 1st-line treatment in newly diagnosed (phase III trial) and recurrent (phase II trial) GBM and is administered at a dosage of 500 mcg rindopepimut/150 mcg GM-CSF, via intradermal injection, biweekly during month 1, then monthly thereafter. Celldex Therapeutics, Inc., Needham, MA Phase III trial (ACT IV) ongoing; phase IIb trial (ReACT) with expansion cohort ongoing in recurrent GBM; FDA granted breakthrough therapy, orphan drug, and fast-track statuses	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., carmustine, cyclophosphamide, lomustine, nitrosourea, procarbazine, temozolomide) Angiogenesis inhibitors (e.g., bevacizumab) Immunotherapeutics (e.g., DCVax-L, HSPPC-96, SL-701 [in development]) mTOR inhibitors (e.g., everolimus) PD-1 antibodies (e.g., nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin) Radiation therapy Vinca alkaloids (e.g., vincristine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Rociletinib for treatment of nonsmall cell lung cancer	Patients with advanced, epidermal growth factor receptor (*EGFR*) mutation–positive, nonsmall cell lung cancer (NSCLC) whose disease has progressed after treatment with an *EGFR* inhibitor	*EGFR*-inhibitor treatments have improved outcomes for patients with *EGFR* mutation–positive NSCLC relative to cytotoxic chemotherapy; however, these inhibitors have limitations. First, NSCLC frequently develops resistance to *EGFR* inhibitors. This resistance is often mediated by a mutation in *EGFR* (T790M), which renders the kinase insensitive to current inhibitors. Second, available *EGFR* inhibitors have activity against wild-type *EGFR* in addition to mutant forms, and the inhibition in noncancer cells can lead to substantial toxicity. Rociletinib (CO-1686) is a novel, irreversible *EGFR* inhibitor that is specific for mutant forms of *EGFR*, including *EGFR* harboring the T790M resistance mutation. Therefore, it has potential efficacy in patients whose disease has progressed during treatment with existing *EGFR* inhibitors and might improve on the tolerability of *EGFR*-inhibitor therapy. In clinical trials, rociletinib is being administered orally, between 500 and 1,000 mg, twice daily. Clovis Oncology, Boulder, CO Phase III trial (TIGER-3) ongoing; FDA granted orphan drug and breakthrough therapy statuses; Aug 2015, rolling new drug application submission completed	Afatinib Docetaxel Erlotinib Pemetrexed	Increased overall survival Increased progression-free survival Improved quality of life
Rose bengal (PV-10) for treatment of advanced melanoma	Patients in whom advanced or metastatic melanoma has been diagnosed	Patients with advanced melanoma have few treatment options and a poor prognosis. PV-10 is a solution of the fluorescein derivative rose bengal. Rose bengal preferentially accumulates in cancer cells because of the increased lipid content of their cell membranes, which allows the drug to cross. Within the cells, rose bengal accumulates in lysosomes, triggering lysosomal release and cellular toxicity. Besides causing local tumor cell lysis, rose bengal has been associated with a bystander effect in which untreated lesions exhibit a response to treatment. This effect is thought to be due to uptake of tumor antigens by cells of the immune system after tumor lysis, leading to a systemic immune response. It is administered by intralesional injection. Provectus Biopharmaceuticals, Inc., Knoxville, TN Phase II trial completed, phase III trial (PV-10-MM-31) ongoing; FDA granted orphan drug status	Dacarbazine Granulocyte colony stimulating factor Interleukin-2 Ipilimumab Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Rucaparib for treatment of ovarian, fallopian tube, or primary peritoneal cancer	Patients in whom platinum-sensitive, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer has been diagnosed. Patients must have undergone at least 2 platinum-based treatments.	Ovarian, fallopian tube, or primary peritoneal cancer frequently recurs in patients who have undergone initial treatment. Rucaparib is a small-molecule inhibitor of poly-ADP ribose polymerase (PARP), which is an important enzyme in a cellular DNA pathway. Cancer cells are thought to particularly sensitive to PARP inhibition, potentially because of underlying defects in alternative DNA repair pathways. Rucaparib is being studied in the maintenance setting after patients have completed successful platinum-based chemotherapy and as a treatment for patients who have undergone at least 2 platinum-based treatments. Rucaparib is a tablet administered orally, twice daily (dose not specified in trial description). Clovis Oncology, Boulder, CO Phase III trial (ARIEL3) ongoing in the maintenance setting; phase II trial (ARIEL2) ongoing in the treatment setting; FDA granted orphan drug and breakthrough therapy statuses	Maintenance setting: Bevacizumab Paclitaxel Treatment setting: Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, liposomal doxorubicin, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ruxolitinib (Jakafi) for treatment of pancreatic cancer	Patients in whom recurrent metastatic pancreatic adenocarcinoma has been diagnosed	Only about 5% of patients with pancreatic cancer respond to the current standard of care (gemcitabine chemotherapy), and the prognosis for these patients is very poor. Pancreatic cancer cells often have dysregulated JAK-STAT activity caused by elevated levels of pro-inflammatory cytokines, which can lead to growth and proliferation of pancreatic cancer cells and resistance to chemotherapy. Ruxolitinib (Jakafi®) is a Janus kinase (JAK) inhibitor that inhibits the activity of both JAK 1 and JAK 2, which are purported to be key targets in pancreatic cancer. In clinical trials, patients are treated twice daily with 15 mg of ruxolitinib in combination with capecitabine. Incyte Corp., Wilmington, DE Phase II trial (RECAP) and phase III trials (Janus 1 and Janus 2) ongoing; FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) Folic acid derivatives (e.g., leucovorin) Multikinase inhibitors (e.g., erlotinib) Platinum-based agents (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life
Ruxolitinib (Jakafi) for treatment of polycythemia vera	Patients in whom polycythemia vera has been diagnosed	Polycythemia vera is a rare myeloproliferative neoplasm with limited treatment options. Patients with polycythemia vera typically have elevated red blood cell counts, and these patients are at increased risk for cardiovascular events and disease symptoms (e.g., enlarged spleen). Many patients with polycythemia vera harbor activating mutations in Janus kinase 2 (JAK2), and JAK2 activity is thought to lead to the blood cell deregulation and overproliferation observed in polycythemia vera. Ruxolitinib (Jakafi®) is a small-molecule inhibitor of JAK1 and JAK2 used in treating the JAK2-associated myeloproliferative neoplasm myelofibrosis. In clinical trials of ruxolitinib in patients with polycythemia vera, the drug is administered at a twice daily dosage of between 5 and 25 mg, depending on patient response. Incyte Corp., Wilmington, DE, in collaboration with Novartis International AG, Basel, Switzerland Phase III trials ongoing; FDA granted orphan drug status; Dec 2014, FDA approved for treating patients with “polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea”	Antiplatelet therapy (e.g., aspirin) Hydroxyurea Interferon Phlebotomy	Decreased progression to myelofibrosis or leukemia Decreased spleen volume Increased complete hematologic response rate Increased hematocrit control rate Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Sacituzumab govitecan for treatment of triple-negative breast cancer	Patients in whom triple-negative breast cancer has been diagnosed	Triple-negative breast cancer (i.e., low expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2) is not amenable to endocrine therapy or treatment with any of the targeted agents developed for breast cancer. Treatment presents a significant clinical challenge because no standard therapy is effective for this disease, and affected patients have a median survival of about 1 year. Sacituzumab govitecan (IMMU-132) is a combination of hRS7, a humanized antibody specific against trophoblast cell-surface antigen (TROP-2), and camptosar, the active metabolite of irinotecan (SN-38). This combination is intended to enable preferential delivery of a highly cytotoxic agent to cells expressing TROP-2 to produce results as good as or better than irinotecan plus chemotherapy, but with reduced side effects. In clinical trials, sacituzumab govitecan is administered at an unspecified dose intravenously once every 3 weeks with or without carboplatin for up to 8 cycles. Immunomedics, Inc., Morris Plains, NJ Phase II trial ongoing; Jan 2015, FDA granted fast-track status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine, pemetrexed) PARP inhibitors (e.g., BMN 673, niraparib, olaparib [under development]) PD-1 antibodies (e.g., pembrolizumab [in development]) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloid (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Selinexor for recurrent or treatment-refractory multiple myeloma	Patients in whom recurrent/refractory multiple myeloma has been diagnosed	Patients with recurrent/refractory multiple myeloma who have undergone treatment with both protease-inhibitor and immunomodulatory drug therapies have few remaining treatment options and a poor prognosis. Tumor suppressors normally function in cells to inhibit the aberrant cellular activities associated with cancer development. Many tumor suppressors (e.g., APC, NPM1, p53, pRB, TOXO) require nuclear localization to function, and many tumor types have been shown to drive cytoplasmic localization of these tumor suppressors through overexpression of the nuclear export factor CRM1 (also known as XPO1). Selinexor (KPT-330) is an antagonist of CRM1 activity that purportedly restores nuclear localization of tumor suppressors to potentially inhibit growth and survival of cancers. Selinexor is administered orally, 80 mg, twice weekly. Clinical trials are testing use of selinexor in combination with various multiple myeloma treatments (e.g., low-dose dexamethasone, lenalidomide and dexamethasone). Karyopharm Therapeutics, Inc., Natick, MA Phase II trials ongoing; FDA granted orphan drug status	Multiple chemotherapy regimens (choice depends on prior therapy and patient condition), including: Bortezomib Bortezomib plus liposomal doxorubicin Carfilzomib Lenalidomide plus dexamethasone Pomalidomide plus dexamethasone	Increased progression-free survival Increased overall survival Improved quality of life
Selinexor for treatment of acute myeloid leukemia	Patients aged 60 years and older with recurrent or refractory acute myeloid leukemia (AML) who are ineligible for high-dose chemotherapy and hematopoietic stem cell transplantation	Many patients with AML who are aged 60 years or older are unable to tolerate high-dose induction chemotherapies. Therefore, disease remission in this patient population is relatively low. Tumor suppressors normally function in cells to inhibit the aberrant cellular activities associated with cancer development. Many tumor suppressors (e.g., p53, pRB, TOXO, APC, NPM1) require nuclear localization to function, and many tumor types have been shown to drive cytoplasmic localization of these tumor suppressors through overexpression of the nuclear export factor CRM1. Selinexor (KPT-330) is an antagonist of CRM1 activity that purportedly restores nuclear localization of tumor suppressors to potentially inhibit growth and survival of cancers. Selinexor is administered orally, 55 mg/m^2, twice weekly. Karyopharm Therapeutics, Inc., Natick, MA Phase II trials ongoing; FDA granted orphan drug status	5-Azacytidine Decitabine Low-dose cytarabine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Selinexor for treatment of diffuse large B-cell lymphoma	Patients with recurrent/refractory de novo diffuse large B-cell lymphoma (DLBCL) who have undergone at least 2 multiagent treatment regimens	Approximately 1/3 of patients with DLBCL will have disease refractory to initial therapy or experience disease recurrence after an initial remission. For patients with recurrent/refractory DLBCL who are ineligible for high-dose chemotherapy followed by allogeneic stem cell transplant, prognosis is poor and few treatment options are available. Tumor suppressors normally function in cells to inhibit the aberrant cellular activities associated with cancer development. Many tumor suppressors (e.g., APC, NPM1, p53, pRB, TOXO) require nuclear localization to function, and many tumor types have been shown to drive cytoplasmic localization of these tumor suppressors through overexpression of the nuclear export factor CRM1 (also known as XPO1). Selinexor (KPT-330) is an antagonist of CRM1 activity that purportedly restores nuclear localization of tumor suppressors to potentially inhibit growth and survival of cancers. Selinexor is administered orally, twice weekly, 60 or 100 mg. Karyopharm Therapeutics, Inc., Natick, MA Phase II trial ongoing; FDA granted orphan drug status	Bendamustine with or without rituximab Lenalidomide with or without rituximab Rituximab	Increased progression-free survival Increased overall survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Selumetinib for treatment of KRAS-positive nonsmall cell lung cancer	Patients with locally advanced or metastatic, *KRAS* mutation–positive nonsmall cell lung cancer (NSCLC) who have undergone 1 round of therapy	The 5-year survival rate for patients with advanced NSCLC is less than 15% with available treatments. The mitogen-activated protein kinase (MAPK)/extracellular signal–regulated kinase (ERK) pathway is a central regulator of cellular responses to growth signals. Aberrant activity of this pathway has been implicated in the development of many cancer types. MAPK kinase (MEK) is a protein kinase that plays a role in this pathway by controlling activation of ERK; therefore, inhibiting MEK activity could inhibit cancer cell growth and survival. However, no MEK inhibitor is available. Selumetinib (AZD6244, ARRY-142886) is a MEK inhibitor under study for treating *KRAS* mutation–positive NSCLC. In clinical trials, selumetinib is administered at an oral dosage of 25 mg, twice daily, in combination with docetaxel and pegylated granulocyte colony stimulating factor. AstraZeneca, London, UK Phase III trial (SELECT-1) ongoing	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Seviprotimut-L therapeutic melanoma antigen vaccine to prevent melanoma recurrence	Patients at high risk of recurrence after surgical resection of stage IIB, IIC, or III melanoma	After surgical resection of a primary melanotic tumor, disease recurs in many patients, and few adjuvant treatments to prevent recurrence are available. Seviprotimut-L (POL-103A) is a polyvalent vaccine that is generated by isolating peptides secreted by 3 human melanoma cell lines grown in culture. In clinical trials, seviprotimut-L was administered intradermally as adjuvant therapy after surgical resection and radiation. Treatment was divided into four 0.2 mL injections. Polynoma LLC subsidiary of CK Life Sciences Int'l (Holdings), Inc., Hong Kong Phase III trial (MAVIS) ongoing; Jun 2006, FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, temozolomide) B-RAF inhibitors (e.g., dabrafenib, vemurafenib) Immunotherapy (e.g., ipilimumab, nivolumab, pembrolizumab) MEK inhibitors (e.g., trametinib [cobimetinib; in development]) Platinum-based agents (e.g., carboplatin) Taxane agents (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life
Siltuximab (Sylvant) for treatment of multicentric Castleman's disease	Patients in whom multicentric Castleman's disease has been diagnosed	Castleman's disease is a lymphoproliferative disorder that can cause serious, possibly life-threatening symptoms or progress to more aggressive diseases such as lymphomas. Patients with the multicentric form of Castleman's disease frequently experience relapses following treatment with cytotoxic chemotherapy. The disease purportedly develops through an autoinflammatory process involving elevated levels of interleukin-6 (IL-6). Siltuximab (Sylvant™) is an IL-6 monoclonal antibody that has the potential to limit IL-6 activity. In clinical trials, siltuximab was administered by intravenous infusion once every 3 weeks at a dose of 11 mg/kg. Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ Phase II trial ongoing; FDA granted orphan drug status; FDA approved Apr 2014 for "the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative"	Various chemotherapy regimens including 1 or more of the following: carmustine, cladribine, chlorambucil, cyclophosphamide, doxorubicin, etoposide, melphalan, vinblastine, and vincristine	Increased remission rate Increased remission duration Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Sorafenib (Nexavar) for treatment of differentiated thyroid cancer	Patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer	RAI-refractory thyroid cancer is difficult to treat and associated with poor prognoses, and affected patients have limited treatment options. Sorafenib is a multiple kinase inhibitor (tyrosine and Raf kinases) that targets the MAP kinase pathway to inhibit tumor cell proliferation and angiogenesis. Sorafenib is an oral medication approved for treating kidney and liver cancer; it is typically administered at a dose of 400 mg, twice daily. Bayer AG, Leverkusen, Germany, and Onyx Pharmaceuticals (now a subsidiary of Amgen, Inc., Thousand Oaks, CA) FDA approved for treating late-stage (metastatic) differentiated thyroid cancer Nov 2013; approved in 2005 for treating advanced kidney cancer and in 2007 for treating surgically unresectable liver cancer	Ablation Multikinase inhibitors (e.g., lenvatinib [cabozantinib, pazopanib, sunitinib, vandetanib; in development]) Radioactive iodine (I-131) Radiation therapy Surgical intervention Thyroid hormone therapy	Increased overall survival Increased progression-free survival Improved quality of life
Spicamycin-derived, nonopioid, nonnarcotic agent (KRN5500) for treatment of chronic cancer pain	Patients with chronic cancer pain, especially chemotherapy-induced neuropathic pain	Pain management medications are not always effective in controlling chronic cancer pain, and their long-term use carries significant side effects (e.g., constipation, nausea, possible opioid addiction, kidney damage, gastrointestinal bleeding associated with nonsteroidal anti-inflammatory drugs [NSAIDs]). KRN5500 is a novel spicamycin derivative that was originally identified as a potential cancer treatment, a compound that could induce differentiation of myeloid leukemia cells. Although KRN5500 did not exhibit efficacy against leukemia, 1 patient with chronic neuropathic pain from previous cancer treatments experienced significant relief from that pain. Additional studies of KRN5500 for pain have been undertaken. DARA BioSciences, Inc., Raleigh, NC Phase IIa trial completed; FDA granted fast-track status in 2011 and orphan drug status in Feb 2014	NSAIDs Opioid analgesics	Reduced pain Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Stool DNA molecular test (Cologuard) for colorectal cancer screening	Patients undergoing routine colorectal cancer (CRC) screening	A test that obviates the need for the bowel preparation required by current screening methods could improve adherence to recommended CRC screening guidelines. This genetic test (Cologuard™) screens stool DNA for genetic mutations and epigenetic modifications commonly found in CRC: 4 genes plus 1 biomarker. This test kit is the next generation of the ColoSure™ test, which looked for epigenetic modification in only a single genetic locus. Exact Sciences Corp., Madison, WI Aug 2014, FDA approved for screening for colorectal cancer in people aged 50 years or older at average risk for CRC	Colonoscopy Computed tomographic colonography Fecal occult blood testing Sigmoidoscopy	Increased sensitivity and specificity for precancerous lesions and CRC Improved positive and negative predictive values Reduced unnecessary followup for screening
Suicide gene–engineered donor lymphocytes (Zalmoxis) after hematopoietic stem cell transplant for treatment of acute leukemias	Patients with acute lymphoblastic leukemia or acute myeloid leukemia (AML) who are undergoing myeloablative chemotherapy followed by hematopoietic stem cell transplant (SCT)	Allogeneic SCT is the most effective treatment for AML; however, its use is complicated by potential adverse events including the development of graft-versus-host disease (GVHD), in which alloreactive donor T cells attack recipient tissues. The traditional approach to reducing GVHD has been the use of T cell–depleted grafts comprised of only hematopoietic stem cells; however, this approach is hampered by reduced levels of hematopoietic cell engraftment and reduced graft-versus-leukemia immune response. Infusion of suicide gene–engineered donor lymphocytes (Zalmoxis®) after hematopoietic SCT is an approach being taken to overcome these shortcomings. In this approach, donor T cells are genetically modified to express herpes simplex virus–derived thymidine kinase. Thymidine kinase converts the prodrug ganciclovir to a toxic agent, thereby conferring selective toxicity on thymidine kinase–expressing cells and providing a means to promote the “suicide” of GVHD-causing T cells. The infusion of T cells after hematopoietic SCT is purported to promote engraftment and graft-versus-leukemia immune activity. MolMed, S.p.A., Milan, Italy Phase III trial ongoing	Hematopoietic SCT	Increased overall survival Decreased time to immune reconstitution Increased engraftment rate Reduced incidence of acute GVHD Reduced incidence of chronic GVHD Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Synthetic hypericin for treatment of cutaneous T-cell lymphoma	Patients in whom cutaneous T-cell lymphoma (CTCL) has been diagnosed	Photodynamic therapy is a mainstay of CTCL treatment; however, current approaches to photodynamic therapy require the use of ultraviolet light, which can damage surrounding tissue and lead to skin burns, increased pigmentation, or secondary skin cancer. SGX-301 is a synthetic hypericin that is thought to act as a photosensitizing agent when used in combination with light within the visible spectrum, potentially avoiding the complications associated with ultraviolet light. SGX-301 is applied topically to the CTCL lesion followed by light activation of the compound. Soligenix, Inc., Princeton, NJ Phase II trial complete; phase III trial approved by FDA, expected to start in 2nd half of 2015; FDA granted orphan drug and fast-track statuses	Ultraviolet A phototherapy with psoralen Ultraviolet B phototherapy	Increased lesion clearance rate Increased disease-free survival Improved quality of life
Talazoparib for treatment of BRCA-mutated breast cancer	Patients in whom locally advanced or metastatic, *BRCA* mutation–positive breast cancer has been diagnosed	Improved treatment options are needed for patients with advanced *BRCA* mutation–positive breast cancers that have recurred or progressed after chemotherapy. Talazoparib (BMN 673) is a novel agent that inhibits the nuclear enzyme poly ADP-ribose polymerase (PARP). PARP is activated by single-strand DNA breaks and catalyzes post-translational ADP-ribosylation of nuclear proteins involved in DNA repair. Talazoparib binds PARP and prevents PARP-mediated DNA repair. Accumulated DNA strand breaks in the cell promote genomic instability and eventually lead to apoptosis, potentially underlying talazoparib's antineoplastic potential. This agent is being tested for treating advanced breast cancers in patients with *BRCA* 1 or 2 mutations. In clinical trials, talazoparib is administered daily, 1 mg, orally, for 21 consecutive days and is being compared with a physician's choice of drug (e.g., capecitabine, eribulin, gemcitabine, vinorelbine). BioMarin Pharmaceutical, Inc., Novato, CA Phase III trial (EMBRACA) ongoing	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine) PARP inhibitors (e.g., niraparib, olaparib, veliparib [under development]) Taxanes (e.g., docetaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Talimogene laherparepvec (T-VEC) for treatment of advanced melanoma	Patients in whom advanced melanoma has been diagnosed	Patients with advanced melanoma have a poor prognosis and few treatment options, suggesting a need for novel treatment options. Talimogene laherparepvec (T-VEC) granulocyte macrophage colony-stimulating factor (GM-CSF) is an oncolytic virus. T-VEC purportedly replicates only in tumor cells. It is engineered to lyse tumor cells and express tumor-specific antigens and GM-CSF, which help generate tumor-specific immune responses for additional benefit. In trials, it is administered up to 4 mL of 10^8 pfu/mL/per intratumoral injection. Amgen, Inc., Thousand Oaks, CA Phase III trial (OPTiM) ongoing; Sep 2014, Amgen submitted a biologics license application to FDA and in Apr 2015, an FDA advisory committee recommended approval, but no decision date has been announced	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, temozolomide) B-RAF inhibitors (e.g., dabrafenib, vemurafenib) Immunotherapy (e.g., ipilimumab, nivolumab, pembrolizumab) MEK inhibitors (e.g., trametinib [cobimetinib; in development]) Platinum-based agents (e.g., carboplatin) Taxane agents (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Taselisib for treatment of estrogen receptor–positive breast cancer	Patients in whom advanced estrogen receptor–positive breast cancer has been diagnosed	Although endocrine therapies (e.g., estrogen receptor [ER] antagonists, aromatase inhibitors) are often effective in treating patients who have advanced, estrogen receptor–positive breast cancer, the response is typically limited to about 1 year. In some ER-positive breast cancer cases, malignant cells also bear mutations in the PI3 kinase gene that constitutively activates the PI3K/Akt/mTOR pathway, which regulates cell growth and survival. Taselisib (RG7604) is a PI3 kinase inhibitor that purportedly prevents proliferation of cells with mutations in the PI3 kinase. In clinical trials, taselisib is administered orally at a daily dose of 4 mg in combination with fulvestrant. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trial (SANDPIPER) ongoing	Anabolic steroids (e.g., fluoxymesterone) Aromatase inhibitors (e.g., anastrozole, exemestane, letrozole) CDK4/6 inhibitors (e.g., palbociclib [abemaciclib, LEE001; in development]) Estrogen inhibitors (e.g., tamoxifen, toremifene) Estrogen receptor inhibitors (e.g., fulvestrant) Protein kinase inhibitors (e.g., everolimus) Synthetic progestogens (e.g., progestin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Telotristat etiprate for treatment of neuroendocrine tumor–associated carcinoid syndrome	Patients in whom metastatic neuroendocrine tumor–associated carcinoid syndrome has been diagnosed	Patients with carcinoid tumors that are not amenable to surgical resection have few treatment options to control disease symptoms, and not all cases respond to current therapies. A hallmark of many carcinoid tumors is the overproduction of serotonin, which leads to complications such as severe diarrhea, flushing, and cardiac damage. Telotristat etiprate (X1606/LX1032) is intended to reduce systemic serotonin levels by inhibiting an enzyme involved in the synthesis of serotonin, tryptophan hydroxylase. In clinical trials, it is administered at a dose of 250 mg, orally, 3 times per day. Lexicon Pharmaceuticals, Inc., The Woodlands, TX Phase III trials (TELEPATH, TELESTAR, TELECAST) ongoing; FDA granted orphan drug and fast-track statuses	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide, dacarbazine, streptozotocin, temozolomide) Antimetabolites (e.g., 5-fluorouracil, capecitabine) Cytokines (e.g., interferon-alfa) Platinum-based agents (e.g., cisplatin) Somatostatin analogues (e.g., octreotide) Topoisomerase inhibitors (e.g, doxorubicin, etoposide)	Decreased rate of bowel movements Decreased 5-HIAA levels Decreased rate of flushing episodes Less discomfort and pain Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tergenpumat-ucel-L (HyperAcute Lung) for treatment of nonsmall cell lung cancer	Patients in whom advanced nonsmall cell lung cancer (NSCLC) has been diagnosed	The 5-year survival rate for patients with advanced NSCLC is less than 15% with current treatments. Tergenpumatucel-L immunotherapy is intended to stimulate an immune response against the patient's lung cancer cells. The therapy consists of 3 allogeneic lung cancer cell lines that represent 3 major types of NSCLC. These cell lines have been genetically engineered to express the enzyme alpha (1,3) galactosyl transferase, which marks the cells with a nonhuman carbohydrate that elicits a strong antibody immune response. Antibody binding to the cell lines leads to complement-mediated cell lysis, potentially leading to the uptake of NSCLC antigens and a systemic immune response against the patient's cancer. In clinical trials, HyperAcute-Lung is being administered by injection on a weekly or biweekly basis. NewLink Genetics Corp., Ames, IA Phase II/III trial ongoing	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Improved overall survival Improved progression-free survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Therapeutic multipeptide vaccine (SL-701) for glioblastoma	Patients with recurrent malignant gliomas, including glioblastoma multiforme (GBM)	GBM can be difficult to treat and is often associated with a poor prognosis. The 5-year survival rate is less than 5%. In about 60% of patients in remission, GBM develops resistance to temozolomide, and they have limited treatment options. A need exists for effective interventions when the disease recurs. SL-701 is a multipeptide vaccine that stimulates the immune response to target and kill GBM cells expressing high levels of glioma-associated antigens. This approach purportedly improves patient outcomes because SL-701 eliminates tumor cells even in treatment-resistant disease. In clinical trials, SL-701 injections will be given to patients in combination with GM-CSF (20 minutes after SL-701) every 14 days for the 1st 155 days and then every 28 days until the disease progresses or unacceptable toxicity develops in the patient. Stemline Therapeutics, Inc., New York, NY Phase I/II trial (STML-701-0114) ongoing; Jan 2015, FDA granted orphan drug status for treating glioma	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., carmustine, cyclophosphamide, lomustine, nitrosourea, procarbazine, temozolomide) Angiogenesis inhibitors (e.g., bevacizumab) Immunotherapeutics (e.g., DCVax-L, HSPPC-96, rindopepimut [in development]) mTOR inhibitors (e.g., everolimus) PD-1 antibodies (e.g., nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin) Radiation therapy Vinca alkaloids (e.g., vincristine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tivantinib for treatment of unresectable hepatocellular carcinoma	Patients with unresectable hepatocellular carcinoma (HCC) that has failed to respond to a sorafenib-containing therapy	Patients with HCC that cannot be surgically resected have few treatment options and a poor prognosis; no effective 2nd-line therapy is available for this type of cancer. Tivantinib (ARQ 197) is a small-molecule inhibitor of c-met receptor tyrosine kinase; c-met has been implicated in a number of tumor-associated biologic processes (e.g., cell dissociation, migration, and proliferation, apoptosis inhibition). No c-met inhibitors are approved. In clinical trials, tivantinib is given orally, 120 mg, twice daily. ArQule, Inc., Woburn, MA, in partnership with Daiichi Sankyo Co., Ltd., Tokyo, Japan Phase III trials (JET-HCC and METIV-HCC) ongoing	Radiofrequency ablation Surgical resection Locoregional treatment with 1 of the following: Transarterial embolization Transcatheter arterial chemoembolization Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Multikinase inhibitors (e.g., regorafenib, sorafenib) Platinum-based agents (e.g., cisplatin, oxaliplatin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Toll-like receptor 9 agonist (MGN1703) maintenance therapy after 1st-line therapy for metastatic colorectal cancer	Patients with metastatic colorectal cancer (mCRC) whose disease has responded to 1st-line chemotherapy	Although many patients have mCRC that responds to 1st-line chemotherapy, disease ultimately progresses in the vast majority of patients. MGN1703 is under study as a maintenance therapy to prevent or delay disease recurrence. MGN1703 is a DNA molecule that is intended to function as an agonist of Toll-like receptor 9 (TLR9). TLR9 signaling is a component of the innate immune system, and agonists of TLR9 purportedly promote immune system activation, possibly through dendritic cell maturation and/or differentiation of B cells into antibody-secreting plasma cells. Immune-response activation by MGN1703 could overcome immune tolerance to tumor-associated antigens, potentially leading to an anticancer immune response. MOLOGEN AG, Berlin, Germany Phase II trial (IMPACT) completed, phase III trial (IMPALA) ongoing	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab [ramucirumab; in development]) Antimetabolites (e.g., 5-fluorouracil, capecitabine) EGFR antibodies (e.g., cetuximab, panitumumab) FOLFIRI (leucovorin, 5-fluorouracil, irinotecan) FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin) Multikinase inhibitors (e.g., regorafenib) Platinum-based agents (e.g., oxaliplatin) Topoisomerase inhibitors (e.g., irinotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tookad photodynamic therapy for treatment of localized prostate cancer	Patients in whom localized low-risk prostate cancer has been diagnosed	Current treatment of localized prostate cancer can adversely affect surrounding healthy tissue and also lead to debilitating temporary and long-term side effects or complications. Tookad is a photosensitive agent that can be excited by a specific wavelength of light to release energy that can cause local necrosis. In a photodynamic therapy procedure using Tookad, the drug is injected by needle into the prostate. After the drug diffuses into the prostate, laser light is used to excite the drug, potentially leading to destruction of targeted prostate tissue while sparing surrounding healthy tissue. Steba Biotech S.A., Cedex, France Phase III trials ongoing	Radiation therapy Radical prostatectomy Watchful waiting Active surveillance	Increased overall survival Increased progression-free survival Fewer therapy-related side effects Improved quality of life
Trabectedin (Yondelis) for treatment of ovarian, fallopian tube, or primary peritoneal cancer	Patients with platinum-sensitive, advanced or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have undergone at least 2 platinum-based treatment regimens	Ovarian, fallopian tube, or primary peritoneal cancer frequently recurs after initial treatment. Trabectedin (Yondelis®) has a unique mechanism of action associated with the minor groove of DNA. The interaction between trabectedin and DNA interferes with gene transcription, cell division, and DNA repair. In phase III clinical trials, trabectedin is being tested in combination with pegylated liposomal doxorubicin for treating advanced/recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. It is administered intravenously, 1.1 mg/m^2, once every 3 weeks. Janssen Pharmaceuticals unit of Johnson & Johnson, New Brunswick, NJ Phase III trials (INOVATYON and unnamed) ongoing	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if *BRCA*1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Trabectedin (Yondelis) for treatment of soft tissue sarcoma	Patients with surgically unresectable soft tissue sarcoma (STS), excluding L-type STS, that has progressed after standard treatment	Worldwide, more than 12,000 cases of STS are reported each year, and about 4,700 die of STS. The high mortality rate is associated with limited therapeutic options for patients whose disease has recurred after treatment. Agents are needed for treating patients who have disease recurrence. Trabectedin (Yondelis®) has a unique mechanism of action that targets the minor groove of DNA. The interaction between trabectedin and DNA purportedly disrupts proliferation of cancer cells by interfering with gene transcription, cell division, and DNA repair. In phase III clinical trials, trabectedin is tested as a single agent for treating STS, administered intravenously, 1.5 mg/m^2, once every 3 weeks. Janssen Pharmaceuticals unit of Johnson & Johnson, New Brunswick, NJ Phase III trials ongoing; Feb 2015, FDA granted priority review after company submitted a new drug application to FDA in Nov 2014	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, ifosfamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., gemcitabine, methotrexate) Platinum-based drugs (e.g., cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, paclitaxel) Tyrosine kinase inhibitors (e.g., imatinib, pazopanib) Vinca alkaloids (e.g., vincristine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Trans sodium crocetinate for treatment of glioblastoma	Patients in whom glioblastoma multiforme (GBM) has been diagnosed	GBM is difficult to treat and associated with a very poor prognosis. New therapies that improve survival and slow disease progression are needed. Radiation therapy is often applied; however, the efficacy of this therapy can purportedly be limited by the hypoxic tumor environment. Trans sodium crocetinate (TSC) is a 1st-in-class small-molecule drug that, when delivered systemically, is said to preferentially re-oxygenate tumor tissue while leaving healthy tissue unaffected. As a result, TSC may sensitize tumor tissues to radiation or chemotherapy. In a clinical trial, TSC is administered in combination with temozolomide and radiation therapy to patients who received no prior therapy other than glucocorticoids. TSC is given at a dose of 0.25 mg/kg, intravenously, for 9–18 doses. Diffusion Pharmaceuticals LLC, Charlottesville, VA Phase II trial ongoing; FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., carmustine, cyclophosphamide, lomustine, nitrosourea, procarbazine, temozolomide) Angiogenesis inhibitors (e.g., bevacizumab) Immunotherapeutics (e.g., DCVax-L, HSPPC-96, rindopepimut, SL-701 [in development]) mTOR inhibitors (e.g., everolimus) PD-1 antibodies (e.g., nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin) Radiation therapy Vinca alkaloids (e.g., vincristine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Trebananib for treatment-refractory ovarian cancer	Patients with epithelial ovarian, primary peritoneal, or fallopian tube cancer	Patients with treatment-resistant ovarian, peritoneal, or fallopian tube cancer have a poor prognosis, and more effective treatments are needed. Trebananib (AMG 386) is a peptibody that binds to the signaling molecules angiopoietin 1 and angiopoietin 2 and consists of a peptide specific for angiopoietin 1/2 fused to the Fc region of a human antibody. It is intended to block activation of the TIE2 receptor by angiopoietin 1/2; the angiopoietin/TIE2 pathway acts in parallel with the vascular endothelial growth factor (VEGF)/VEGF receptor pathway to promote angiogenesis. The drug represents a novel 1st-in-class neutralizing inhibitor of angiopoietin 1/2. It is being tested in the 2nd-line setting in combination with paclitaxel or pegylated doxorubicin after a platinum-based chemotherapy regimen and in the 1st-line setting in combination with paclitaxel and carboplatin. In clinical trials, trebananib is administered at a dose of 15 mg/kg, intravenously, once weekly. Amgen, Inc., Thousand Oaks, CA Phase III trials (TRINOVA-1, TRINOVA-2 and TRINOVA-3) ongoing in 1st and 2nd-line treatment settings; FDA granted orphan drug status for treating ovarian cancer	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if *BRCA*1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Trifluridine-tipiracil hydrochloride oral combination (TAS-102) for treatment-refractory metastatic colorectal cancer	Patients with metastatic colorectal cancer (mCRC) that is refractory to standard chemotherapies	Although many patients have mCRC that responds to 1st-line chemotherapy, disease ultimately progresses in the vast majority of patients. Current 2nd-line treatments for mCRC are of limited efficacy, and the median overall survival of these patients is less than 1 year. TAS-102 is a combination antitumor agent made up of trifluridine (FTD) and tipiracil hydrochloride (TPI). FTD is deoxyuridine nucleoside analogue that can be incorporated into DNA and has a -CF_3 group bound to the uridine, which prevents base pairing between complementary DNA strands. TPI prevents FTD degradation by inhibiting thymidine phosphorylase; therefore, a sustained concentration of FTD blocks DNA replication in cancer cells. The FTD and TPI combination purportedly targets colorectal cancer tumors that are refractory to multiple chemotherapies (i.e., fluoropyrimidines, irinotecan, oxaliplatin, bevacizumab, anti-EGFR targeted therapy, 5-FU). In clinical trials, TAS-102 is taken orally, twice daily, on days 1–5 and 8–12 of a 28-day cycle, at a dose of 35 mg/m^2. Taiho Oncology, Inc., Princeton, NJ, a unit of Otsuka Holdings Co., Ltd., Tokyo, Japan Phase III trials (RECOURSE and TERRA) ongoing; Oct 2014, FDA granted fast-track status; Feb 2015, company announced FDA accepted new drug application for review; drug also is being tested for treating small cell lung cancer	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab [ramucirumab; in development]) Antimetabolites (e.g., 5-fluorouracil, capecitabine) EGFR antibodies (e.g., cetuximab, panitumumab) FOLFIRI (leucovorin, 5-fluorouracil, irinotecan) FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin) Multikinase inhibitors (e.g., regorafenib) Platinum-based agents (e.g., oxaliplatin) Topoisomerase inhibitors (e.g., irinotecan)	Increased overall survival Increased progression-free survival Improved tolerability Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ulixertinib for treatment of *BRAF* mutation–positive melanoma	Patients in whom stage IIb/IV *BRAF* mutation–positive melanoma has been diagnosed	Patients with *BRAF* mutation–positive melanoma frequently demonstrate a response to *BRAF* inhibitor drugs; however, these responses are typically short-lived. ERK is a kinase that functions downstream of *BRAF* in the pathway driving melanoma pathogenesis in *BRAF* mutation–positive melanoma. Dual inhibition of *BRAF* and ERK may increase the duration of response to agents targeting the RAS/RAF/MEK/ERK pathway. Ulixertinib (BVD-523) is a small molecule, a potent inhibitor of ERK; it purportedly has cytotoxic activity in cancer cells that rely on ERK for growth and survival. In the phase I part of a clinical trial, the maximum tolerated dose of ulixertinib is 600 mg, administered orally, twice a day. BioMed Valley Discoveries, Inc., Kansas City, MO Phase I/II trial ongoing; Jun 2013, FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, temozolomide) *BRAF* inhibitors (e.g., dabrafenib, vemurafenib) Immunotherapy (e.g., ipilimumab, nivolumab, pembrolizumab) MEK inhibitors (e.g., trametinib [cobimetinib; in development]) Platinum-based agents (e.g., carboplatin) Taxane agents (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Veliparib for treatment of advanced or metastatic squamous nonsmall cell lung cancer	Previously untreated patients in whom advanced or metastatic squamous nonsmall cell lung cancer (NSCLC) has been diagnosed	The 5-year survival rate for patients with advanced NSCLC is less than 15%, and patients whose disease progresses after 1st-line chemotherapy have few treatment options. Veliparib (ABT-888) is a small-molecule inhibitor of poly adenosine diphosphate-ribose polymerase (PARP), an enzyme involved in DNA repair. By inhibiting PARP's DNA repair, veliparib may potentiate the anticancer activity of cytotoxic chemotherapy drugs whose mechanism of action induces DNA damage. In a phase III trial, veliparib is being tested at an unspecified oral dosage in combination with the platinum chemotherapy agent carboplatin and the taxane paclitaxel. AbbVie, North Chicago, IL Phase III trial ongoing	Chemotherapy with 1 or more of the following: ALK inhibitors if *ALK*-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) *EGFR* inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased complete response rate Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Veliparib for treatment of breast cancer	Patients with early stage, triple-negative breast cancer or locally advanced/metastatic HER2-negative, *BRCA* mutation-positive breast cancer	Triple-negative breast cancer (i.e., low expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2) is not amenable to endocrine therapy or treatment with any of the targeted agents developed for breast cancer, and treatment presents a significant clinical challenge. Veliparib (ABT-888) is a small-molecule inhibitor of poly adenosine diphosphate-ribose polymerase (PARP), an enzyme involved in DNA repair. By inhibiting PARP's DNA repair, veliparib may potentiate the anti-cancer activity of cytotoxic chemotherapy drugs whose mechanism of action involves inducing DNA damage. Additionally, PARP inhibition may exhibit synthetic lethality with cells harboring loss-of-function mutations in the *BRCA1* gene (a breast cancer predisposition gene that is also involved in DNA repair), and triple-negative breast cancers frequently harbor such mutations. Testing for BRCA mutation status will require use of companion diagnostic test. Veliparib is an orally administered medication. In a phase III trial in the neoadjuvant setting for patients with triple-negative breast cancer, veliparib is being tested at an unspecified dosage in combination with the platinum chemotherapy agent carboplatin and the taxane paclitaxel followed by doxorubicin plus cyclophosphamide. In a phase III trial in the metastatic setting for patients with *BRCA* mutation-positive breast cancer, veliparib is being tested in combination with carboplatin and paclitaxel. AbbVie, North Chicago, IL Phase III trials ongoing; AbbVie has partnered with Myriad Genetics, Inc. (Salt Lake City, UT), to use Myriad's BRACAnalysis test as the companion diagnostic test for veliparib	Combination or single agent chemotherapy with 1 of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine) PARP inhibitors (e.g., BMN 673, niraparib, olaparib [under development]) Taxanes (e.g., docetaxel, paclitaxel)	Increased overall survival Increased complete response rate Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Venetoclax for treatment of chronic lymphocytic leukemia	Patients with recurrent or refractory chronic lymphocytic leukemia (CLL) who have undergone at least 1 chemotherapy	Ability to avoid programmed cell death (i.e., apoptosis) is a hallmark of cancer. In certain malignancies, this trait is thought to be mediated by the anti-apoptotic protein Bcl-2. Because of this, inhibition of Bcl-2 is a promising target in treating various cancers, including CLL. Venetoclax (ABT-199) is a small-molecule inhibitor of Bcl-2 that purportedly leads to apoptosis in the malignant B-cells of CLL. In an ongoing phase III trial, venetoclax is being given at a daily, oral dose of 400 mg, in combination with chemoimmunotherapy consisting of rituximab and bendamustine. AbbVie, North Chicago, IL, in collaboration with F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trial ongoing; 2012, FDA granted orphan drug status; May 2015, FDA granted breakthrough therapy status for treating patients who have recurrent/refractory CLL with a 17p deletion	Ibrutinib Idelalisib Ofatumumab Various chemoimmunotherapy regimens, including rituximab plus bendamustine	Increased overall survival Increased progression-free survival Improved quality of life
Vesigenurtacel-L for treatment of nonmuscle-invasive bladder cancer	Patients with nonmuscle-invasive bladder cancer who have undergone transurethral resection of bladder tumor (TURBT)	Nonmuscle-invasive bladder cancer has a 5-year survival rate of 85% if detected and treated early. Unfortunately, surgically resected bladder cancers frequently recur and can progress to an advanced stage; in patients with lymph node–positive and/or metastatic disease, the survival rate decreases to 14%. A need exists for interventions that can prevent the recurrence of bladder cancer after it has been surgically resected. Vesigenurtacel-L (HS-410) is based on immune pan antigen cytotoxic therapy (imPACT), in which bladder cancer cells are modified to express antigens that are normally overexpressed in patients with bladder cancer. After vesigenurtacel-L is injected into patients, the cells purportedly activate a cytotoxic T cell response against cancer cells, thus preventing disease recurrence after TURBT. In clinical trials, patients receive weekly vesigenurtacel-L inoculations containing $1x10^7$ cells. For the 1st 6 weeks, inoculations are given in combination with bacillus Calmette-Guérin (BCG), followed by 6 weeks without BCG, and finally 3 weeks again in combination with BCG. Heat Biologics, Inc., Durham, NC Phase I/II trial (HS-410-101) ongoing; Mar 2015, FDA granted fast-track status	Surgery (cystectomy) Radiotherapy combined with chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Platinum-based agents (e.g., cisplatin) Taxanes (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Volasertib for treatment of acute myeloid leukemia	Elderly patients in whom acute myeloid leukemia (AML) has been diagnosed	Many patients with AML who are aged 65 years or older are unable to tolerate high-intensity induction chemotherapies; therefore, the disease remission rate in this patient population is relatively low. Volasertib (BI 6727) inhibits pololike kinase (PLK), which plays a key role in cell cycle progression. Inhibiting PLK purportedly leads to cell-cycle arrest and cell death in rapidly dividing cells. Volasertib is administered intravenously. In clinical trials, it is being used in combination with low-dose cytarabine. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trial ongoing; Apr 2014, FDA granted orphan drug status and Sept 2013, granted breakthrough therapy status	5-azacytidine Decitabine Low-dose cytarabine	Increased overall survival Increased progression-free survival Improved quality of life
Vosaroxin (Qinprezo) for treatment of recurrent or refractory acute myeloid leukemia	Patients in whom acute myeloid leukemia (AML) has been diagnosed	For patients with recurrent AML, the only potentially curative treatment is a hematopoietic stem cell transplant; however, in some patients, disease relapses after transplantation or they are not candidates or cannot find a suitable donor. Vosaroxin (Qinprezo™) is a 1st-in-class, anticancer quinolone derivative. During normal topoisomerase activity, the enzyme cleaves and then re-ligates double-strand breaks to maintain DNA topology during replication; vosaroxin purportedly intercalates into DNA and inhibits topoisomerase II activity, which results in replication-dependent, site-selective, double-strand breaks in DNA leading to G2 arrest and apoptosis. Unlike other topoisomerase II inhibitors, vosaroxin is not a P-glycoprotein substrate, evading the most common mechanism for multidrug resistance. It may be used in combination with cytarabine. It is given as an intravenous infusion, 90 mg/m^2 for days 1 and 4 for induction and 70 mg/m^2 for all other cycles. Sunesis Pharmaceuticals, Inc., South San Francisco, CA Phase III trial ongoing	Chemotherapy including 1 or more of the following: Anthracycline Cladribine Clofarabine Cytarabine Etoposide Fludarabine Granulocyte colony-stimulating factor Idarubicin Mitoxantrone	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Xilonix for treatment of cancer-related cachexia	Patients in whom cancer-related cachexia has been diagnosed	Although a number of treatments have been developed to address cancer-related cachexia (wasting of skeletal muscle mass), many patients do not respond to these treatment options. Cancer-related cachexia may limit patients' ability to tolerate further treatment and/or directly affect survival. Cancer-related cachexia is caused by metabolic and neurochemical alterations in the body that lead to the wasting of skeletal muscle mass. Although the mechanism by which tumors induce cachexia is poorly understood, 1 hypothesis states that interleukin-1-alpha–mediated pro-inflammatory signals to the central nervous system may induce systemic cachexia. Xilonix™ (MABp1) is a monoclonal antibody that acts as an interleukin-1-alpha antagonist, potentially disrupting this pro-inflammatory signaling. It is administered intravenously. XBiotech, Austin, TX Phase III trials ongoing; FDA granted fast-track status	Appetite stimulants (e.g., cannabinoids, corticosteroids, cyproheptadine, progesterone derivatives) Dietary counseling Melanocortin antagonists Metabolic disturbance modulators (e.g., anti-cytokine antibodies, pentoxifylline, thalidomide)	Increased body weight Increased lean body mass Increased muscle strength Increased overall survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Zoptarelin doxorubicin for treatment of endometrial cancer	Patients in whom endometrial cancer has been diagnosed	Cytotoxic chemotherapy such as doxorubicin has proven anticancer effects; however, efficacy is inhibited by dose-limiting toxicities on normal tissues. Zoptarelin doxorubicin (AEZS-108) is a conjugate of a luteinizing hormone–releasing hormone (LHRH) analogue and doxorubicin. The LHRH analogue targets cells that express the LHRH receptor, which includes the cells of many cancer types. Compared with naked doxorubicin, zoptarelin doxorubicin is purported to preferentially target LHRH receptor–expressing cells, potentially sparing normal tissue from the toxic effects of the conjugated chemotherapeutic agent. In trials, the agent is being given as an intravenous infusion, 267 mg/m^2, every 3 weeks, for up to 9 treatment cycles. AEterna Zentaris, Inc., Quebec, Quebec, Canada, in partnership with the German branch of Ergomed, plc, Guilford, UK Phase III trial (ZoptEC) ongoing; additional trials are testing zoptarelin doxorubicin for treating prostate and breast cancer	Chemotherapy with 1 or more of the following: Aromatase inhibitors (e.g., anastrozole, exemestane, letrozole) Estrogen inhibitors (e.g., tamoxifen, toremifene) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., doxorubicin HCl liposome injection, doxorubicin) Synthetic progestogens (e.g., progestin)	Increased overall survival Increased progression-free survival Improved quality of life

Table 3. AHRQ Priority Condition: 03 Cardiovascular Disease: 53 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
3-D printed endograft for treatment of abdominal aortic aneurysms	Patients in whom abdominal aortic aneurysms (AAAs) have been diagnosed	Every year in the U.S., more than 150,000 patients are diagnosed with AAAs. A ruptured aneurysm can lead to significant blood loss and death. Surgical options to treat AAAs include open abdominal and minimally invasive endovascular graft surgeries. The relatively large size of available stent systems for endovascular repair has made patients with small or unique vessel anatomy ineligible for endovascular repair of AAAs. Approximately 30% to 40% of patients who undergo repair surgery are unsuitable for proper graft placement and anchoring. 3-dimensional (3-D) printing has been used to create an implantable, customized implant based on a computed tomographic image of individual patient anatomy. According to the manufacturer, proprietary technology is used to improve graft placement and anchoring, thus minimizing leaks and device migration. Aortica Corp., Kirkland, WA FDA investigational device exemption pivotal trial ongoing	Endovascular stent grafts Open surgical repair	Reduced leakage Reduced rupture Decreased mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Active compression-decompression device (ResQPump) for improved cardiopulmonary resuscitation	Adult patients who have experienced out-of-hospital, nontraumatic cardiac arrest	According to the U.S. Centers for Disease Control and Prevention (CDC), approximately 300,000 people each year experience cardiac arrest requiring cardiopulmonary resuscitation (CPR) outside of a hospital setting. Although CPR can save lives, the procedure requires emergency medical service (EMS) responders to perform manual compression until a patient is able to be resuscitated or administered other life-saving techniques, such as defibrillation. The ResQCPR System is intended to assist EMS personnel in performing CPR on adults experiencing out-of-hospital, nontraumatic cardiac arrest. It consists of 2 devices, the ResQPump Active Compression Decompression CPR Device and the ResQPod 16.0 Impedance Threshold Device. The ResQPump consists of a double-grip handle that attaches to the patient's chest with a suction cup. EMS responders can push to deliver compressions and lift for decompressions. The ResQPump also includes a pressure gauge and timing mechanism which can assist the responder with delivering the recommended compression depth and rate. The ResQPod device impedes airflow into the chest during decompression, which is intended to increase blood flow to the heart and potentially improve overall circulation compared to standard CPR. This device can be fitted onto a rescue face mask or breathing tube. Advanced Circulatory Systems, Inc., Roseville, MN FDA approved Mar 2015	CPR	Increased survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Alferminogene tadenovec gene therapy (Generx) for chronic stable angina pectoris	Patients in whom coronary artery disease and stable angina have been diagnosed	Angina pectoris is a debilitating manifestation of coronary artery disease. According to 2007 American Heart Association statistics, more than 8.9 million people in the U.S. live with chronic angina pectoris, and angina is diagnosed in an estimated additional 400,000 Americans each year. Treatment strategies include surgical revascularization or pharmacologic agents. Many patients who are not suitable candidates for revascularization procedures experience chronic angina despite pharmacologic treatment. Alferminogene tadenovec gene therapy (Generx®) is a DNA-based angiogenic growth factor (adenovirus 5 fibroblast growth factor-4 [Ad5FGF-4]) product that purportedly increases myocardial blood flow by developing collateral blood vessels around the heart to try to relieve angina symptoms. To administer alferminogene tadenovec, an interventional cardiologist uses balloon angioplasty to temporarily occlude a coronary artery and produce transient ischemia while infusing the gene therapy product along with nitroglycerin. The company states that this facilitates the “transfection of Generx into heart cells by several mechanisms, including enhanced penetration through microvessel endothelium and upregulation of Coxsackie-Adenovirus Receptor.” The intended delivery of the gene therapy is 40% to the right coronary circulation and 60% to the left coronary circulation. Taxus Cardium Pharmaceuticals Group, Inc., San Diego, CA Phase III trial ongoing (ASPIRE)	Angioplasty Beta blockers Calcium channel blockers Coronary bypass surgery Coronary stents Long-acting nitrates Ranolazine	Decreased angina Fewer cardiovascular events Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Alirocumab (Praluent) for treatment of statin-resistant hypercholesterol-emia	Patients in whom hypercholesterolemia has been diagnosed	In the U.S., more than 34 million people have hypercholesterolemia. Treatments include lifestyle changes, such as diet and exercise, and pharmacotherapy. Alirocumab represents a new mechanism of action for hypercholesterolemia treatment. It is a monoclonal antibody that targets PCSK9 (proprotein convertase subtilisin/kexin type 9) to inhibit its activity. PCSK9 is a protein involved in regulating circulating low-density lipoprotein (LDL) levels through degradation of the LDL receptor; therefore, pharmacologic inhibition of PCSK9 might decrease circulating LDL levels. In clinical trials, alirocumab is being administered subcutaneously every other week, in addition to daily oral statin therapy. Sanofi, Paris, France, and Regeneron Pharmaceuticals, Inc., Tarrytown, NY FDA approved alirocumab Jul 24, 2015, “for use in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or patients with clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL cholesterol.”	Pharmacotherapy (e.g., statins)	Improved lipid levels Reduced morbidity Reduced mortality
Anacetrapib for lipid management in coronary artery disease	Patients in whom coronary artery disease (CAD) has been diagnosed or who are at risk of developing the disease	According to the American Heart Association, in the U.S., more than 16 million adults are living with CAD and more than 1 million new cases are diagnosed each year. Treatments include lifestyle modifications, pharmacotherapies, and surgery. Anacetrapib is a cholesterol ester transfer protein inhibitor intended to raise high-density lipoproteins by 100% and reduce low-density lipoproteins, thereby improving lipid profiles. Its precursor was torcetrapib, whose development was stopped because of a high rate of cardiovascular adverse events. Anacetrapib has been reported to not raise blood pressure of subjects in clinical trials thus far; it is given 100 mg once daily for 76 weeks in addition to a statin. Ongoing clinical trials are evaluating anacetrapib for modifying cholesterol levels in addition to established statin therapy. Merck & Co., Inc., Whitehouse Station, NJ Phase III trials ongoing for indications including CAD, hypercholesterolemia, and heterozygous familial hypercholesterolemia	Lifestyle changes Pharmacotherapy (e.g., statins)	Improved cardiovascular outcomes Reduced risk of heart attack

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Andexanet alfa for reversal of factor Xa inhibitors	Patients experiencing a major bleed from factor Xa inhibitor anticoagulant therapy who need reversal to stop bleeding	Factor Xa inhibitors are prescribed to millions of patients in the U.S. for both treating and preventing deep vein thrombosis (DVT), pulmonary embolism (PE), and stroke from atrial fibrillation. This class of anticoagulant drugs directly binds to and inhibits factor Xa without having an effect on other components of the coagulation cascade. Patients treated with factor Xa inhibitors may experience a major bleeding event that could result in a need for emergency surgery. Andexanet alfa is a modified factor Xa molecule intended to directly reverse major bleeding in patients treated with factor Xa inhibitors. Andexanet alfa purportedly acts as a factor Xa decoy by sequestering factor Xa inhibitors in the blood, thus restoring normal hemostatic processes. In clinical trials, it has been intravenously administered at a dose of 400 mg, followed by a continuous infusion of 480 mg at 4 mg/minute for 120 minutes. Portola Pharmaceuticals, Inc., South San Francisco, CA, in collaboration with Bayer AG, Leverkusen, Germany, and the Janssen Pharmaceuticals unit of Johnson & Johnson, New Brunswick, NJ Phase IV trial ongoing; FDA granted breakthrough therapy status; the companies plan to file a biologics license application in 2015 under an accelerated approval pathway; FDA granted orphan drug status Feb 2015	Transfusion	Reduced major bleeding

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous bone marrow stem cells (C-Cure) for treatment of heart failure	Patients in whom severe heart failure (HF) has been diagnosed	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have HF. About 50% of people with HF die within 5 years of diagnosis. Projections suggest that HF prevalence will increase 25% from 2013 to 2030 and that costs will increase 120%. HF treatments depend on disease stage. No treatments are available to repair heart tissue and reverse HF. Options to treat end-stage HF include ventricular assist device implants, total artificial heart implant, or a heart transplant. C-Cure® consists of stem cells derived from a patient's bone marrow and cultured in a proprietary laboratory process to become cardiac lineage cells intended to improve heart function when injected into the patient's heart. The company states that the process "reprograms" cells so they become heart precursor cells with "the aim of replicating the normal process of cardiac development in the embryo" and purportedly stimulating heart-tissue repair. The company has developed a proprietary catheter called C-Cath®ez® to deliver the processed cells to the patient. Celyad S.A., formerly Cardio3 BioSciences, S.A., Mont-Saint-Guibert, Belgium Phase III trial (CHART-1) ongoing; phase III CHART-2 registered, but not yet recruiting	Angiotensin-converting enzyme inhibitors Angiotensin II receptor blockers Beta blockers Digoxin Diuretics Heart transplantation Minimally invasive heart surgery Ventricular assist devices	Increased left ventricular ejection fraction and other heart-function outcomes Improved activities of daily living Increased survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bucindolol hydrochloride (Gencaro) for treatment of atrial fibrillation	Patients in whom atrial fibrillation (AF) has been diagnosed	AF has a prevalence of more than 2.7 million people in the U.S. and is associated with 15% to 25% of all strokes. Long-term anticoagulant therapy is the most effective stroke-prevention strategy in patients with AF; however, contraindications, bleeding complications, and patient adherence to therapy make this strategy difficult. Bucindolol hydrochloride (Gencaro) is a pharmacologically unique beta blocker and mild vasodilator being investigated for treating AF. According to the manufacturer, bucindolol hydrochloride is considered part of the beta blocker class because it blocks beta-1 and beta-2 receptors in the heart. This action purportedly prevents these receptors from binding with other, receptor-activating molecules. In a planned clinical trial, the manufacturer intends to enroll patients who respond favorably to bucindolol hydrochloride because they have a genetic variant of the beta-1 cardiac receptor. In clinical trials, the drug is being administered as a twice-daily capsule, in doses of 6.25, 12.5, 25, 50, or 100 mg. A companion diagnostic genetic test is also in development. ARCA Biopharma, Inc., Broomfield, CO Phase IIb/III GENETIC-AF trial ongoing; Jan 2014, FDA accepted investigational device exemption application for trial for a companion diagnostic test to detect common genetic variations associated with AF; Apr 2015, FDA granted fast-track status	Amiodarone (Cordarone®, Pacerone®) Dronedarone (Multaq®) Propafenone (Rythmol®) Sotalol (Betapace®) Dofetilide (Tikosyn®) Flecainide (Tambocor™)	Improved cardiac function Reduced AF

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cardiac contractility modulation (Optimizer III Implantable Pulse Generator system) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have HF. About 50% of people with HF die within 5 years of diagnosis. Projections suggest that the prevalence of HF will increase 25% from 2013 to 2030 and that costs will increase 120%. Optimizer III™ system is a device implant intended to treat patients who have New York Heart Association Class III HF and an ejection fraction or 25% to 45%. These patients are unable to achieve desired optimal medical therapy goals and are not candidates for cardiac resynchronization therapy. According to the manufacturer, the device is "typically implanted in the right pectoral region and is connected to 3 standard pacemaker leads that are threaded through veins into the right side of the heart. 1 lead is used to sense atrial activity, and the other 2 are used to sense ventricular activity…." It purportedly delivers nonexcitatory electrical signals during the absolute refractory period (between beats) to produce more forceful contraction during the heartbeat. It is intended as an adjunct to optimal medical therapy. The system also uses the OMNI Programmer System, a portable programmer intended to enable medical personnel to tailor Optimizer signal parameters to individual patient needs. It uses a battery that can be charged in the patient's home. Impulse Dynamics, NV, Willemstad, Netherlands Antilles Phase II/III FIX-HF-5B trial ongoing; CE marked	Angiotensin-converting enzyme inhibitors Angiotensin II receptor blockers Beta blockers Digoxin Diuretics Heart transplantation Minimally invasive heart surgery Ventricular assist devices	Delayed progression of HF Delayed need for ventricular assist devices Improved 6-minute walk test Improved symptom relief Reduced hospitalizations Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Catheter-based ventricular restoration implant (Parachute) for treatment of heart failure	Patients in whom ischemic heart failure (HF) has been diagnosed	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have HF. About 50% of people with HF die within 5 years of diagnosis. Projections suggest that the prevalence of HF will increase 25% from 2013 to 2030 and that costs will increase 120%. Treatments for HF depend on the stage of disease. Left ventricular remodeling (enlargement) occurs in many patients who experience a myocardial infarction, resulting in decreased cardiac output, fatigue, and shortness of breath. The unaffected portion of the heart compensates for this output loss and becomes overloaded. The Parachute™ Ventricular Partitioning Device purportedly has the potential to be the 1st minimally invasive, catheter-based treatment for ischemic HF. According to its manufacturer, the Parachute implant is deployed in the left ventricle to partition the damaged portion of the heart from the functional heart segment, potentially decreasing the left ventricle's volume and restoring its geometry and function. According to the company, the procedure is performed with the patient under conscious sedation in a catheterization lab and takes about 75 minutes. CardioKinetix, Inc., Menlo Park, CA Phase III trials ongoing (PARACHUTE IV pivotal trial in U.S.; other trials ongoing in Europe and Asia); Oct. 2012, received CE mark	Angiotensin-converting enzyme inhibitors Angiotensin II receptor blockers Beta blockers Digoxin Diuretics Heart transplantation Minimally invasive heart surgery Ventricular assist devices	Improved HF symptoms Increased cardiac output Increased survival Reduced left ventricular volume Reduced morbidity

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Central arteriovenous anastomosis (ROX coupler) for treatment-resistant hypertension	Patients in whom uncontrolled hypertension has been diagnosed	Many pharmacotherapies are available for treating hypertension, and typically 3 types of drugs are used in conjunction to try to lower blood pressure. Yet, many cases of hypertension are not controlled with these interventions, and because such treatment-resistant hypertension is associated with high morbidity (e.g., end-organ damage) and mortality, novel interventions are warranted. Central arteriovenous anastomosis with the ROX coupler is a minimally invasive, catheter-based procedure purported to treat patients who have uncontrolled hypertension. During the procedure, surgeons create an anastomosis (connection) between the distal external iliac vein and artery. A small, metal alloy coupler is implanted to establish a connection that allows some blood flow between the vessels, thus purportedly reducing peripheral vascular resistance and lowering overall blood pressure. Surgery is performed in a cardiac catheterization laboratory without general anesthesia, and takes about 40 minutes. ROX Medical, San Clemente, CA Phase III trial ongoing	Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers) Renal artery stents	Controlled hypertension with fewer or no medications Reduced rates of blindness, heart attack, kidney failure, and stroke
Cerebral protection device (TriGuard) for prevention of stroke during transcatheter aortic valve implantation	Patients undergoing transcatheter aortic valve implantation or replacement	Aortic stenosis occurs in about 4% to 5% of people aged 75 years or older, and an estimated 300,000 people have the condition worldwide. Causes of severe aortic stenosis include buildup of calcium deposits on the aortic valve, prior radiation therapy, certain medications, and a history of rheumatic fever. An estimated 30% of patients with symptomatic, severe aortic stenosis are not suitable candidates for open-heart valve implantation but may be candidates for a less invasive option, transcatheter aortic valve implantation. However, this procedure is associated with a risk of embolic debris being released during the procedure and causing a stroke or death. The TriGuard™ cerebral protection device is intended to deflect embolic debris during endovascular procedures. It consists of a self-positioning nitinol frame and mesh purported to provide full coverage to all brain areas. Using a 9-French–diameter catheter, the filter is advanced via femoral access into the aortic arch where it deflects embolic debris from entering the brachiocephalic artery, left common carotid artery, and the left subclavian artery. After completing the procedure, clinicians recapture the filter inside the catheter and remove it from the patient. Keystone Heart, Ltd., Caesarea Business Park, Israel Phase II/III trial (REFLECT) ongoing; Sept 2013, CE marked	Embolic protection devices (e.g., balloons, baskets, filters)	Increased embolic protection

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cerebral protection system (Sentinel) for prevention of stroke during transcatheter aortic valve implantation	Patients undergoing transcatheter aortic valve implantation or replacement	Aortic stenosis occurs in about 4% to 5% of people aged 75 years or older, and an estimated 300,000 people have the condition worldwide. Causes of severe aortic stenosis include buildup of calcium deposits on the aortic valve, prior radiation therapy, certain medications, and a history of rheumatic fever. An estimated 30% of patients with symptomatic, severe aortic stenosis are not suitable candidates for open-heart valve implantation but may be candidates for the less-invasive transcatheter aortic valve implantation procedure. However, this approach is associated with a risk of embolic debris being released during the procedure and causing a stroke or death. The Sentinel™ Cerebral Protection System is a device intended to capture and remove embolic debris during endovascular procedures. It consists of a handle assembly, articulating sheath, and 2 deployable filters. Before valve implantation, the filters are advanced via radial approach. Using a 6-French–diameter catheter, the proximal filter is delivered to the brachiocephalic artery, and then a distal filter is delivered to the left common carotid artery. The procedure can be performed with each filter in place to capture any debris that may enter cerebral circulation. After completing the procedure, the clinician recaptures both filters inside the catheter and removes them from the patient. Claret Medical, Inc., Santa Rosa, CA Pivotal investigational device exemption trial (SENTINEL) ongoing; received CE mark	Embolic protection devices (e.g., balloons, baskets, filters)	Increased embolic protection

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Coronary sinus implant (Reducer) for treatment-refractory angina pectoris	Patients in whom chronic angina pectoris has been diagnosed	Angina pectoris is a manifestation of coronary artery disease. According to 2007 American Heart Association statistics, more than 8.9 million people in the U.S. live with chronic angina pectoris, and angina is diagnosed in an estimated additional 400,000 Americans each year. Treatment strategies include surgical revascularization or pharmacologic agents. Many patients who are not suitable candidates for revascularization procedures experience chronic angina despite pharmacologic treatment. Device implantation with the Neovasc Reducer is a minimally invasive, catheter-based procedure purported to treat patients with chronic or treatment-refractory angina. Surgeons implant the device in the patient's coronary sinus using a procedure similar to coronary artery stenting. The device purportedly modulates blood outflow from the heart through the coronary sinus, redistributing oxygenated blood flow to ischemic areas of the heart. Neovasc, Inc., Vancouver, British Columbia, Canada Phase II trial completed and company announced in Feb 2015 it had raised funds for a phase III trial; CE marked	Angioplasty Beta blockers Calcium channel blockers Coronary bypass surgery Coronary stents Long-acting nitrates Ranolazine	Decreased angina Fewer cardiovascular events Increased exercise tolerance Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Electrical stimulation of carotid baroreceptors (Barostim neo System) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have HF. About 50% of people with HF die within 5 years of diagnosis. Projections suggest that the prevalence of HF will increase 25% from 2013 to 2030 and that costs will increase 120%. Baroreceptors in the aortic arch and the carotid sinuses are fibers that act as natural blood pressure sensors and control nervous system activity in the heart, kidneys, and peripheral blood vessels. When baroreceptors are stimulated by an increase in blood pressure, sympathetic efferent nerves are inhibited. Signaling by sympathetic efferent nerves typically increases blood pressure through its effects on cardiac, renal, and vasomotor targets. Therefore, blocking sympathetic nervous system activity in response to elevated blood pressure, combined with a simultaneous increase in parasympathetic activity, can act as a negative-feedback loop to stabilize blood pressure by reducing heart rate and fluid volume and dilating arteries. Researchers are investigating baroreceptor stimulation for treating HF. The Neo System has 1 carotid sinus lead, and implantation requires only a unilateral incision. The company purports that this and a smaller lead design lead to a shorter procedure time and a greater patient safety profile than its 1st-generation Rheos system. In 2 trials, the system is being implanted in adult patients with left ventricular ejection fraction of 35% or less. CVRx, Inc., Minneapolis, MN U.S. pivotal trial ongoing; Sept 2014, CE marked for treating heart failure; Aug 2011, CE marked for treating uncontrolled hypertension; Dec 2014, CE marked as MR conditional for use in patients undergoing an MRI	Angiotensin-converting enzyme inhibitors Angiotensin II receptor blockers Beta blockers Digoxin Diuretics Heart transplantation Minimally invasive heart surgery Ventricular assist devices	Improved left ventricular ejection fraction Fewer cardiovascular events Improved quality of life
Evacetrapib for treatment of high-risk cardiovascular disease	Patients in whom high-risk cardiovascular disease (CVD) has been diagnosed	Despite available treatments, CVD remains the leading cause of mortality worldwide. Evacetrapib (LY2484595) is a cholesteryl ester transfer protein (CETP) inhibitor that is intended to raise functional high-density lipoprotein (HDL) by modulating CETP activity through a mechanism that purportedly differs from other CETP inhibitors in development. It purportedly has effects not only on HDL cholesterol, but also low density lipoprotein (LDL) cholesterol, and cholesterol efflux. In trials, it has been administered orally as a 130 mg tablet once daily, in addition to standard of care. Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing	Bile acid sequestrants Fibrates Niacin Statins	Improved HDL profile Reduced cardiovascular morbidity and mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Evolocumab (Repatha) for treatment of hypercholesterol-emia	Patients in whom familial hypercholesterol-emia or hyperlipidemia has been diagnosed	Despite available therapies, cholesterol levels of some patients with familial hypercholesterolemia or severe hyperlipidemia are not adequately managed, and cardiovascular risk remains high. Reductions in low-density lipoprotein cholesterol (LDL-C) levels are associated with decreased cardiovascular events. Statins are typically used to decrease cardiovascular risk in patients with high LDL-C levels; however, many patients are intolerant to statins or do not achieve a sufficient response. Evolocumab (Repatha™) is a monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9). It purportedly decreases LDL-C levels by increasing the number of LDL receptors at the hepatocellular surface. In clinical trials, evolocumab has been given as subcutaneous injections in doses of 70, 105, or 140 mg, every 2 weeks, or doses of 280, 350, or 420 mg, every 4 weeks. In some trials, it has been given combination with statins. Amgen, Inc., Thousand Oaks, CA Aug 2015, FDA approved as “adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol (LDL-C);” Jul 2015, European Commission granted marketing authorization to treat uncontrolled cholesterol in patients who require additional intensive lowering of LDL-C8 phase III trials ongoing for hyperlipidemia as monotherapy, as combination therapy with statins, and as therapy for familial-related hypercholesterolemia. Several late-phase trials ongoing	Lomitapide (Juxtapid®) Mipomersen (Kynamro®) Statins	Fewer cardiovascular events

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Extra-aortic balloon counter-pulsation heart-assist device (C-Pulse) for treatment of class III or IV heart failure	Patients with New York Heart Association Class III or ambulatory Class IV heart failure (HF)	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have HF. About 50% of people with HF die within 5 years of diagnosis. Projections suggest that the prevalence of HF will increase 25% from 2013 to 2030 and that costs will increase 120%. Treatments for HF depend on the stage of disease. Available implanted devices for HF (e.g., left ventricular-assist devices) contact the patient's blood, elevating the risk of blood clots and stroke. Thus, patients must take daily anticoagulant therapy. The C-Pulse® heart-assist system is an implanted device that does not require taking anticoagulants. It consists of a mechanical balloon cuff that is wrapped around the outside of the aorta during a minimally invasive or full sternotomy procedure. The device is intended to reduce the workload of the left ventricle. The system's driver operates outside the body and is connected to the C-Pulse device. According to the manufacturer, when the balloon inflates, blood flow to the coronary arteries increases, potentially providing additional oxygen to the heart. The company claims that during deflation, the workload required by the left ventricle is reduced. The company also states that the balloon counter-pulsation inflation and deflation is synchronized to the patient's electrocardiogram (similar to a pacemaker). The company cautions that the device is not MRI compatible and that some brands of cell phones have interfered with the C-Pulse driver system. Sunshine Heart, Inc., Eden Prairie, MN Pivotal phase III investigational device exemption trial (COUNTER HF™) ongoing; in Apr 2015, trial enrollment halted per protocol after 4 of 1st 20 patients died; May 2015, FDA allowed trial enrollment to resume after patient deaths judged not device-related; Aug 2015, FDA approved trial protocol change providing that future trial halts will be for device- or procedure-related deaths, not all-cause deaths; CE marked Jul 2012	Angiotensin-converting enzyme inhibitors Angiotensin II receptor blockers Beta blockers Digoxin Diuretics Heart transplantation Minimally invasive heart surgery Ventricular assist devices	Increased cardiac output Increased survival Reduced cardiac workload Reduced risk of stroke or thrombi Decreased morbidity

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Freedom Driver System (portable driver) for Total Artificial Heart as bridge to heart transplantation	Patients with nonreversible biventricular failure who are candidates for heart transplantation	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have heart failure (HF). About 50% of people with HF die within 5 years of diagnosis. Projections suggest that the prevalence of HF will increase 25% from 2013 to 2030 and that costs will increase 120%. The temporary Total Artificial Heart (TAH-t) functions in place of ventricles and valves by pumping blood to both the pulmonary and systemic circulations. This TAH-t is distinguished from earlier devices by its portable driver (Freedom® driver), the system that powers the device and is intended to allow patients to recover and remain at home, rather than remaining hospitalized. The driver weighs 13.5 lb, compared with the 418 lb weight of the hospital-based system. The driver includes 2 onboard batteries and a power adaptor. SynCardia Systems, Inc., Tucson, AZ FDA approved Jun 2014 for clinically stable patients in whom the SynCardia TAH-t is implanted (FDA approved TAH-t in 2004); Health Canada approved May 2011; CE marked Mar 2010; worldwide, as of Jun 2015, 221 patients had received system for out-of-hospital use; Aug 6, 2015, SynCardia Systems sent an Urgent Medical Device Recall letter to customers about replacing the driver because it could have a failure in which the pump stopped working without warning. SynCardia is replacing the drivers with new ones.	TAH-t used with in-hospital driver	Extended survival for patients awaiting heart transplantation Reduced hospitalization costs Restored mobility Improved quality of life
Idarucizumab for reversal of dabigatran-induced anticoagulation	Patients in whom reversal of dabigatran-induced anticoagulation is needed	Dabigatran etexilate mesylate (Pradaxa®) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, to treat deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5–10 days, and to reduce the risk of recurrent DVT and PE. If bleeding occurs from dabigatran, no antidote exists to reverse it. Idarucizumab is a fully humanized antibody fragment being investigated as an antidote for dabigatran etexilate mesylate. In a phase III trial, idarucizumab was shown to completely reverse bleeding with 5 g intravenous administration. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trial ongoing, FDA granted breakthrough therapy status; Mar 2015, the company submitted a biologics licensing application to FDA and also to Health Canada and the European Medicines Agency	Blood transfusion	Reduced major bleeding

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Implantable cardiac monitor (AngelMed Guardian System) for detecting myocardial infarction	Patients at high risk of myocardial infarction (MI)	MI is a leading killer of both men and women in the U.S. and the mean time from MI symptom onset to arrival at a hospital is reported to be about 3 hours, even for people who have had a previous heart attack. Patients who have had 1 MI are often at high risk of another. Early treatment can prevent or limit damage to the heart muscle. Preventive measures are aimed at lowering risk factors for coronary artery disease. The AngelMed Guardian® system is an implantable cardiac device intended to detect rapid ST-segment changes that might signal a major cardiac event. When it detects an ST-segment change, the system is intended to alert patients so they can seek immediate medical care. The system alerts the patient through a series of vibrations, sounds, and visual warnings. Angel Medical Systems, Shrewsbury, NJ Phase III ALERTS pivotal trial ongoing with completion expected Jun 2015, but trial information has not been verified since Jul 2013; CE marked Sept 2010	Conventional, external MI detection technologies Patient report Routine physician followup	Earlier detection of impending heart attack Prevented heart damage Increased overall survival
Injectable biopolymer (Algisyl-LVR) for prevention or reversal of advanced heart failure	Patients with advanced heart failure (HF) and an enlarged left ventricle from mitral valve regurgitation, ischemia, dilated cardiomyopathy, or other disorders	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have HF. About 50% of people with HF die within 5 years of diagnosis. Projections suggest that the prevalence of HF will increase 25% from 2013 to 2030 and that costs will increase 120%. Treatments for HF depend on the stage of disease. Algisyl-LVR™ is a polysaccharide biopolymer made from marine algae. It is intended to be injected during open-heart surgery directly into myocardium in the left ventricle; it then thickens, forming gel-like bodies that remain in heart muscle as permanent implants. These implants are intended to thicken heart muscle wall, reduce chamber size, decrease local muscle wall stress, and allow for reshaping of dilated ventricle. The material is inert (i.e., does not interact with the human immune system). Cardio Polymers, now part of LoneStar Heart, Inc., Laguna Hills, CA Phase II/III trial ongoing (Augment-HF); Oct 2014, received CE mark	Drug therapy Ventricular assist devices	Increased left ejection fraction Reduced progression of HF Increased regression of HF Improved cardiovascular outcomes Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ivabradine (Corlanor) for treatment of heart failure	Patients with symptomatic (New York Heart Association class II–IV) chronic heart failure (HF) and systolic dysfunction who are on stable background therapy and in a normal sinus rhythm	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have HF. About 50% of people with HF die within 5 years of diagnosis. Projections suggest that the prevalence of HF will increase 25% from 2013 to 2030 and that costs will increase 120%. Treatments for HF depend on the stage of disease. Ivabradine (Corlanor®) is a selective inhibitor of hyperpolarization-activated cyclic-nucleotide–gated "funny" current involved in pacemaking and responsiveness of the sinoatrial node. It is intended to slow heart rate and allow more time for blood to flow to the heart. Ivabradine is administered orally at a starting dosage of 5 mg twice per day. Servier, Neuilly sur Seine, France (EU manufacturer) Amgen, Inc., Thousand Oaks, CA (U.S. manufacturer) FDA approved Apr 2015 "to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) ≤35 percent, who are in sinus rhythm with resting heart rate ≥70 beats per minute (bpm) and either are on maximally tolerated doses of beta blockers or have a contraindication to beta blocker use." Phase III trials completed and ongoing; approved in European Union in 2005 as Procoralan	Angiotensin-converting enzyme inhibitors Angiotensin II receptor blockers Beta blockers Digoxin Diuretics Heart transplantation Minimally invasive heart surgery Ventricular assist devices	Reduced HF hospitalizations Fewer coronary events Reduced incidence of myocardial infarction Improved quality of life Increased survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Leadless pacemaker (Micra Transcatheter Pacing System) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have HF. About 50% of people with HF die within 5 years of diagnosis. Projections suggest that the prevalence of HF will increase 25% from 2013 to 2030 and that costs will increase 120%. HF treatment depends on the stage of disease. Cardiac resynchronization therapy (CRT) is an approved therapy for patients with HF who have a low ejection fraction and a prolonged QRS duration. Approved CRT pacemakers or defibrillators require that surgeons implant leads, 1 of which is threaded to the left ventricle in a technically challenging process associated with risk of lead failure and infection. Because of these limitations, many patients who are appropriate candidates for CRT do not opt to receive the therapy. The Micra Transcatheter Pacing System (TPS) is a leadless implantable device intended to treat HF. The device is implanted in a catheter-guided procedure directly into the ventricle of the heart. The manufacturer purports that Micra TPS is the world's smallest pacemaker, at a size approximating a "large vitamin" to 10% of the size of a standard pacemaker, but does not report exact dimensions. Medtronic, plc, Dublin, Ireland Phase III trial ongoing	Ventricular pacing with leads	Fewer adverse events Fewer lead complications Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Leadless pacemaker (Nanostim) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have HF. About 50% of people with HF die within 5 years of diagnosis. Projections suggest that the prevalence of HF will increase 25% from 2013 to 2030 and that costs will increase 120%. HF treatments depend on the stage of disease. Cardiac resynchronization therapy (CRT) is an approved therapy for patients with HF who have a low ejection fraction and a prolonged QRS duration. Approved CRT pacemakers or defibrillators require that surgeons implant leads, 1 of which is threaded to the left ventricle in a technically challenging process associated with risk of lead failure and infection. Because of these limitations, many patients who are appropriate candidates for CRT do not opt to receive the therapy. The Nanostim leadless pacemaker may offer an alternative as a leadless implantable device intended to treat HF. The device is implanted via a catheter-guided procedure directly into the ventricle of the heart. Nanostim is purported to be less than 10% the size of traditional pacemakers (41.4 mm) and can also be fully retrieved if necessary. The competing Micra TPS leadless pacemaker in development by Medtronic also purports to be about 10% of the size of a standard pacemaker, but does not report exact dimensions. St. Jude Medical, Inc., St. Paul, MN Phase III U.S. investigational device exemption trial ongoing (LEADLESS II IDE); CE marked in 2013	Ventricular pacing device with leads	Fewer adverse events Fewer lead complications Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Levosimendan (Simdax) for treatment of low cardiac output syndrome	Patients undergoing cardiac surgery who are at risk for low cardiac output syndrome	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have heart failure (HF). About 50% of people with HF die within 5 years of diagnosis. Projections suggest that the prevalence of HF will increase 25% from 2013 to 2030 and that costs will increase 120%. Treatments for HF depend on the stage of HF. Levosimendan (Simdax®) is a calcium sensitizer approved outside the U.S. for treating acute decompensated HF and in clinical trials in the U.S. The drug purportedly increases the heart's sensitivity to calcium, thus increasing myocardial contractility. It is being investigated for treating patients who are at risk for low cardiac output syndrome after cardiac surgery. In clinical trials, levosimendan is being administered intravenously at a dose of 0.2 mcg/kg/minute for the 1st hour, followed by 0.1 mcg/kg/minute for an additional 23 hours. Tenax Therapeutics, Inc., Morrisville, NC Phase III trial (LEVO-CTS) ongoing under FDA special protocol assessment; FDA granted fast-track status; approved in Sweden in 2000 and numerous other countries outside U.S.	Heart transplantation Minimally invasive heart surgery Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics) Ventricular assist devices	Improved left ventricular ejection fraction Reduced cardiovascular events Improved quality of life
Median nerve stimulation for treatment-resistant hypertension	Patients in whom uncontrolled hypertension has been diagnosed	Many pharmacotherapies are available for treating hypertension, and typically 3 types of drugs are used in conjunction to try to lower blood pressure. Yet, many cases of hypertension are not controlled with these interventions, and because such treatment-resistant hypertension is associated with high morbidity (e.g., end-organ damage) and mortality, novel interventions are warranted. Median nerve stimulation with a subcutaneous neuromodulation system (SNS) purportedly affects multiple signal pathways in the brain that control blood pressure. The SNS device is an implantable, coin-sized nerve stimulator intended to lower treatment-resistant hypertension. Clinicians implant SNS devices in both forearms of patients during a 20-minute outpatient procedure. The device uses low-powered electric current to stimulate the median nerve for 30 minutes per week. Valencia Technologies Corp., Valencia, CA Pilot trial completed; phase II trial ongoing in New Zealand, Canada, Taiwan; U.S. trial planned for 2016	Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers) Renal denervation	Controlled hypertension with fewer or no medications Reduced rates of heart attack, kidney failure, and stroke

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mobile unit for treatment of stroke	Patients in whom acute stroke is suspected	Although stroke is a leading cause of death in the U.S., only a single drug, tissue plasminogen activator (tPA), is approved for neuroprotection. It is effective only when administered within a narrow time window of symptom onset, and only 2% to 7% of patients experiencing an acute stroke receive tPA, because most do not present for treatment in time. The mobile stroke unit consists of specially outfitted ambulances that can treat patients with stroke symptoms in an emergency medical services situation. Emergency responders use telemedicine (broadband video) to communicate with in-hospital stroke neurologists to interpret symptoms. An onboard paramedic, critical care nurse, and a computed tomography (CT) technologist perform a neurological evaluation of the patient. When stroke is detected, tPA is immediately administered. Cleveland Clinic, Cleveland, OH University of Texas Health Science Center, Houston Phase II/III trial ongoing	Anticoagulant therapy (e.g., tPA [alteplase], aspirin) as indicated by patient history and time of presentation for care	Improved clot lysis Improved tPA administration time Reduced stroke-related morbidity and mortality
MRI-compatible Implantable cardioverter-defibrillator (Evera MRI ICD system) for treatment of ventricular tachyarrhythmias	Patients with ventricular tachyarrhythmia (VT) who might need MRI scans in the future	VT describes a broad class of abnormal heart rhythms that originate in ventricular tissue and includes ventricular tachycardia (i.e., rapid heartbeat) and ventricular fibrillation (i.e., irregular heartbeat). Implantable cardioverter-defibrillators (ICDs) are the preferred treatment for patients with ventricular fibrillation who are at risk for sudden cardiac death. More than half of patients receiving an ICD are expected to need MRI within a decade of receiving an ICD. Traditionally, MRI use in patients with ICDs has been contraindicated because of the risk of device malfunction caused by the magnetic field. The Evera MRI™ ICD system is intended for patients who may need to undergo MRI in the future. The device is purportedly the 1st ICD that allows full-body MRI scans. The device consists of a tiny computer and battery contained in a titanium case about the size of a pocket watch. Like conventional ICDs, the device is implanted below the clavicle and connected to the heart with transvenous leads. The Evera system includes SureScan® technology, which enables the device to be set to the appropriate mode for an MRI environment. The manufacturer previously developed an MRI-compatible pacemaker (REVO) that uses the same SureScan technology. Medtronic, Inc., Minneapolis, MN Pivotal investigational device exemption trial ongoing	Other implantable defibrillators	Reduced device interactions with MRI

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Neuroprotectant (NA-1) to prevent ischemic stroke–induced disability	Patients in whom acute stroke has been diagnosed by paramedics in the field using a local stroke triage tool	Available stroke treatments are designed to restore blood flow to brain tissue. No agents are available to protect brain cells during periods of ischemia or reperfusion. NA-1 is a 1st-in-class postsynaptic density protein 95 (PSD-95) inhibitor intended for neuroprotection after acute stroke onset. Paramedics administer the drug in the field via a single, 10-minute, intravenous infusion. NoNO Inc., Toronto, Ontario, Canada Phase III trials ongoing	Catheter-based thrombectomy Tissue plasminogen activator (administered intravenously or intra-arterially)	Reduced disability from stroke Improved quality of life
Off-label anakinra interleukin-1 receptor antagonist for prevention of new-onset heart failure after acute myocardial infarction	Patients who have experienced an acute myocardial infarction (MI)	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have heart failure (HF). About 50% of people with HF die within 5 years of diagnosis. HF can occur after an acute MI. Anakinra is a recombinant protein that inhibits interleukin-1 (IL-1) receptors, which may play a role in the inflammatory process. IL-1 blockade with anakinra is being investigated for preventing HF in patients who have experienced acute MI. In clinical trials, anakinra is being administered to patients who have experienced acute “chest pain (or equivalent) with an onset within 12 hours and ECG [electrocardiographic] evidence of ST segment elevation (>1 mm) in 2 or more anatomically contiguous leads” or acute decompensated HF within the previous 24 hours with screening plasma C-reactive protein levels at either >5 mg/L or >2 mg/L (depending on the trial). The drug is administered as a 100 mg, subcutaneous, daily injection for 14 days or a high dose of 100 mg, twice daily, for the 1st 3 days followed by 100 mg daily on days 4–14. Virginia Commonwealth University, Richmond American Heart Association, Dallas, TX National Heart, Lung, and Blood Institute, Bethesda, MD Phase II and III trials ongoing; anakinra (Kineret®) FDA approved in 2001 for treating rheumatoid arthritis; manufacturer does not appear to be sponsoring any of the completed or planned clinical trials	Angiotensin-converting enzyme inhibitors Angiotensin II receptor blockers Beta blockers Diuretics Inotropes Nesiritide Vasodilators	Decreased morbidity Decreased mortality Improved HF symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label methotrexate for treatment of diabetes-associated cardiovascular disease	Patients with type 2 diabetes mellitus (T2DM) or metabolic syndrome who have had a heart attack	Inflammation is thought to play an important role in cardiovascular disease; however, it is not known whether treating inflammation will decrease the risk of cardiovascular disease. Conditions such as T2DM and metabolic syndrome are associated with an enhanced proinflammatory response, and patients with these conditions are at increased risk of experiencing myocardial infarction (MI) and stroke. The anti-inflammatory agent methotrexate is being investigated to prevent stroke, MI recurrence, and cardiovascular death in patients with T2DM or metabolic syndrome who have a history of MI. In a clinical trial, methotrexate is being administered orally, 15–20 mg, weekly, plus 1.0 mg folic acid 6 days per week. National Heart, Lung, and Blood Institute, Bethesda, MD Brigham and Women's Hospital, Boston, MA 389 other institutions and physician practices in U.S. and Canada Phase III trial ongoing	Anticoagulants Antidiabetes agents Antihypertensives Antiplatelets Cholesterol-lowering agents Lifestyle changes	Decreased risk of stroke Decreased risk of MI recurrence Decreased risk of cardiovascular death Improved quality of life
Off-label rituximab for treatment of systemic sclerosis-associated pulmonary artery hypertension	Patients in whom systemic sclerosis-associated pulmonary artery hypertension (SSc-PAH) has been diagnosed	About 1,000 new cases of PAH are diagnosed in the U.S. each year. Women are twice as likely as men to develop the condition. PAH has no cure and can result in heart failure and death. PAH is typically treated with medication, although surgical treatment options may also be considered. 1-year survival for patients with SSc-PAH ranges from 50% to 81%, and treatment is limited to vasodilator therapy. Rituximab, a genetically engineered anti-CD20 antibody for treating B-cell lymphoma, is being investigated for immune mechanisms associated with B-cell dysregulation and pathogenic autoantibody response in SSc-PAH. It is being administered in 2 infusions, 1,000 mg each, 14 days apart. National Institute of Allergy and Infectious Diseases, Bethesda, MD (trial sponsor) Phase II trial ongoing	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalization

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oral prostacyclin analogue (beraprost sodium) for treatment of pulmonary artery hypertension	Patients in whom pulmonary artery hypertension (PAH) has been diagnosed	No cure exists for PAH. Available treatments target symptom reduction but cannot slow or halt disease progression. Beraprost 314*d* modified release (BPS-314*d*-MR) is a single isomer prostacyclin analogue intended to promote vasodilation of the pulmonary arteries. In a clinical trial, it is being given as 1 or 2 oral tablets (15 mcg each), taken 4 times daily in combination with inhaled prostacyclin. Lung Biotechnology PBC unit of United Therapeutics Corp., Silver Spring, MD, and Research Triangle Park, NC Phase III trial ongoing	Calcium channel blockers Endothelin receptor antagonists Inhaled prostacyclin analogues Intravenous or injected prostacyclin analogues Oral prostacyclin analogues Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafil)	Improved symptoms Reduced side effects Reduced need for intravenous prostacyclin therapy Reduced need for surgery due to disease progression
Pediatric cardiac anticoagulation program for preventing stroke from congenital heart defects	Patients with congenital heart defects; program enlists patients from birth through adulthood (oldest reported patient was 55 years old)	Children born with a congenital heart defect are at increased lifetime risk of ischemic stroke due to blood clots. Higher survival rates after premature births in the U.S. increase the risk of congenital heart defects in this population. Children with heart defects may require life-long oral anticoagulation to reduce the risk of blood clots and stroke, and optimizing anticoagulation can be especially complicated in growing children. A clinic that specializes in addressing anticoagulation needs for patients with congenital heart defects may provide a standardized approach to treatment compared with that offered by general family or pediatric practitioners. The dedicated Pediatric Cardiac Anticoagulation Program (CAMP) provides centralized anticoagulation management, initially with warfarin, for pediatric patients with heart defects. The center is a disease-specific resource for families and helps providers devise new strategies to address changing trends in anticoagulation therapy. The center is staffed by an attending primary pediatric cardiologist, a full-time nurse practitioner, and an administrative assistant, with dedicated support from pharmacy and nutrition staff. Boston Children’s Hospital, Boston, MA CAMP in operation more than 5 years	Individualized, office-based anticoagulation management	Improved anticoagulation management

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Percutaneous left atrial appendage ligation (Lariat Suture delivery device) for prevention of atrial fibrillation–associated stroke	Patients in whom nonvalvular atrial fibrillation (AF) has been diagnosed who are increased risk for stroke and systemic embolism	AF has a prevalence of more than 2.7 million people in the U.S. and is associated with 15% to 25% of all strokes. Long-term anticoagulant therapy is the most effective stroke-prevention strategy in patients with AF; however, contraindications, bleeding complications, and patient adherence to therapy make this strategy difficult. Percutaneous ligation of the left atrial appendage (LAA) has been proposed for reducing stroke risk in patients with AF by preventing clots that may have formed in the LAA from entering the systemic circulation. Percutaneous LAA ligation using the Lariat® Suture Delivery Device involves 2 catheters placed inside and outside the heart to facilitate delivery of a snare-like suture loop over the LAA to seal it off from the left atrium. The Lariat LAA ligation procedure is performed in a cardiac catheterization laboratory or hybrid operating room under fluoroscopic and transesophageal echocardiographic guidance with patients under general anesthesia. SentreHEART, Inc., Redwood City, CA Nonphased aMAZE trial ongoing under FDA investigational device exemption status to evaluate Lariat device for percutaneous LAA ligation as adjunctive treatment to pulmonary vein isolation in patients with persistent or longstanding persistent AF; FDA 510(k) cleared in 2009 for “suture placement and knot tying for use in surgical applications where soft tissues are being approximated and/or ligated with a pre-tied polyester suture”; Jul 2015, FDA issued a safety communication citing 45 serious adverse events including 6 deaths through Jun 2015 related to off-label use of Lariat device for percutaneous LAA occlusion	Cryoablation Long-term oral anticoagulation therapy Radiofrequency ablation Watchman® LAA device	Decreased atrial fibrillation–associated stroke occurrence Decreased morbidity

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Percutaneous left atrial appendage occlusion device (Amplatzer cardiac plug) for prevention of atrial fibrillation–associated stroke	Patients in whom nonvalvular atrial fibrillation (AF) has been diagnosed who are increased risk for stroke and systemic embolism	AF has a prevalence of more than 2.7 million people in the U.S. and is associated with 15% to 25% of all strokes. Long-term anticoagulant therapy is the most effective stroke-prevention strategy in patients with AF; however, contraindications, bleeding complications, and patient adherence to therapy make this strategy difficult. The Amplatzer™ device is a permanent implant that is placed in the left atrial appendage (LAA) to prevent strokes in patients with AF. Stroke prevention is accomplished by occluding the LAA opening to prevent clots that have formed in the LAA from entering the systemic circulation. The device purports to differ from other LAA occlusion devices by using a system that seals the LAA neck and provides full cross-sectional orifice coverage. The system also includes a delivery catheter, which is used to access the LAA and serves as a conduit for device delivery. The implantable device has a self-expanding frame with a permeable fabric; once expanded, the fabric covers the atrium-facing surface of the device. Fixation anchors on the frame allow the device to be secured in the LAA. It is implanted in a percutaneous catheterization procedure, using a standard transseptal technique and fluoroscopic guidance. St. Jude Medical, Inc., St. Paul, MN Pivotal trial completed	Cryoablation Lariat® Suture Delivery LAA device (off label) Long-term oral anticoagulation therapy Radiofrequency ablation Watchman® LAA device	Reduced morbidity Reduced stroke risk Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Percutaneous left atrial appendage occlusion device (Watchman) for prevention of atrial fibrillation–associated stroke	Patients in whom nonvalvular atrial fibrillation (AF) has been diagnosed who are increased risk for stroke and systemic embolism	AF has a prevalence of more than 2.7 million people in the U.S. and is associated with 15% to 25% of all strokes. Long-term anticoagulant therapy is the most effective stroke-prevention strategy in patients with AF; however, contraindications, bleeding complications, and patient adherence to therapy make this strategy difficult. The Watchman® device is a permanent implant that is placed in the left atrial appendage (LAA) to prevent strokes in patients with AF. Stroke prevention is accomplished by occluding the LAA opening to prevent clots that may have formed in the LAA from entering the systemic circulation. The implantable device is a component of a 3-part system called the Watchman LAA Closure Technology. This system also includes a delivery catheter and transseptal access sheath, which is used to access the LAA and serves as a conduit for the delivery catheter. The implantable device has a self-expanding nitinol frame with a permeable polyester fabric that is preloaded within the delivery catheter. Once expanded, the fabric covers the atrium-facing surface of the device. Fixation barbs on the frame allow the device to be secured in the LAA. The Watchman device is available in 5 sizes (i.e., 21, 24, 27, 30, and 33 mm). It is implanted in a percutaneous catheterization procedure, using a standard transseptal technique and fluoroscopic guidance. Boston Scientific Corp., Marlborough, MA FDA approved Mar 2015 for reducing the risk of thromboembolism from the LAA in patients with nonvalvular AF who are at increased stroke risk and who “have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.”	Cryoablation Lariat® Suture Delivery Device (off label) Long-term oral anticoagulation therapy Radiofrequency ablation	Reduced morbidity Reduced stroke risk Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Percutaneous left atrial appendage occlusion device (WaveCrest) for prevention of atrial fibrillation–associated stroke	Patients in whom nonvalvular atrial fibrillation (AF) has been diagnosed who are increased risk for stroke and systemic embolism	AF has a prevalence of more than 2.7 million people in the U.S. and is associated with 15% to 25% of all strokes. Long-term anticoagulant therapy is the most effective stroke-prevention strategy in patients with AF; however, contraindications, bleeding complications, and patient adherence to therapy make this strategy difficult. The WaveCrest® left atrial appendage (LAA) occlusion system is a permanent implant that is placed in the LAA to prevent strokes in patients with atrial fibrillation. Stroke prevention is accomplished by occluding the LAA opening to prevent clots that have formed in the LAA from entering the systemic circulation. The system also includes a delivery catheter, which is used to access the LAA and serves as a conduit for implant delivery. The implantable device has a self-expanding frame with a permeable fabric that is preloaded within the delivery catheter. Once expanded, the fabric covers the atrium-facing surface of the device. Fixation anchors on the frame allow the device to be secured in the LAA. The WaveCrest LAA occluder is implanted in a percutaneous catheterization procedure, using a standard transseptal technique and fluoroscopic guidance. Coherex, Inc., Inc., Salt Lake City, UT Pilot trial completed in Europe; U.S. pivotal trial being planned; Sept 2013, CE marked	Cryoablation Lariat® Suture Delivery Device (off label) Long-term oral anticoagulation therapy Radiofrequency ablation Watchman® LAA device	Reduced AF-associated stroke risk

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Portable warm blood perfusion system (Organ Care System) for normothermic heart transplantation	Patients who require heart transplantation	According the U.S. Department of Health and Human Services, nearly 29,000 people in the U.S. received an organ transplant in 2013. Currently, donor hearts being transported for transplantation are stopped and transported on ice, in a cooler (i.e., cold ischemic storage). This method has limits, such as a narrow treatment window, the potential for damage, and the inability to test the heart for function. The Organ Care System (OCS Heart) is intended to keep the heart in a “living” state as it is transported. Through an internal gas supply, internal monitor, and pulsatile pumping system, OCS Heart purportedly provides blood oxygenation and flow, warms the heart as necessary, maintains humidity, and protects the heart from contamination from the time of removal from the donor to implantation in the recipient. The manufacturer states that with this method, the heart may withstand longer periods of time outside of the body and be less vulnerable to damage during transportation, and it can be tested for function and tissue matching. The system includes a compact wireless unit to monitor heart function during transport. TransMedics, Inc., Andover, MA Phase III (PROCEED II) pivotal trial completed Apr 2015, manufacturer announced intention to submit premarket approval application to FDA; additional international phase III trial registered but not yet recruiting; OCS is also in clinical trials for preserving donor livers and lungs	Cold ischemic storage	Increased graft survival Decreased graft dysfunction Increased use of available organs Reduced total cost of care

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Sacubitril/Valsar-tan (Entresto) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have HF. About 50% of people with HF die within 5 years of diagnosis. Projections suggest that HF prevalence will increase 25% from 2013 to 2030 and that costs will increase 120%. HF treatments depend on the stage of disease. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are used to treat stage A (i.e., early stage) disease, but are sometimes ineffective or suboptimally effective. Sacubitril/valsartan (Entresto®; formerly LCZ696) is a 1st-in-class angiotensin receptor neprilysin inhibitor (ARNI) with 2 active ingredients (i.e., the antihypertensive drugs sacubitril and valsartan) that purportedly acts in several ways on the neurohormonal systems of the heart. It reportedly blocks receptors that exert harmful effects while at the same time promoting protective mechanisms. In this way, sacubitril/valsartan is believed to reduce strain on a failing heart so the heart muscle can recover. In clinical trials, it is being administered at twice-daily doses of 50, 100, or 200 mg. Novartis International AG, Basel, Switzerland Jul 2015, FDA approved for treating HF after previously granting fast-track status and priority review; pivotal phase III PARADIGM-HF trial was closed early after recommendation from data monitoring committee in Mar 2014 because of strength of interim results	ACE inhibitors ARBs Beta blockers Diuretics Inotropes Nesiritide Vasodilators	Decreased morbidity Decreased mortality Improved HF symptoms Improved quality of life
Selexipag (Uptravi) for treatment of pulmonary artery hypertension	Patients in whom pulmonary artery hypertension (PAH) has been diagnosed	About 1,000 new cases of PAH are diagnosed in the U.S. each year. Women are twice as likely as men to develop the condition. PAH has no cure and can result in heart failure and death. PAH is typically treated with medication, although surgical treatment options may also be considered. Selexipag (Uptravi) is a 1st-in-class, selective prostacyclin (PGI2) receptor agonist; prostacyclin counteracts the vasoconstrictor and prothrombotic activity of endothelin. Selexipag is a long-acting, nonprostanoid prostacyclin receptor agonist that mimics the actions of endogenous prostacyclin and exerts vasodilating effects. It is administered as an oral tablet, twice daily. Actelion Pharmaceuticals, Ltd., Allschwil, Switzerland Phase III trials ongoing; Dec 2014, company submitted a new drug application to FDA, decision expected by Dec 2015	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Fewer hospitalizations Improved exercise capacity Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Serelaxin (Reasanz) for treatment of acute heart failure	Patients in whom acute heart failure (HF) has been diagnosed	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 in the U.S. have HF. About 50% of people with HF die within 5 years of diagnosis. Projections suggest that the prevalence of HF will increase 25% from 2013 to 2030 and that costs will increase 120%. About 80% of patients admitted to the hospital with acute HF experience dyspnea as a major symptom. In these patients, 50% do not experience relief 24 hours after treatment, and 25% still experience dyspnea at the time of discharge. New therapies for acute HF are needed for faster and more complete symptom resolution. Serelaxin (Reasanz™) is recombinant, human relaxin-2, a naturally occurring vasoactive peptide hormone that regulates hemodynamic adaptations to pregnancy and is being investigated in treating acute HF. In clinical trials, serelaxin (30 mcg/kg) was administered intravenously for 48 hours after acute HF diagnosis. Novartis International AG, Basel, Switzerland Phase III trials ongoing; Jun 2013, FDA granted breakthrough therapy status; May 2014, FDA rejected new drug application citing insufficient evidence of efficacy and issued a complete response letter requiring further efficacy data for approval	Diuretics Vasodilators	Relief of dyspnea Decreased mortality
Stem cell mobilization using granulocyte-colony stimulating factors for treatment of peripheral artery disease	Patients in whom critical limb ischemia (CLI) from peripheral artery disease has been diagnosed	Patients with CLI are at high risk of amputation and are limited in their ability to walk because of ulceration and pain. Small-vessel peripheral vascular disease and other coexisting morbidities preclude many patients from surgical treatment, and noninvasive treatment options are needed. The use of granulocyte-colony stimulating factors (G-CSFs) to mobilize a patient's stem cells to create angiogenic potential (i.e., minute vessel-forming capability) so they circulate and promote angiogenesis in ischemic areas is a minimally invasive treatment option under study. The intervention purportedly improves vascularization in ischemic limb areas of patients with CLI. In an ongoing clinical trial, G-CSFs are being injected subcutaneously, 250 mcg/m^2, 3 times weekly, for 2 weeks. Sponsored by Northwestern University, Evanston, IL Unphased PROPEL study ongoing	Arterial bypass surgery Peripheral balloon angioplasty with or without stent placement	Improved blood flow Improved ambulation Decreased ulceration Decreased pain Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Synthetic urodilatin (Ularitide) for treatment of acute heart failure	Patients in whom acute decompensated heart failure (ADHF) has been diagnosed	ADHF is a public health burden because of the large number of hospitalizations and the cost of care. Despite treatment, patients with ADHF have both an increased mortality risk and a high risk of hospital readmission. Thus, new treatment options are needed. Ularitide is a synthetic form of urodilatin, the natriuretic peptide that is formed in the kidneys and increases sodium excretion in urine. Ularitide is under investigation for treating ADHF. Ularitide purportedly has a longer half-life in circulation than urodilatin and may improve hemodynamics, diuresis and natriuresis, and block neurohormonal activation. In clinical trials, it is being administered intravenously for 48 hours at a dosage of 15 ng/kg/min. Cardiorentis, Ltd., Zug, Switzerland Phase III TRUE-AHF trial ongoing	Diuretics Inotropes Nesiritide Vasodilators	Improvement in heart failure symptoms Decreased morbidity Decreased mortality Improved quality of life
Targeted ventricular reshaping (VenTouch System) for treatment of functional mitral regurgitation	Patients in whom functional mitral regurgitation (MR) has been diagnosed	MR is a backward flow of blood from the heart's left ventricle into the left atrium that reduces the heart's pumping efficiency and increases its workload. Left untreated, MR can lead to congestive heart failure or serious cardiac arrhythmias. Functional MR occurs when the valve leaflets are intact but the valve opening becomes dilated and prevents the leaflets from closing effectively. Guidelines recommend surgical valve repair to treat MR, but not all patients are eligible for surgery. The VenTouch device is a synthetic sleeve delivered through a small incision between the ribs and fitted over the heart from the apex (bottom) under fluoroscopic guidance. A small, impermeable bladder within the sleeve in positioned over the left ventricle. A physician fills the bladder with saline under transesophageal echocardiographic guidance, thereby applying external pressure intended to decrease mitral valve dilation and reduce MR. Device implantation takes about 45 minutes and does not require vascular access or cardiopulmonary bypass. After implantation, a physician can adjust internal bladder pressure in the office setting via a permanently accessible, subcutaneous port. Mardil Medical, Inc., Plymouth, MN Pilot trial completed	MitraClip® percutaneous mitral valve repair Mitral valve surgery Pharmacotherapy	Reduced risk of cardiac events Reduced mitral regurgitation Reduced operative morbidity Reduced mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation	Patients with degenerative mitral valve disease with prolapse who are not good candidates for open surgical repair	Mitral regurgitation (MR) is a cardiac valve disease that typically occurs slowly without symptoms as progressive damage to the mitral valve prevents the mitral leaflets from closing properly. Poorly functioning leaflets allow blood to flow backward between the chambers as the heart pumps. Left untreated, severe MR can lead to congestive heart failure or serious cardiac arrhythmias. Some patients are not candidates for open surgery and could benefit from a minimally invasive option. The MitraClip® purportedly provides a minimally invasive transcatheter approach that requires a transseptal puncture to access the left heart chambers. In lieu of sutures, a flexible metal clip covered in polyester fabric (MitraClip) is used to grasp both leaflets of the mitral valve, thus providing for greater closure and leak reduction. The device is intended for patients whose valve disease originates mainly from the center of the valve. Abbott Laboratories, Abbott Park, IL FDA approved Oct 2013 for use in patients “with significant symptomatic degenerative mitral regurgitation who are at prohibitive risk for mitral valve surgery”	Open surgical mitral valve repair Pharmacotherapy	Decreased cost of HF complications Reduced mitral regurgitation Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Transcatheter mitral valve (Tiara) for treatment of mitral regurgitation	Patients in whom severe mitral regurgitation (MR) has been diagnosed	MR is a cardiac valve disease that typically occurs slowly without symptoms as progressive damage to the mitral valve prevents the mitral leaflets from closing properly. Poorly functioning leaflets allow blood to flow backward between the chambers as the heart pumps. Left untreated, severe MR can lead to congestive heart failure or serious cardiac arrhythmias. Some patients are not candidates for open surgery and could benefit from a minimally invasive option. The transcatheter mitral valve (Tiara™) implantation uses fluoroscopic guidance in a minimally invasive procedure to replace the native mitral heart valve without open-heart surgery; a 32-French–diameter catheter is used for delivery of a self-expanding nitinol frame stent with a bovine pericardial tissue valve. According to the manufacturer, the valve is “shaped to match the natural orifice of the mitral valve and minimize obstruction of the LV [left ventricular] outflow tract.” It is implanted using a transapical, transcatheter approach. Rather than repairing the mitral valve, the Tiara valve is intended to replace the diseased valve. Neovasc, Inc., Vancouver, British Columbia, Canada Feasibility trial (TIARA-I) ongoing in Europe and North America, including U.S. in an investigational device exemption trial	MitraClip® Open surgical mitral valve repair Pharmacotherapy	Reduced MR Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ultrasound-guided external focused ultrasound (Kona Surround Sound) for treatment-resistant hypertension	Patients in whom treatment-resistant hypertension has been diagnosed	Many pharmacotherapies are available for treating hypertension, and typically 3 types of drugs are used in conjunction to try to lower blood pressure. Yet, many cases of hypertension are not controlled with these interventions, and because such treatment-resistant hypertension is associated with high morbidity (e.g., end-organ damage) and mortality, novel interventions are warranted. Focused ultrasound therapy might offer an option for this patient population. Hyperactivity of the afferent and efferent sympathetic nerves from and to the kidneys are thought to play a role in blood pressure regulation and the pathophysiology of hypertension, and deactivating these nerves might reduce this hyperactivity, potentially lowering blood pressure. The Kona Surround Sound® system uses a mobile platform consisting of ultrasound image-guided focused ultrasound energy. The ultrasound imaging component tracks the position of renal nerves and delivers focused ultrasound energy externally to ablate them without damaging the renal artery. It is distinguished from magnetic resonance-guided focused ultrasound in that it uses an ultrasound platform for both the imaging and the ablation. According to the manufacturer, the noninvasive, mobile delivery platform system provides an alternative to minimally invasive, catheter-based renal denervation; it can be performed in any hospital exam room and does not require the use of a catheterization laboratory. Kona Medical, Inc., Bellevue, WA Phase II trial ongoing	Catheter-based renal denervation systems (in development) Optimal medical therapy with 3 antihypertensive agents Renal artery stents	Controlled hypertension with fewer or no medications Reduced rates of blindness, heart attack, kidney failure, and stroke

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vagus nerve stimulation (CardioFit) for treatment of heart failure	Patients in whom severe congestive heart failure (HF) has been diagnosed	Data from 2007 to 2010 from the National Health and Nutrition Examination Survey indicate that 5.1 million people older than the age of 20 years in the U.S. have HF. About 50% of people with HF die within 5 years of diagnosis. Projections suggest that the prevalence of HF will increase 25% from 2013 to 2030 and that costs will increase 120%. Treatments for HF depend on the stage of disease. CardioFit® vagus nerve stimulation is an implantable device intended to improve heart-pumping capacity in patients with severe congestive HF. The system is intended to stimulate the vagus nerve, which purportedly controls parasympathetic innervation of the heart. The company purports that stimulation will stimulate the parasympathetic nervous system, potentially lowering the heart rate, lessening the heart's workload, and alleviating heart failure symptoms. The system consists of a stimulator that is implanted subcutaneously in the right subclavicular region (similar to a pacemaker); a sensing lead, which is passed through a vein into the right ventricle where it monitors heart activity and can halt stimulation as needed; and a stimulation lead, placed around the right vagus nerve about 2–3 cm below the carotid artery bifurcation. The stimulator is wirelessly programmed by the clinician. The manufacturer states that the procedure can be conducted using either local or general anesthesia. BioControl Medical, Yehud, Israel Phase III INOVATE-HF investigational device exemption trial expanded to allow full enrollment in final phase of pivotal trial; trial is ongoing	Angiotensin-converting enzyme inhibitors Angiotensin II receptor blockers Beta blockers Digoxin Diuretics Heart transplantation Minimally invasive heart surgery Ventricular assist devices	Improved left ventricular ejection fraction Improved 6-minute walk test Reduced need for medication Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vepoloxamer for treatment of acute limb ischemia	Patients in whom acute limb ischemia has been diagnosed	Acute limb ischemia results from a blood flow obstruction caused suddenly by an embolism or thrombosis. Patients with acute limb ischemia experience poor outcomes, with many requiring amputation. Treatment strategies target thrombolysis of the obstruction with pharmacological agents or surgery. Vepoloxamer (MST-188) is a pharmaceutical agent being investigated as adjunct therapy for patients with acute limb ischemia currently treated with tissue plasminogen (tPA). It purportedly improves the clot-busting action of tPA and minimizes perfusion injury. According to the manufacturer, vepoloxamer inhibits multiple inflammatory processes and binds to damaged cellular membranes, thus increasing blood flow to the extremities. In clinical trials, the drug is being injected via continuous fusion, 100 mg/kg, for 1 hour followed by 30 mg/kg/hour, for up to 48 hours. Mast Therapeutics, Inc., San Diego, CA Phase II trial ongoing; FDA granted orphan drug and fast-track statuses	Surgery Thrombolytics	Improved circulation Reduced need for amputation Reduced morbidity and mortality
Volanesorsen for treatment of hypertriglyceri-demia	Patients in whom hypertriglyceridemi a has been diagnosed	Patients with hypertriglyceridemia, a condition often caused or exacerbated by diabetes mellitus and obesity, are at risk for coronary artery disease. The primary treatment strategy consists of dietary changes, which are often unsuccessful because strict adherence is required. Volanesorsen (APOCIIIRx) is an antisense drug that inhibits production of apolipoprotein C-III (apoC-III) in the liver. Lower production of apoC-III is linked to reduced levels of triglycerides and low-density lipoprotein–cholesterol levels and increased levels of high-density lipoprotein–cholesterol, thus reducing the risk of cardiovascular disease. The drug is intended to avoid side effects of current triglyceride-lowering medications. In clinical trials, volanesorsen is being administered subcutaneously, 300 mg, once weekly. Isis Pharmaceuticals, Inc., Carlsbad, CA Phase III trial (COMPASS) ongoing; FDA granted orphan drug status for familial chylomicronemia syndrome (FCS), and phase III trial (APPROACH) ongoing for FCS	Bile acid sequestrants Diet and exercise Fibrates Niacin Omega acids Statins	Reduced triglyceride levels Reduced cardiovascular risk Improved metabolic syndrome

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Wireless monitoring system (CardioMEMS HF System) for management of heart failure	Patients in whom moderately severe heart failure (HF) has been diagnosed	An estimated 5.8 million adults in the U.S. have HF and about half of people with HF die within 5 years of diagnosis. Projections suggest that the prevalence of HF will increase 25% by 2030 and that costs will increase 120%. In hospitalized patients, catheters placed temporarily within the heart to monitor left atrial pressure are the gold standard for tracking blood movement (hemodynamics) and worsening HF; however, no devices have been available for monitoring ambulatory patients. About 1/3 of HF patients who have been discharged from the hospital are readmitted within 30 days, usually for worsening signs and symptoms of congestion. This congestion is caused by increases in intracardiac and pulmonary artery pressures, which occur several days to weeks before the onset of worsening signs, symptoms, and hospital admission. Researchers suggest that monitoring these pressures might enable earlier intervention to reduce hospital readmissions for HF. The system consists of 3 parts: a battery-free, paper-clip-size implantable sensor/monitor placed in the pulmonary artery; a delivery system consisting of a transvenous catheter; and a hospital and patient electronics system that acquires and processes signals from the sensor and transfers pulmonary artery measurements to a secure database. Clinicians access the data to determine appropriate intervention for the patient. St. Jude Medical, St. Paul, MN, and CardioMEMS, Inc., Atlanta, GA Postapproval study ongoing; FDA approved May 2014 for wirelessly measuring and monitoring pulmonary artery pressure and heart rate in patients with New York Heart Association Class III HF who have been hospitalized in the previous year	Symptom monitoring Weight monitoring (for fluid retention)	Improved clinician access to changes in patient symptoms Earlier medical intervention Reduced hospitalizations Improved morbidity and mortality

Table 4. AHRQ Priority Condition: 04 Dementia (including Alzheimer's Disease): 20 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
[^{18}F] FDDNP positron emission tomography for diagnosis of chronic traumatic encephalopathy	Patients at risk of developing chronic traumatic encephalopathy (CTE)	An estimated 1.6 million to 3.8 million repetitive, mild traumatic brain injuries occur in contact sports each year. CTE is a progressive neurodegenerative disease seen most often in athletes with a history of repetitive brain trauma. It can lead to dementia, memory loss, anger, confusion, and depression. The disease is diagnosed only after evaluating brain tissue posthumously for evidence of degenerated tissue and elevated tau protein. To find ways to diagnose the disease in living patients, researchers have studied positron emission tomography (PET) imaging with 2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene)malononitrile (FDDNP). It is a radiotracer that binds to tau protein and amyloid deposits and may prove useful in locating these tau protein deposits in the amygdala and subcortical regions of the brain. In clinical trials using PET imaging with FDDNP, results showed increased tau protein deposition in former professional football players with probable CTE; these deposits are purportedly distinctive from tau deposition observed in Alzheimer's disease, and may allow characterization and differentiation between healthy patients, patients with probable CTE, and patients with other neurodegenerative indications. TauMark, Los Angeles, CA University of California, Los Angeles Phase II trial ongoing; Feb 2015, FDA ruled that TauMark was violating the Federal Food, Drug & Cosmetic Act by making claims on its Web site "in a promotional context regarding the safety and efficacy" of its unapproved radiotracer, and ordered it to cease making such claims; as of Sept 2015, TauMark had not provided a response	Posthumous diagnosis	Improved treatment protocol Reduced mild cognitive impairment and other CTE symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Aducanumab for treatment of Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. No approved disease-modifying agents are available for treating AD; therapy is limited to managing symptoms. Aducanumab (BIIB037) is an investigational human monoclonal antibody that preferentially binds parenchymal amyloid peptide, targeting aggregated amyloid beta forms including insoluble fibrils and soluble oligomers. These deposits are associated with AD progression and have been identified posthumously and in patients who have advanced probable AD. Researchers originally derived aducanumab from cognitively healthy older adults, concluding that these patients' resistance to cognitive decline was in part due to resilient immune systems; these researchers further hypothesize that aducanumab treatment may improve AD patient outcomes by reducing characteristic amyloid plaques. In late-phase clinical trials, aducanumab is infused intravenously, once monthly, at 1 of 2 dosages, for up to 78 weeks. Biogen, Cambridge, MA Phase III trials ongoing	Behavior therapy Nutrition therapy Pharmacotherapy (i.e., donepezil, galantamine, memantine, rivastigmine)	Reduced amyloid beta load in brain Regressed or slowed disease progression Reduced morbidity and mortality Improved quality of life
Azeliragon for treatment of mild Alzheimer's disease	Patients in whom mild probable Alzheimer's disease (AD) has been diagnosed	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million patients by 2050. No approved disease-modifying agents are available for treating AD; available therapy options are limited to managing symptoms. In many cases of AD, postmortem analysis of the patient's brain tissues reveals an accumulation of amyloid-beta, in the form of amyloid plaques. Researchers hypothesize that these accumulations trigger a cycle of chronic inflammation and inflammatory response, also involving nuclear factor kappa B (NF-kappaB) and the receptor for advanced glycation endproducts (RAGE). Preliminary research suggests that regulating NF-κB or RAGE activity may reduce amyloid-beta accumulation and subsequently prevent or minimize cognitive and behavioral symptoms associated with AD. Azeliragon (TTP448) is a small-molecule drug purported to block endogenous ligands, including amyloid-beta, from binding to RAGE. In late-phase clinical trials, azeliragon is administered orally, 5 mg, once daily, for 18 months. vTv Therapeutics LLC (formerly TransTech Pharma, Inc.), High Point, NC Pivotal phase III trial ongoing; Mar 2013, FDA granted fast-track status	Behavior therapy Deep brain stimulation (investigational) Nutritional therapy Pharmacotherapy (i.e., donepezil, galantamine, memantine, rivastigmine)	Reduced amyloid plaque accumulation Reduced caregiver burden Reduced cognitive decline Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Beta-amyloid precursor protein site–cleaving enzyme inhibitor (AZD3293, LY3314814) for treatment of Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. No approved disease-modifying agents are available for treating AD; therapy is limited to managing symptoms. AZD3293 is a beta-amyloid precursor protein site–cleaving enzyme (BACE) inhibitor being investigated for treating AD and prodromal AD. The drug is intended to inhibit BACE, an enzyme known to play a role in initiating synthesis of amyloid beta peptide. Abnormal accumulation of amyloid beta peptide is thought to play a role in the progression of AD, and it is hypothesized that BACE inhibitors may improve AD patient outcomes by reducing peptide aggregation. In the ongoing clinical trial, AZD3293 is administered orally, once daily, 20 or 50 mg. AstraZeneca, London, UK (manufacturer and codeveloper) Eli Lilly and Co., Indianapolis, IN (lead development partner) Phase II/III trial ongoing	Behavior therapy Deep brain stimulation (investigational) Nutrition therapy Pharmacotherapy (i.e., donepezil, galantamine, memantine, rivastigmine)	Reduced amyloid beta load in brain Regressed or slowed disease progression Reduced morbidity and mortality Improved quality of life
Brexpiprazole for treatment of agitation associated with Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. Besides the neurocognitive declines associated with AD, patients also have physical or verbal outbursts not associated with confusion or patient needs; as a group, these behaviors are classified as agitation. Drugs commonly used to treat agitation are not consistently effective and have multiple side effects. Additional pharmaceutical interventions are needed. Neurobiologic data suggest that agitation may be the result of reduced serotonin levels and increased levels of noradrenaline and dopamine. Brexpiprazole (OPC-34712) is a dopamine D_2 receptor partial agonist purported to reduce agitation in patients with AD. In clinical trials, brexpiprazole is administered as a daily oral tablet, with dosages uptitrated from an initial dosage of 0.25 mg/day to a maximum of 2 mg/day, based on efficacy and tolerability. Otsuka Holdings Co., Ltd., Tokyo, Japan, in collaboration with H. Lundbeck a/s, Valby, Denmark Phase III trials ongoing; Jul 2015, FDA approved brexpiprazole (as Rexulti®) for treatment of schizophrenia and adjunctive treatment of major depressive disorder	Caregiver intervention and environmental modification (removed or alleviated stressors) Pharmaceutical combinations that are not antipsychotics (e.g., antiepileptics, lithium, anxiolytics, analgesics, beta-adrenoceptor antagonists, cannabinoid receptor agonists, hormonal agents) Physician-selected typical and atypical antipsychotics Prazosin	Potentially reduced cost of care Reduced agitation (as measured by accepted rating scales and inventories) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Deuterated dextromethorphan-quinidine (AVP-786) for treatment of agitation associated with Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. Besides the neurocognitive declines associated with the disease, patients with AD also have physical or verbal outbursts not associated with confusion or patient needs; as a group, these behaviors are classified as agitation. Drugs commonly used to treat agitation are not consistently effective and have multiple side effects. Additional pharmaceutical interventions are needed. AVP-786 is an investigational therapy for treating AD agitation; the drug is a combination of deuterium-modified dextromethorphan, a cough suppressant and *N*-methyl-D-aspartate (NMDA) receptor antagonist, and quinidine, a class Ia antiarrhythmic agent. AVP-786's exact mechanism of action is unknown; however, another dextromethorphan-quinidine formulation, with a higher quinidine dosage, is hypothesized to function as a presynaptic and postsynaptic glutamate modulator. In clinical trials, AVP-786 is administered twice daily, as an oral capsule, for up to 12 weeks. Avanir Pharmaceuticals, Inc., Aliso Viejo, CA Phase III trials registered but not yet recruiting; AVP-786 is also under investigation for treating major depressive disorder	Caregiver intervention and environmental modification (removed or alleviated stressors) Pharmaceutical combinations that are not antipsychotics (e.g., antiepileptics, lithium, anxiolytics, analgesics, beta-adrenoceptor antagonists, cannabinoid receptor agonists, hormonal agents) Physician-selected typical and atypical antipsychotics Prazosin	Reduced cost of care Reduced AD-related agitation Reduced caregiver burden Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Encenicline (EVP-6124) for treatment of Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. No approved disease-modifying agents are available for treating AD; available therapies are limited to symptom management. In patients with AD, cells in the medial temporal lobe begin to die, interrupting memory storage and recall. AD is also marked by a decline in the amount of cholinergic neurons and the associated acetylcholine (ACh) neurotransmitter in the brain. Encenicline is an alpha-7 nicotinic ACh receptor agonist that purportedly has a novel mechanism for treating cognitive impairment in AD, acting as a co-agonist with ACh to enhance cognition. By acting as a co-agonist and sensitizing the alpha-7 receptor, encenicline purportedly allows smaller amounts of ACh to activate the receptor. In clinical trials, patients received daily capsules of encenicline at doses of 0.1, 0.3, or 1.0 mg, alone or with previously prescribed donepezil or rivastigmine. FORUM Pharmaceuticals, Inc., (formerly EnVivo Pharmaceuticals), Watertown, MA Phase III trials ongoing; encenicline is also being investigated for treating cognitive impairment comorbid to schizophrenia	Behavior therapy Deep brain stimulation (investigational) Nutritional therapy Pharmacotherapy (i.e., donepezil monotherapy, galantamine, memantine, rivastigmine monotherapy)	Reduced caregiver burden Reduced cost of care Improved quality of life
Idalopirdine plus donepezil for treatment of Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. No approved disease-modifying agents are available for treating AD; therapy is limited to managing symptoms. Idalopirdine (Lu AE58054) is a serotonin 5-HT_6 antagonist intended to treat cognitive impairments symptomatic of AD and other neurocognitive disorders, adjunct to donepezil therapy. In preliminary clinical trials, idalopirdine was well-tolerated and associated with improved cognitive function among patients with moderate AD who were also receiving stable doses of donepezil. Ongoing trials are investigating optimal idalopirdine dosages, with patients administered daily oral doses of 30 or 60 mg idalopirdine adjunct to 10 mg donepezil. H. Lundbeck a/s, Valby, Denmark, and Otsuka Holdings Co., Tokyo, Japan 4 phase III trials ongoing	Behavioral therapy Deep brain stimulation (investigational) Nutritional therapy Pharmacotherapy (i.e., donepezil monotherapy, galantamine, memantine, rivastigmine)	Reduced cognitive impairment symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Masitinib for treatment of Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed Patients with mild cognitive impairment who are at risk of developing probable AD	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. No approved disease-modifying agents are available for treating AD; therapy is limited to managing symptoms. Masitinib is an investigative medication that is thought to inhibit tyrosine kinases c-Kit, Fyn, and Lyn. Investigators hypothesize that inhibiting tyrosine kinase reduces mast cell–mediated neuroinflammation, beta-amyloid signalling, and tau phosphorylation, potentially making masitinib a multifaceted pharmacotherapy for AD. In clinical trials for treating mild-to-moderate AD, masitinib is administered orally, at daily doses ranging from 3 to 4.5 mg/kg, adjunct to standard therapy with cholinesterase inhibitors or memantine. AB Science S.A., Paris, France Phase III trial ongoing; masitinib is also under investigation for treating a wide variety of cancers and other indications, including amyotrophic lateral sclerosis, severe asthma, and rheumatoid arthritis	Donepezil Galantamine Memantine monotherapy Rivastigmine	Decreased beta-amyloid load and tau phosphorylation Delayed disease progression Reduced cognitive-impairment symptoms Improved quality of life
Methylthioninium chloride (TRx0237) for treatment of Alzheimer's disease and behavioral variant frontotemporal dementia	Patients in whom probable Alzheimer's disease (AD) or probable behavioral variant frontotemporal dementia (bvFTD) has been diagnosed	No approved disease-modifying agents are available for treating AD or bvFTD; therapy is limited to managing symptoms. As these forms of dementia progress, patients' cognitive and psychosocial skills decline, severely limiting functional independence. Methylthioninium chloride (TRx0237) is a proprietary, purified form of methylene blue, a widely used anti-malarial drug. Investigators are developing TRx0237 as an investigational AD therapy that purportedly inhibits tau aggregation and dissolves tau protein tangles and oligomers. These tangles and oligomers are classic biomarkers of probable dementia states, including AD; investigators hypothesize that preventing their formation may reverse dementia or delay disease progression. In clinical trials, TRx0237 is administered daily as an oral tablet, at doses up to 300 mg. TauRx Pharmaceuticals, Ltd., Singapore, Republic of Singapore Phase III trials ongoing	Behavior therapy Deep brain stimulation (investigational) Nutritional therapy Pharmacotherapy (approved; i.e., donepezil, galantamine, memantine, rivastigmine)	Increased survival Slowed progression of AD symptoms Slowed progression of bvFTD symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
MRI and neuropsychologic assessment for diagnosis of Alzheimer's disease	Patients in whom symptoms of mild cognitive impairment indicative of probable Alzheimer's disease (AD) have been diagnosed	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. A diagnosis of probable AD, however, can be made only after the disease has progressed to a point at which cognitive impairment and disease-associated biomarkers (e.g., accumulation of beta-amyloid protein or presence of tau protein tangles) are irreversible. The ability to advance diagnostic timelines might enable better treatment outcomes for patients at risk of AD. This diagnostic method combines neuropsychologic assessment of cognitive function (and impairment) with analysis of brain structural data acquired using MRI. The combination of diagnostic tools purportedly increases the classification, sensitivity, and specificity of identifying patients who will progress to dementia indicative of probable AD. Results of reported studies identify specific cognitive predictors (deficits in free recall and recognition episodic-memory tasks) and brain structural changes (thinning of right anterior cingulate gyrus) as highly suggestive of progression to dementia. Institut Universitaire de Gériatrie de Montréal/Université de Montréal, Montreal, Quebec, Canada No ongoing clinical trials	Cognitive assessment Noninvasive retinal imaging (in development) Structural neuroimaging evaluation (PET imaging)	New diagnostic models Contribution to comprehensive early intervention programs Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Noninvasive brain-computer interface cognitive training system for treatment of cognitive decline in elderly adults	Patients in whom age-related cognitive decline, dementia, mild cognitive impairment (MCI), or probable Alzheimer's disease (AD) has been diagnosed	Patients with deterioration in general or specific forms of cognitive function are classified as experiencing cognitive decline. Although various neurodegenerative conditions, including dementia, MCI, and AD, are closely associated with cognitive decline, many healthy adults also experience cognitive decline as they age. Investigators hypothesize that tasks that engage certain mental resources can help maintain cognitive functioning, and many noninvasive techniques and tools purportedly address this goal. However, these tools' efficacy is mixed across patients, and few have been robustly demonstrated to prevent decline in patients whose cognitive functioning has already decreased. Brain-computer interface (BCI) systems provide a potential noninvasive tool to reinforce cognitive functioning in healthy older adults and potentially reduce or prevent cognitive decline in these patients. The systems communicate directly between patients' brains and a computer training system, via electroencephalograph (EEG) recordings. EEG recordings are processed by the computer to determine patients' attention states and incorporated into training paradigms. In registered clinical trials, adults with normal and deteriorating cognitive functioning complete 24, 30-minute training sessions, conducted over 8 weeks. Duke University, Durham, NC Duke-National University of Singapore, Singapore Phase II/III trial ongoing	Nonautomated cognitive training tools	Increased patient independence Reduced or prevented cognitive decline Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Noninvasive computer-based psychophysics system (Cognivue) for early detection of age-related cognitive decline and dementia	Older adult patients at risk for age-related cognitive decline or dementia	Older adults are a large and rapidly growing patient pool; experts estimate that by 2050, the population will include more than 83 million Americans aged 65 years or older. As these patients age, their risk of dementia and cognitive decline increases. Early and accurate diagnosis of declining cognitive function is key to successful subsequent treatment. Although assessment tools are available, several are limited because of issues of measurement efficacy, testing bias, or diffusion among clinicians. An unmet need exists for additional diagnostic tools for early assessment of cognitive decline. Cognivue® is a noninvasive device intended to provide quantitative assessments of cognitive function in 10 minutes or less. This computer-based device uses adaptive visual stimulus signals to assess focal cortical function; through repeated testing, clinicians can potentially detect and monitor a patient's changing cognition. Patients interact with Cognivue using a 1-handed steering wheel (called a manipulandum) to identify highlighted stimuli. Cognivue's developers purport that this diagnostic could allow for earlier treatment of cognitive decline and more accurate treatment-effectiveness monitoring. The manufacturer will market device solely for clinician use. Cerebral Assessment Systems, Inc., Pittsford, NY Jun 2015, FDA granted de novo clearance to Cognivue as a computerized cognitive assessment aid, indicated for use as an adjunctive tool for evaluating perceptual and memory function in individuals aged 55–95 years	Standardized brief cognitive assessments (e.g., Brief Cognitive Assessment Tool, Folstein Mini-Mental Status Exam, General Practitioner Assessment of Cognition, Mini-Cog)	Advanced detection of cognitive decline Improved early treatment of cognitive decline and dementia Reduced long-term cognitive decline–associated care costs Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Noninvasive digital retinal imaging for screening for Alzheimer's disease	Patients at risk for developing Alzheimer's disease (AD)	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. A diagnosis of probable AD, however, can be made only after the disease has progressed to a point at which cognitive impairment and disease-associated biomarkers (e.g., accumulation of beta-amyloid protein or presence of tau protein tangles) are irreversible. The ability to advance diagnostic timelines with an early screening test might enable better outcomes for patients at risk of AD. Research has shown that beta-amyloid plaques, commonly hypothesized to indicate AD in living and postmortem patient analyses, are localized in brain regions and in the retina. The NeuroVision Imaging System (NVI) is a noninvasive digital retinal fluorescence imaging technology that reportedly can accurately identify these plaques in retinal tissue of patients 15–20 years earlier than standard clinical diagnostics. It is intended for screening as an adjunct to brain imaging. The technology uses curcumin, a component of tumeric, as a plaque-labeling agent. Patients receive a curcumin supply during an office visit and return another day for imaging. The curcumin shows as a fluorescent yellow color to display the amyloid-beta plaques in the retina. Researchers believe that it the test result correlates with brain images, it can be used for screening for AD. The patient sits in front of the imaging machine with his or her head positioned in a chin and forehead rest during the procedure. In clinical trials, patients ingest 20 g curcumin, mixed in pudding, along with 500 IU vitamin E, for 7 days, with retinal imaging conducted at baseline and after 7 days. Hollywood Private Hospital, Nedlands, Western Australia, Australia (international clinical trial collaborator) McCusker Alzheimer's Research Foundation, Nedlands, Western Australia, Australia (international clinical trial sponsor) NeuroVision Imaging, LLC, Sacramento, CA, in collaboration with Cedars-Sinai Medical Center, Los Angeles, CA (developer) Phase II Australian trial ongoing	Cognitive assessment of probable AD Combined brain imaging analysis (MRI) with neuropsychologic assessment (in development) Structural neuroimaging evaluation (positron emission tomography imaging) of probable AD	New diagnostic models Contribution to comprehensive early intervention programs Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label atomoxetine (Strattera) for treatment of mild cognitive impairment	Patients in whom mild cognitive impairment (MCI) has been diagnosed	MCI may be a precursor to various forms of dementia, including Alzheimer's disease (AD). An unmet need exists for interventions that treat MCI, particularly options that are effective in early disease stages. Atomoxetine (Strattera®) is a selective norepinephrine reuptake inhibitor (SNRI) that is approved for improving attention span and decreasing impulsiveness and hyperactivity in children and adults with attention-deficit/hyperactivity disorder. SNRIs have been demonstrated to increase brain levels of norepinephrine, a neuromodulator implicated in behavioral control; consequently, investigators hypothesize that these properties may make atomoxetine effective for treating MCI. In clinical trials, atomoxetine is administered orally, up to 100 mg, daily. Emory University, Atlanta, GA National Institute on Aging, Bethesda, MD Phase II trial ongoing	Behavior therapy Nutrition therapy Pharmacotherapy (i.e., donepezil, galantamine, memantine, rivastigmine)	Improved cognitive performance Delayed progression to AD Reduced morbidity
Off-label carvedilol (Coreg) for treatment of Alzheimer's disease	Patients in whom probable mild Alzheimer's disease (AD) has been diagnosed	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. No approved disease-modifying agents are available for treating AD; therapy is limited to managing symptoms. Carvedilol (Coreg®) is a beta-adrenergic receptor antagonist indicated for hypertension and certain types of heart failure. Research suggests that inhibiting the beta adrenergic system might reduce amyloid beta load and slow cognitive decline from AD. Carvedilol is available as an oral tablet in doses from 3.125 to 25.0 mg; a controlled-release formulation is also available at doses from 10 to 80 mg. In clinical trials for patients with mild AD, carvedilol is administered daily at a dose of 25 mg. GlaxoSmithKline, Middlesex, UK (manufacturer) Johns Hopkins University, Baltimore, MD (study sponsor) Mount Sinai School of Medicine, New York, NY (study sponsor) Phase IV trial ongoing	Behavior therapy Deep brain stimulation (investigational) Nutritional therapy Pharmacotherapy (i.e., donepezil, galantamine, memantine, rivastigmine)	Decreased beta-amyloid levels in cerebrospinal fluid Delayed disease progression Improved episodic memory Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label deep brain stimulation for treatment of Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. No approved disease-modifying agents are available for treating AD; available therapy options are limited to symptom management. Deep brain stimulation (DBS) involves implanting a battery-operated neurostimulator in the brain to deliver electrical stimulation to targeted areas that moderate neural activity in the memory circuit, including the entorhinal and hippocampal areas. Researchers suggest that continuous stimulation in these areas might reverse impaired glucose utilization in the temporal and parietal lobes, which some researchers hypothesize are involved in AD. Independent and manufacturer-supported investigators including: Functional Neuromodulation, Ltd., Toronto, Ontario, Canada Ohio State University, Columbus University of Cologne, Cologne, North Rhine-Westphalia, Germany 1 phase I/II and multiple unphased trials ongoing	Behavioral therapy Nutritional therapy Pharmacotherapy (i.e., donepezil, galantamine, memantine, rivastigmine)	Delayed progression to AD Reduced morbidity Improved quality of life
Off-label pioglitazone to delay onset of mild cognitive impairment due to Alzheimer's disease	Patients at risk of developing mild cognitive impairment (MCI) due to Alzheimer's disease (AD)	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. As many as 300,000 younger adult Americans are found to have early onset AD, a genetically predisposed form of AD. Before a diagnosis of early-onset AD, patients usually exhibit MCI, a neuropsychological status characterized by small but significant declines in working memory, short- and long-term memory, and general executive functioning. An unmet need exists for therapies that can address MCI and improve health outcomes in patients with early-onset AD. Pioglitazone is a thiazolidinedione that functions as a hypoglycemic and anti-inflammatory drug. Researchers hypothesize that pioglitazone's anti-inflammatory properties may delay the onset of MCI in patients who have a genetic predisposition to developing AD. In clinical studies, pioglitazone is administered orally at low dosages, up to 0.8 mg, once daily for up to 5 years. Takeda Pharmaceutical Co., Ltd., Osaka, Japan (manufacturer) Zinfandel Pharmaceuticals, Inc., Durham, NC (clinical trial partner) 2 phase III trials ongoing; in 1999, FDA approved pioglitazone (as Actos®) for treating type 2 diabetes mellitus	Behavioral therapy Deep brain stimulation (investigational) Nutritional therapy Pharmacotherapy (i.e., donepezil, galantamine, memantine, rivastigmine)	Delayed onset of MCI symptomatic of early AD Reduced long-term cost of care Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Solanezumab for treatment of Alzheimer's disease	Patients in whom mild probable Alzheimer's disease (AD) has been diagnosed	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. No approved disease-modifying agents exist for treating AD; therapy is limited to managing symptoms. Solanezumab is a fully humanized anti–beta-amyloid antibody that binds to soluble beta amyloid and is intended to draw the peptide away from the brain through the blood to promote clearance of beta-amyloid protein from damaged sites in the brain. Solanezumab is being developed primarily for treating mild-to-moderate AD; however, additional trials are investigating this drug as a preventative intervention for patients determined to be at-risk for dementia and AD. In ongoing clinical trials, solanezumab is administered intravenously, 400 mg every 4 weeks for 80 weeks. Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing for treating mild-to-moderate AD and preventing AD in at-risk patients	Behavior therapy Deep brain stimulation (investigational) Nutritional therapy Pharmacotherapy (i.e., donepezil, galantamine, memantine, rivastigmine)	Decreased brain beta-amyloid load Slowed or halted disease progression Improved memory and cognition Improved survival Improved quality of life
Verubecestat for treatment of Alzheimer's disease	Patients in whom probable, prodromal, or mild to moderate Alzheimer's disease (AD) has been diagnosed	Experts estimate that more than 5 million Americans aged 65 years or older have AD; without significant therapeutic developments, this population is predicted to approach 14 million by 2050. No approved disease-modifying agents are available for treating AD; therapy is limited to managing symptoms. Verubecestat (MK-8931) is a beta-amyloid precursor protein site–cleaving enzyme (BACE) inhibitor being investigated for treating AD and prodromal AD. BACE is known to play a role in initiating synthesis of amyloid beta peptide. Because abnormal amyloid beta peptide accumulation is hypothesized to be a biomarker of AD and AD progression, researchers purport that BACE inhibitors may potentially halt or delay AD. In clinical trials, verubecestat is administered as a once-daily oral dose of 12 or 40 mg. Merck & Co., Inc., Whitehouse Station, NJ Phase II/III and III trials ongoing	Behavior therapy Deep brain stimulation (investigational) Nutritional therapy Pharmacotherapy (i.e., donepezil, galantamine, memantine, rivastigmine)	Reduced amyloid beta load in brain Regressed or slowed disease progression Reduced morbidity and mortality Improved quality of life

Table 5. AHRQ Priority Condition: 05 Depression and Other Mental Health Disorders: 19 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bright-light adjunctive therapy for nonseasonal major depressive disorder and bipolar depression	Patients in whom nonseasonal major depressive disorder (MDD) or bipolar depression (BPD) has been diagnosed	Many pharmacologic and psychotherapeutic options are available for patients with MDD or BPD, yet fewer than half of these patients achieve remission. Many available treatments have undesirable side effects; a need exists for additional effective, well-tolerated therapies for these indications. Bright-light therapy (BLT) has long been used to treat seasonal affective disorder but not for nonseasonal forms of MDD. The exact mechanism of action unknown, but BLT is thought to target depression-associated neurotransmitter systems (serotonin, noradrenaline, dopamine) and the same brain structures as antidepressant pharmacotherapy. Ongoing clinical trials are investigating BLT as a standalone or adjunctive treatment, with varied dosing protocols, for patients with MDD or BPD with or without comorbidities. Douglas Mental Health University Institute, Montreal, Quebec, Canada National Institute of Mental Health, Bethesda, MD New York State Psychiatric Institute, New York, NY University of British Columbia, Vancouver, Canada University of Pittsburgh, Pittsburgh, PA Phase III Canadian trial completed; unphased and early phase trials ongoing	Cognitive behavior therapy Deep brain stimulation Electroconvulsive therapy Off-label ketamine Off-label scopolamine Psychotherapy Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors Transcranial magnetic stimulation Tricyclic antidepressants Vagal nerve stimulation	Improved depression rating scale scores Reduced symptom severity Improved quality of life
Combination opioid receptor modulator (ALKS 5461) for treatment of major depressive disorder	Patients in whom major depressive disorder (MDD) or treatment-resistant MDD has been diagnosed	Fewer than half of patients with MDD achieve remission with approved antidepressant therapy, and available pharmacotherapies are often associated with undesirable side effects. ALKS 5461 is a novel adjunctive medication that purportedly safely treats MDD through a combination of agonists and antagonists, including the selective mu-opioid receptor modulator samidorphan and the opioid modulator buprenorphine, that act on opioid receptors. In late-phase clinical trials, ALKS 5461 is administered as a sublingual tablet, once daily, at 1 of 2 experimental titration schedules. Alkermes, plc, Dublin, Ireland Pivotal phase III trials ongoing; Oct 2013, FDA granted fast-track status	Drugs (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants) Procedures (e.g., deep brain stimulation, electroconvulsive therapy, transcranial magnetic stimulation [investigational], vagus nerve stimulation) Psychotherapy	Improved depression rating scale scores Reduced symptom severity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Comprehensive evidence-based therapy (EnCoRE program) for treatment of veterans who have schizophrenia	Military veterans in whom schizophrenia has been diagnosed	Veterans often struggle to reintegrate to civilian life; problems are compounded when these veterans have mental health disorders, such as schizophrenia. Among other potentially debilitating symptoms, negative symptoms—including social withdrawal, anhedonia, and other behavioral issues—can strain daily functioning. Several behavioral therapy techniques are proved to improve patients' coping skills. Unfortunately, veterans do not always have access to these interventions; an unmet need exists for targeted interventions for this patient population. EnCoRE (Engaging in Community Roles and Experiences) is an investigational program comprised of multiple evidence-based psychosocial therapies intended to address behavioral deficits in veterans with schizophrenia. EnCoRE includes approaches such as motivational enhancement, cognitive therapy, and social skills training in an effort to maximize veterans' functional recovery and social reintegration. In ongoing clinical trials, EnCoRE is designed to train service providers and deliver services to veterans for up to 12 weeks. Baltimore VA Medical Center, Baltimore, MD (clinical trial site) Department of Veterans Affairs, Washington, DC (clinical trial sponsor) Phase II/III trial ongoing	Single-approach behavioral therapy	Improved behavior therapy service delivery Improved social reintegration Improved symptoms Improved quality of life
Deep brain stimulation of the subcallosal cingulate (Libra System) for treatment-resistant major depressive disorder	Patients in whom treatment-resistant depression or major depressive disorder (MDD) has been diagnosed	Fewer than half of patients with MDD achieve remission with approved antidepressant therapy, and available pharmacotherapies are often associated with undesirable side effects. When medications, psychotherapy, and electroconvulsive therapy have failed, no treatment options are available for MDD. Additional interventions are needed for patients with treatment-refractory MDD. The Libra™ Deep Brain Stimulation (DBS) System is intended to send mild pulses of current from an implanted device to the brain, stimulating discrete areas. The mechanism of action of DBS is unknown, but investigators hypothesize that electrical stimulation modulates activity in brain areas believed to be hyperactive in patients with MDD. For treating MDD, the manufacturer is investigating placement of the leads in Brodmann area 25 of the subcallosal cingulate gyrus. St. Jude Medical, Inc., St. Paul, MN Unphased trial ongoing	DBS with other systems or in other brain areas Electroconvulsive therapy Off-label ketamine Off-label scopolamine Repetitive transcranial magnetic stimulation Vagus nerve stimulation	Improved depression rating scale scores Reduced symptom severity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ecopipam for treatment of Tourette's syndrome	Patients in whom Tourette's syndrome (TS) has been diagnosed	About 200,000 people in the U.S. have received a diagnosis of TS, and many patients have severely debilitating disease that does not respond to available pharmacotherapy, or they experience serious adverse events. An unmet need exists for more effective treatments. Dopamine D_1 receptor overactivity is thought to be a primary cause of TS symptoms, particularly tics. Ecopipam is a selective dopamine 1 (D_1)/dopamine 5 (D_5) antagonist under investigation for treating prominent TS symptoms. In clinical trials enrolling adolescent patients, ecopipam is administered orally in the evening for 8 weeks, at a daily dosage of 50 mg for the 1st 2 weeks, and 100 mg for 6 weeks. Psyadon Pharmaceuticals, Inc., Germantown, MD Phase II trial ongoing; Sept 2010, FDA granted orphan status for treating TS in children younger than 16 years	Palliative pharmacotherapy (e.g., antidepressants, botulinum toxin type A [Botox] injections, central adrenergic inhibitors, fluphenazine, pimozide, stimulant medications)	Reduced tic frequency and severity Improved quality of life
Encenicline (EVP-6124) for adjunctive treatment of cognitive symptoms of schizophrenia	Patients with clinically stable schizophrenia who are being treated with 1 or 2 atypical antipsychotic medications	Schizophrenia is a severe mental health disorder estimated to affect approximately 1.1% of adult Americans. Existing pharmacotherapies for schizophrenia have limited efficacy and are associated with unwanted side effects in many patients. Additionally, available treatments inadequately address the negative and cognitive symptoms of schizophrenia. Encenicline is a selective compound, an alpha-7 nicotinic acetylcholine receptor co-agonist that acts along with acetylcholine (ACh). Encenicline purportedly sensitizes the alpha-7 receptor, allowing smaller amounts of naturally occurring ACh to activate the alpha-7 receptor. The company purports that this mechanism could treat cognitive symptoms of schizophrenia while alleviating the potentially toxic side effects of other systemic compounds (e.g., acetylcholinesterase inhibitors). In ongoing clinical trials for treating schizophrenia, 2 unspecified dose levels are being tested as a once-daily, oral adjunct treatment for patients with clinically stable schizophrenia being treated with 1 or 2 chronic atypical antipsychotic therapies. FORUM Pharmaceuticals (formerly EnVivo Pharmaceuticals), Watertown, MA Phase III trials ongoing; Jun 2015, FDA granted fast-track status for treating cognitive symptoms of schizophrenia; encenicline is also under investigation for treating cognitive symptoms of mild Alzheimer's disease	Antidepressants Antipsychotics Cognitive behavioral therapy Combination therapy Mood stabilizers (i.e. lithium) Psychotherapy	Improved cognitive symptoms Improved social functioning Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multi-family integrative therapy group for treatment of anorexia nervosa	Patients in whom anorexia nervosa (AN) has been diagnosed	AN is a psychiatric eating disorder characterized by distorted body image, disturbed eating behavior, and abnormal preoccupation with losing weight. In the U.S., AN has the 3rd-highest lifetime prevalence among eating disorders and has the highest mortality rate among psychiatric illnesses. Epidemiologic studies have also shown that AN is more prevalent in women than men and is the 3rd most common chronic illness among adolescents. Neuroimaging research has demonstrated that patients with AN display deficits in cognitive control, central coherence, and emotional processing. Consequently, many experts consider individual behavior therapy as the standard treatment for AN, although its long-term efficacy has not been established. An unmet need exists for alternative interventions that promote sustained AN symptom management and reduction. The multi-family therapy group (MFTG) approach uses a relational-motivational treatment approach that purportedly addresses intra- and interpersonal disconnections underlying patients' AN symptoms. Within a group treatment environment, therapists can engage patients and their relatives in an integrated effort to develop positive connections and reduce AN symptoms. In a proposed clinical trial model, MFTG consists of sixteen 90-minute therapy sessions involving patients and family members, conducted over 26 weeks; this design also includes followup assessments conducted 6 months after completion of MFTG sessions. Investigators include the following: Golisano Children's Hospital, Division of Adolescent Medicine, Rochester, NY Western NY Comprehensive Care Center for Eating Disorders, Rochester, NY University Health Network, Toronto, Ontario, Canada University of California, San Diego University of Rochester School of Nursing, Rochester, NY University of Toronto, Toronto, Ontario, Canada No registered clinical trials ongoing	Combination cognitive behavior therapy and medical therapy Group behavior therapy (without relational/motivational and disconnection management components) Individual cognitive behavior therapy Single-family psychotherapy (e.g., Maudsley family therapy)	Increased intra- and interpersonal connection between patients and families Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label armodafinil (Nuvigil) for treatment of binge-eating disorder	Adult patients in whom binge-eating disorder (BED) has been diagnosed	Only 1 pharmacotherapy, Vyvanse®, is FDA-approved for treating BED. However, this drug, along with commonly prescribed off-label BED medications, is associated with limited efficacy, undesirable side effects, and low patient adherence to treatment recommendations. Armodafinil is a wakefulness-promoting drug with an unknown mechanism of action, approved for treating excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work disorder. Some investigators have suggested that BED may be mediated by relationships between narcolepsy and obesity; accordingly, researchers are investigating the efficacy of armodafinil, a proven anti-narcoleptic, for treating BED. In clinical trials for this indication, armodafinil is administered orally, at a variable dosage between 150 mg and 250 mg daily. Lindner Center of Hope, Mason, OH (clinical trial sponsor) Teva Pharmaceutical Industries, Ltd., Petah-Tikva, Israel (manufacturer and clinical trial collaborator) University of Cincinnati, Cincinnati, OH (clinical trial collaborator) Phase III trial completed May 2015; Jun 2007, FDA approved armodafinil (as Nuvigil®) for treating disorders associated with excessive sleepiness	Off-label pharmacotherapies (e.g., antiepileptics, norepinephrine reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors)	Reduced symptoms Reduced morbidity Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label deep brain stimulation for treatment-resistant Tourette's syndrome	Patients in whom Tourette's syndrome (TS) has been diagnosed	About 200,000 people in the U.S. have received a diagnosis of TS, and many patients have severely debilitating disease that does not respond to available pharmacotherapy, or they experience serious adverse events. An unmet need exists for more effective treatments. Deep brain stimulation (DBS) involves implanting a battery-operated neurostimulator in the brain to deliver electrical stimulation to targeted areas, such as the globus pallidus internus, centromedian-parafascicular, or ventralis oralis complex of the thalamus. Studies are testing various stimulation delivery models—including unilateral or bilateral and continuous or intermittent—and targeting various areas in the brain (e.g., globus pallidus, thalamus). Although the mechanism of action is unclear, investigators hypothesize that DBS affects cortico-basal ganglia-thalamocortical circuits, which have been shown to oscillate abnormally in both models of TS and in frequency-band recordings of some patients with TS. The type of DBS device being used is not indicated in all ongoing studies, but Medtronic, plc (Dublin, Ireland), is an example of a company that makes DBS devices that have been approved for other indications, such as Parkinson's disease and obsessive-compulsive disorder. Ongoing clinical trial are attempting to establish optimal treatment protocols and responsive patient subpopulations. Investigators include: Johns Hopkins University, Baltimore, MD University of Florida Center for Movement Disorders and Neurorestoration, Gainesville, FL University Hospitals, Cleveland, OH Phase II and III trials ongoing	Botulinum toxin type A injections Pharmacotherapy (e.g., antidepressants, central adrenergic inhibitors, fluphenazine, pimozide, stimulants)	Reduced symptom burden Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label intranasal oxytocin for treatment of schizophrenia	Patients in whom schizophrenia has been diagnosed	Schizophrenia is a severe mental health disorder estimated to affect about 1.1% of adult Americans. Existing pharmacotherapies for schizophrenia have limited efficacy and are associated with unwanted side effects in many patients. Additionally, available treatment options inadequately address the negative and social cognitive symptoms of the disease. An unmet need exists for therapies that improve these symptoms. Studies have linked endogenous and exogenous oxytocin with social bonding, empathy, and trust, and researchers hypothesize that this drug may improve negative symptoms of schizophrenia and their associated social cognition deficits. In clinical trials, patient-administered intranasal oxytocin is being studied using daily doses up to 84 IU and single and chronic treatment regimens. Clinical trial sponsors include the following: National Institute of Mental Health, Bethesda, MD University of California, Los Angeles University of Maryland, College Park University of North Carolina, Chapel Hill Phase II, III, and unphased trials ongoing	Antidepressants Antipsychotics Cognitive behavioral therapy Combination therapy Mood stabilizers (i.e., lithium) Psychotherapy	Improved social cognition Improved quality of life
Off-label ketamine for treatment of posttraumatic stress disorder	Patients in whom posttraumatic stress disorder (PTSD) has been diagnosed	PTSD is a mental health disorder marked by experiencing recurrence (flashbacks, nightmares, and event-related negative thoughts), avoidance, and hyperarousal symptoms after a traumatic event. According to the National Institute of Mental Health, 6.8% of adult Americans will experience PTSD during their lifetimes. Many patients with PTSD do not respond adequately to prescribed drugs or psychotherapy; therefore, an unmet need exists for alternative treatments. Ketamine, an FDA-approved anesthetic with known analgesic and amnestic properties, is being investigated for treating both civilian- and combat-related PTSD and treatment-resistant PTSD. In ongoing clinical trials, ketamine is administered intravenously in a single 0.5 mg/kg dose, infused over 40 minutes. Mount Sinai School of Medicine, New York, NY (lead investigator) U.S. Department of Defense, Arlington, VA (collaborator) Phase II and II/III trials ongoing	Antidepressants (for PTSD and depression) Antipsychotics (for PTSD and anxiety, paranoia, or other mental health symptoms) Benzodiazepines (for PTSD and sleep or relaxation difficulty) Paroxetine Psychotherapy Sertraline	Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label ketamine for treatment-resistant major depressive disorder or bipolar depression	Patients in whom treatment-resistant major depressive disorder (MDD) or bipolar depression (BPD) has been diagnosed	Fewer than half of patients with MDD or BPD achieve remission with approved antidepressant therapy, and available pharmacotherapies are often associated with undesirable side effects. Available options for treatment-resistant MDD or BPD are either surgically invasive (e.g., deep brain stimulation, vagus nerve stimulation) or must be performed under clinical supervision (e.g., transcranial magnetic stimulation, repetitive transcranial magnetic stimulation). Ketamine is an anesthetic under study for rapid relief of severe, treatment-resistant depression and suicidal ideation. The drug is under study in 2 formulations: intravenous administration of 0.1–1.0 mg/kg once or more weekly, and intranasal administration up to 50 mg per single dose; case studies using oral and sublingual ketamine have also been reported for this indication. Ketamine is being studied as both a monotherapy and as an augmentative therapy to electroconvulsive therapy. National Institute of Mental Health (NIMH), Bethesda, MD (sponsor for multiple clinical trials) Academic and medical institutions (trial sponsors, cosponsors, and case report publications) Phase II, III, and IV trials ongoing	Deep brain stimulation Electroconvulsive therapy Psychotherapy Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors Transcranial magnetic stimulation Tricyclic antidepressants Vagal nerve stimulation	Rapid improvement in depression symptoms Improved depression rating scale scores Improved treatment adherence Reduced symptom severity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label nitrous oxide for treatment-resistant bipolar depression	Patients in whom treatment-resistant bipolar depression (BPD) has been diagnosed	Fewer than half of patients with BPD achieve remission with approved antidepressant therapy, and available pharmacotherapies are often associated with undesirable side effects. Available options for treatment-resistant BPD are either surgically invasive (e.g., deep brain stimulation, vagus nerve stimulation) or must be performed under clinical supervision (e.g., transcranial magnetic stimulation, repetitive transcranial magnetic stimulation). Additionally, many patients continue to experience depressive symptoms even while prescribed effective treatments; an unmet need exists for well-tolerated, rapidly effective BPD therapies. Nitrous oxide is an inhaled *N*-methyl-D-aspartate (NMDA) receptor antagonist with anesthetic and analgesic properties; this gas is under investigation as a fast-acting therapy for treatment-resistant BPD. Researchers hypothesize that besides quickly relieving depressive symptoms through NMDA receptor modulation, nitrous oxide may also increase frontal cortical perfusion and endothelial functioning, 2 processes recently implicated in depressive disorders. In clinical trials, patients inhale nitrous oxide in an initial mixture of 10% nitrous oxide in pure oxygen for 5 minutes, followed by a mixture of 25% nitrous oxide in pure oxygen for 20 minutes. Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada Phase II trial ongoing	Antipsychotics Cognitive behavior therapy Combination therapy Mood stabilizers (i.e., lithium) Psychotherapy	Improved depression symptoms Improved anxiety symptoms Improved ability to function Improved quality of life
Off-label nitrous oxide for treatment-resistant major depressive disorder	Patients in whom treatment-resistant major depressive disorder (MDD) has been diagnosed	Fewer than half of patients with MDD achieve remission with antidepressant therapy, and available pharmacotherapies are often associated with undesirable side effects. An unmet need exists for additional interventions for these patients. Nitrous oxide (laughing gas) is a NMDA inhibitor, commonly used as an anesthetic and analgesic and approved for treating pediatric respiratory illness. Researchers hypothesize that, like ketamine, which is another intervention under study, nitrous oxide's NMDA inhibitory properties may make it a safe, rapidly-acting antidepressant. In ongoing clinical trials, patients are administered nitrous oxide in a 1:1 mixture with pure oxygen, at two 1-hour sessions separated by 1 week. Nitrous oxide has also been investigated as an adjunct to isoflurane or scopolamine for treating MDD. Washington University School of Medicine, St. Louis, MO Phase II trial ongoing	Deep brain stimulation Electroconvulsive therapy Ketamine (investigational) Psychotherapy Scopolamine (investigational) Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors Transcranial magnetic stimulation Tricyclic antidepressants Vagal nerve stimulation	Improved depression rating scale scores Reduced symptom severity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label riluzole (Rilutek) for treatment-resistant major depressive disorder	Patients in whom treatment-resistant depression (TRD) or major depressive disorder (MDD) has been diagnosed	Fewer than half of patients with MDD achieve remission with approved antidepressant therapy, and available pharmacotherapies are often associated with undesirable side effects. Available options for treatment-resistant MDD or TRD are either surgically invasive (e.g., deep brain stimulation, vagus nerve stimulation) or must be performed under clinical supervision (e.g., transcranial magnetic stimulation and repetitive transcranial magnetic stimulation). Riluzole (Rilutek®) is a novel glutamatergic modulator purported to treat MDD by inhibiting glutamate release, enhancing glutamate reuptake, and protecting glial cells against glutamate excitotoxicity. In clinical trials, riluzole is administered at an oral dose of 50–100 mg, daily, and is being investigated as both an individual and adjunctive intervention. Multiple clinical trial sponsors, including: Brigham and Women's Hospital, Boston, MA National Institute of Mental Health, Bethesda, MD Yale University, New Haven, CT Phase II trials ongoing; Dec 1995, FDA approved riluzole for treating amyotrophic lateral sclerosis	Deep brain stimulation Electroconvulsive therapy Psychotherapy Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors Transcranial magnetic stimulation Tricyclic antidepressants Vagal nerve stimulation	Improved depression rating scale scores Reduced symptom severity Improved quality of life
Off-label scopolamine (intravenous, transdermal, oral) for treatment of major depressive disorder	Patients in whom treatment-resistant depression or major depressive disorder (MDD) has been diagnosed	Fewer than half of patients with MDD achieve remission with approved antidepressant therapy, and available pharmacotherapies are often associated with undesirable side effects. Depression treatments also typically take 3–6 weeks before patients experience relief, warranting the need for better, faster-acting medications. Researchers have indicated that acetylcholine-mediated activity could play a role in depression. Scopolamine is a muscarinic antagonist that blocks the muscarinic acetylcholine receptors, thus blocking the actions of acetylcholine (anticholinergic effect), and pilot study results have suggested it might yield results quickly—within days. In ongoing studies, scopolamine is being administered alone and in conjunction with other medications. It is being tested as an intravenous drug given about 3–5 days apart at varying dosages (e.g., 2, 3, or 4 mcg/kg followed by 45 minutes of saline infusion), as a transdermal patch, and as oral medication (e.g., 0.5 mg twice daily). Massachusetts General Hospital, Boston 2 unphased clinical trials ongoing	DBS Electroconvulsive therapy Pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants) Psychotherapy TMS (investigational) VNS	Improved depression rating scale scores Reduced symptom severity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Patient-centered early intervention (RAISE program) for treatment of prodromal stage schizophrenia	Patients in whom prodromal stage schizophrenia has been diagnosed or who are at high risk of developing schizophrenia	Clinical indications of prodromal (early) stage schizophrenia include dramatic changes in patterns of communication, perception, affect, and thoughts (attenuated positive symptom syndrome); short, inconsistently recurring periods of psychotic thoughts (brief intermittent psychotic syndrome); and high genetic risk of developing schizophrenia, coupled with declines in performance at work and school or inattention to regular life activities (e.g., hygiene, hobbies). Early intervention purportedly dramatically improves patient recovery and cost of in-patient services. RAISE (Recovery After an Initial Schizophrenia Episode) is a government-led, early intervention program for patients experiencing initial symptoms of schizophrenia. These patients may benefit from lower dosages of known effective antipsychotic medications and are more likely to successfully reintegrate into their previous lives. The 2 funded study arms of the program are the RAISE Early Treatment Program (ETP) and RAISE Connection. Both studies are designed for patients aged 18–35 years who have experienced initial episodes of schizophrenia, and they provide up to 2 years of multifaceted services that include individual counseling and psychiatric services, low-dosage antipsychotics, substance-abuse treatment, and job and school reintegration support. National Institute of Mental Health, Bethesda, MD, in collaboration with multiple research centers and State-level mental health programs Phase II/III clinical trials ongoing	Higher-dosage typical and atypical antipsychotic medications Self-help groups Talk therapy (including cognitive behavior therapy and group therapy)	Changed care delivery models Increased patient knowledge and awareness of disease and holistic intervention options Advanced intervention timelines Reduced but efficacious pharmaceutical dosages Improved quality of life
Rapastinel for treatment-resistant major depressive disorder	Patients in whom major depressive disorder (MDD) or treatment-resistant MDD has been diagnosed	Fewer than half of patients with MDD achieve remission with antidepressant therapy, and available pharmacotherapies are often associated with undesirable side effects. An unmet need exists for safe, effective interventions. Rapastinel (GLYX-13), a functional partial agonist selective modulator of the NMDA receptor (NMDAR), is an experimental medication purported to treat MDD using a novel mechanism, targeting glycine-site regions of the NMDAR. In clinical trials, rapastinel is administered intravenously at doses of 5 mg/kg biweekly, or 5 or 10 mg/kg weekly, as an adjunct therapy to a patient's current antidepressant prescription. Allergan, plc, Dublin, Ireland (manufacturer) Naurex, Inc., Evanston, IL (original developer and clinical trial sponsor) Phase II trials ongoing; Mar 2014, FDA granted fast-track status as adjunct therapy for treatment-resistant MDD	Cognitive behavior therapy Combination treatment Other NMDAR modulators (e.g., ketamine) Psychotherapy Selective serotonin reuptake inhibitors	Improved depression rating scale scores Reduced symptom severity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Telemedicine-facilitated psychotherapy for treatment of post-traumatic stress disorder	Patients in whom post-traumatic stress disorder (PTSD) has been diagnosed Rurally-residing patients in whom combat-related PTSD has been diagnosed	PTSD is a mental health disorder marked by an individual experiencing recurrence (flashbacks, nightmares, and event-related negative thoughts), avoidance, and hyperarousal symptoms after a traumatic event. According to the National Institute of Mental Health, 6.8% of adult Americans will experience PTSD during their lifetimes; 9% of military veterans (nearly 500,000 Americans) have received a diagnosis of PTSD. Although many patients reside in areas with access to expansive PTSD treatment, a disproportionate number of patients, particularly veterans—more than 40%—live in rural or remote areas with limited services. An unmet need exists for interventions that can be employed to treat rurally located patients who have PTSD. Telemedicine (telepsychiatry)-based collaborative care enables remote delivery of psychiatric and psychological care, clinician consultation and pharmacotherapy prescription, and patient management by trained professionals. Using this model, patients in rural locales receive comprehensive, cost-effective, evidence-based mental health services, similar to their more urban-residing counterparts. Telemedicine can also facilitate improved patient adherence and function as an adjunct to face-to-face treatment. In clinical trials, telemedicine is used to deliver 1 of several standard PTSD psychotherapies (e.g., cognitive processing therapy, cognitive behavior therapy, prolonged exposure); psychotherapy is delivered on the same schedule as standard in-person therapy. Study sponsors and collaborators include: Veterans Affairs Boston Healthcare System, Boston, MA (study sponsor) Veterans Affairs Puget Sound Health Care System, Seattle, WA (study sponsor) U.S. Department of Defense, Arlington, VA (collaborator) U.S. Department of Veterans Affairs, Washington, DC (collaborator) University of Pennsylvania, Philadelphia (collaborator) Phase II, III, and unphased clinical trials ongoing	In-person clinical evaluation and psychotherapy	Improved symptoms and reduced comorbidities Reduced geographically based mental health care disparities Reduced secondary health care burden on local and national Veterans Affairs systems Improved health care resource management Improved quality of life

Table 6. AHRQ Priority Condition: 06 Developmental Delays, Attention-Deficit/Hyperactivity Disorder, and Autism: 7 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Controlled-release oral diazoxide choline (DCCR) for treatment of Prader-Willi syndrome	Patients in whom Prader-Willi syndrome (PWS) has been diagnosed	PWS is a rare genetic disorder caused by random deletion or lack of expression of specific genes on the paternal copy of chromosome 15. Patients who have PWS may exhibit multiple symptoms, including mild to severe deficits in learning, attention, auditory processing, and spoken-language skills; and extreme appetite (hyperphagia), potentially leading to morbid obesity. Investigators have not found a cure for PWS, and standard treatments, such as hormone treatments and speech and occupational therapy, focus primarily on addressing patients' most severe symptoms. DCCR, a controlled-release crystalline salt formulation of diazoxide, is being investigated as a potential treatment. Diazoxide is a potassium channel activator that inhibits insulin secretion and is approved for treating hypoglycemia; as an allosteric potentiator of AMPA receptors, diazoxide may also improve or reinforce cognitive function. Hypothetically, a controlled form of this drug may treat both cognitive and hyperphagic PWS symptoms. In clinical trials, DCCR is administered as an oral tablet, from 1.5 to 5.1 mg/kg, titrated every 14 days. Essentialis, Inc., Carlsbad, CA Phase III trial ongoing; May 2014, FDA granted orphan drug status	Behavioral and cognitive therapy Dietary intervention and close management	Improved cognitive function Reduced abnormal appetite Reduced rate of morbid obesity Improved quality of life
Dasotraline for treatment of attention-deficit/hyperactivity disorder	Patients in whom attention-deficit/hyperactivity disorder (ADHD) has been diagnosed	Among Americans, ADHD is a common disorder, affecting about 4.4% of adults and a similar percentage of children. Treatments primarily include stimulants and antidepressants but are often not effective and may have significant side effects and potential for abuse. Dasotraline (SEP-225289) is an antidepressant derivative of sibutramine (an appetite suppressant voluntarily withdrawn from the market because of increased risk of cardiovascular events in clinical trials) that functions as a reuptake inhibitor of serotonin, norepinephrine, and dopamine. Because it maintains a stable level in the bloodstream throughout a full day, single, daily dasotraline doses are purported to effectively treat ADHD symptoms. In clinical trials, adults patients are administered dasotraline orally, once daily, in flexible doses of 4, 6, or 8 mg; pediatric patients are administered daily oral doses up to 4 mg. Sunovion division of Dainippon Sumitomo Pharma Co., Ltd., Osaka, Japan Phase II/III and III trials ongoing	Antidepressants (e.g., bupropion) Atomoxetine (Strattera®) Extended-release metadoxine (experimental) Stimulants (e.g., dextroamphetamine, dextroamphetamine-amphetamine, lisdexamfetamine)	Increased attentiveness Improved scores on standardized ADHD scales (e.g., Sheehan Disability Scale, Behavior Rating Inventory of Executive Function®-Adult Version) Reduced risk of abuse and improved safety profile, compared with existing treatments Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Extended-release metadoxine for treatment of adult predominantly inattentive type attention-deficit/ hyperactivity disorder	Adults in whom predominantly inattentive attention-deficit/hyperactivity disorder (ADHD) has been diagnosed	Among Americans, adult ADHD is a common disorder, affecting about 4.4% of the population. The most common subtype of ADHD is the predominantly inattentive type (also referred to as ADHD-I or PI-ADHD), which is marked by maladaptive levels of inattention, without hyperactivity and impulsivity. It can range in severity from well-managed to significantly debilitating. Treatments primarily include stimulants and antidepressants, but these treatments are often not well-tolerated or effective and may have significant side effects and potential for abuse. Metadoxine (MG01C1) is a nonstimulant, extended-release, ion-pair salt of pyridoxine and 2-pyrrolidone-5-carboxylate. It purportedly treats adult predominantly inattentive type ADHD by improving general cognitive performance and reducing observed ADHD symptoms, as measured by Connors' Adult ADHD Rating Scale. In a late-phase clinical trial, metadoxine is administered orally at a daily dose of 1,400 mg for 6 weeks. Alcobra, Ltd., Tel Aviv, Israel Phase II and III trials ongoing	Antidepressants (e.g., bupropion) Atomoxetine (Strattera®) Stimulants (e.g., dextroamphetamine, dextroamphetamine-amphetamine, lisdexamfetamine)	Increased attentiveness Improved scores on standardized ADHD scales (e.g., Connors') Reduced risk of abuse and improved safety profile, compared with existing treatments Improved quality of life
Multi-family group psychoeducation program (Transitioning Together) for treatment of adolescent autism spectrum disorders	Adolescent patients in whom autism spectrum disorders (ASDs) have been diagnosed and their parents or primary guardians	According to the U.S. Centers for Disease Control and Prevention, autism spectrum disorders (ASDs) are diagnosed in about 9 of 1,000 people in the U.S; among adolescent Americans, 1 in 88 have diagnosed ASDs. Few nonpharmaceutical interventions exist for treating these adolescents, and available treatments do not adequately address the impact of these disorders on interpersonal family dynamics. Transitioning Together is a group psychoeducational intervention that purports to treat adolescents with ASD and their parents, who are often primary caregivers and subject to ASD-related stress and other adverse effects. This intervention focuses on reducing family stress and addressing ASD-related behavioral problems in an effort to improve patients' and families' daily functioning and quality of life; the multi-family aspect is also hypothesized to provide an effective venue for open, nonjudgmental exchange and interaction among those affected by ASDs. In pilot studies, patients and their families completed an 8-week program, consisting of 2 individual-family sessions and 8 multi-family group sessions, each administered by a trained facilitator. Waisman Center, University of Wisconsin-Madison Unphased clinical trials ongoing	Individual cognitive behavior therapy	Improved patient-guardian interfamily dynamics Reduced ASD-related behavioral symptoms Reduced caregiver stress Improved patient and caregiver quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label mecasermin (Increlex) for treatment of Rett's syndrome	Children aged 2–12 years in whom Rett's syndrome has been diagnosed	Rett's syndrome is a rare neurological disorder caused by mutations to the *MECP2* gene. This disorder predominantly affects females and has a prevalence of 1 in 10,000 live female births. Patients with Rett's syndrome have significant cognitive and motor impairment and many experience seizures and repetitive stereotyped hand movements; these symptoms can be mistaken for Angelman's syndrome, autism, or cerebral palsy. No cure exists for Rett's syndrome, but research has shown that recovering *MECP2* function may be a potential curative pathway. Mecasermin (Increlex®) is a synthetic form of insulin-like growth factor-1 (IGF-1). Investigators hypothesize that mecasermin stimulates synaptic maturation, improving cognitive function and reversing *MECP2*-mutation effects in patients with Rett's syndrome. In clinical trials, mecasermin is administered twice daily, via subcutaneous injection, in escalating doses up to 120 mcg/kg. Children's Hospital of Boston, Boston, MA International Rett Syndrome Foundation, Cincinnati, OH Phase II trial ongoing; Aug 2005, FDA approved mecasermin for treating children with short stature due to IGF-1 deficiency	Common palliative interventions (e.g., antidepressants and antipsychotics [for mood and behavioral issues]; beta blockers [for long-QT symptoms]; occupational, physical, and speech therapy; sleep aids)	Improved cognitive functioning Reduced behavioral symptoms Improved quality of life
Video game-based therapy for attention-deficit/ hyperactivity disorder	Adolescents in whom attention-deficit/hyperactivity disorder (ADHD) has been diagnosed	ADHD is the most-diagnosed behavioral disorder in children, affecting about 3% to 5% of children. ADHD can cause depression, sleeping problems, anxiety, learning disabilities, and other behavioral abnormalities. Available ADHD treatments have variable outcomes, warranting the development of more innovative treatments. Research has suggested that action video games can improve a person's cognitive abilities. Video game therapy is intended to improve concentration skills, reduce anxiety, and enforce correct and quick decisionmaking, skills lacking in patients with neurological conditions such as ADHD. Therapy is delivered online. 2 companies have petitioned FDA to have their software regulated as devices delivering therapy. Akili Interactive Labs, Boston, MA (developer/manufacturer) Posit Science Corp., San Francisco, CA (developer/manufacturer) Brain Plasticity, Inc., San Francisco, CA (licensee) Multiple unphased clinical trials ongoing	Behavior therapies Combination therapies Drug therapies	Improved attentiveness and academic performance Reduced behavioral abnormalities Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Virtual reality social cognition training for treatment of adult autism spectrum disorders	High-functioning adult patients in whom autism spectrum disorders (ASDs) have been diagnosed	According to the U.S. Centers for Disease Control and Prevention, autism spectrum disorders (ASDs) are diagnosed in about 9 of 1,000 people in the U.S. Even for high-functioning adults with these diagnoses, deficits in social and emotional cognition can inhibit their ability to successfully navigate social situations, including maintaining close friendships and interacting in work environments. Cognitive behavior therapy may improve performance in these situations, but has limited effectiveness for many patients, who are unable to functionally translate techniques outside of therapeutic sessions. Virtual reality social cognition training is a computer-based intervention that allows patients to experience dynamic, real-life social interactions in a simulated environment, purportedly allowing effective, nonthreatening opportunities to practice and improve social skills. In clinical trials, patients participate in virtual reality training for 2 hours per week, for 5 weeks. Yale Child Study Center, Yale University, New Haven, CT University of Texas at Dallas Unphased clinical trial ongoing	Cognitive behavior therapy	Improved independent functioning Increased social cognition, emotional skills, and engagement Reduced social anxiety Improved patient quality of life

Table 7. AHRQ Priority Condition: 07 Diabetes Mellitus: 17 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Alpha-1 antitrypsin (Glassia) for treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus (T1DM) has been diagnosed	Nearly 26 million children and adults in the U.S., or 8.3% of the population, have diabetes mellitus, and about 5% of these are cases of T1DM. In about 7.0 million of all those with diabetes, the disease remains undiagnosed. In 2010, clinicians diagnosed 1.9 million new cases of diabetes in U.S. people aged 20 years or older. Treatment requires a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and for T1DM and some cases of type 2 diabetes, taking insulin. Alpha-1 antitrypsin (AAT; Glassia®) has shown anti-inflammatory properties, and although the level of AAT in diabetes patients is normal, its activity appears to be significantly lower. These anti-inflammatory properties are believed to have potential to interfere with or even prevent autoimmune destruction of beta cells in the pancreas. AAT is administered intravenously at 40, 60, or 80 mg per dose, in 4-week intervals. Kamada, Ltd., Ness Ziona, Israel National Institute of Allergy and Infectious Disease, Bethesda, MD University of Colorado, Denver, in collaboration with Omni Bio Pharmaceuticals, Inc., Greenwood Village, CO Phase II/III trial ongoing; Aug 2011, FDA granted orphan drug status	Insulin modifications Islet cell transplantation Pancreas transplantation	Reduced daily insulin usage Improved glycated hemoglobin (HbA_{1c}) levels Reduced complications of diabetes Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Artificial pancreas device systems for treatment of diabetes requiring exogenous insulin	Patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) who require insulin and are highly motivated to use a closed system and monitor its function	Nearly 26 million children and adults in the U.S., or 8.3% of the population, have diabetes mellitus, and about 5% of these are cases of T1DM. In about 7.0 million of all those with diabetes, the disease remains undiagnosed. In 2010, clinicians diagnosed 1.9 million new cases of diabetes in U.S. people aged 20 years or older. Treatment requires a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and for T1DM and some cases of type 2 diabetes, taking insulin. An artificial pancreas device system (APDS) is a closed-loop system consisting of an insulin pump, a real-time glucose monitor, and a sensor to detect glucose levels. Various manufacturers have made components required for the artificial pancreas; however, no single manufacturer has yet succeeded in creating a total closed-loop system. Several systems are in trials, and the 1st low-glucose suspend system, a 1st step to a total APDS, is commercially available. Various manufacturers in collaboration with JDRF, New York, NY More than 25 early and mid-phase ongoing trials; FDA placed APDSs on innovation pathway and issued final regulatory guidance on the systems Nov 2012; FDA is prioritizing review of research protocols, setting performance and safety standards, holding discussions between government and private researchers, sponsoring public forums, and finding ways to shorten study and review time.	Insulin modifications Islet cell transplantation Pancreas transplantation	Halted or delayed progression of secondary complications Reliable glycemic control at desired levels Reduced risk of acute and nighttime hypoglycemia Reduced postprandial (after meal) hyperglycemia Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous dendritic cell immunotherapy (DV-0100) for type 1 diabetes	Patients in whom type 1 diabetes mellitus (T1DM) has been diagnosed	Nearly 26 million children and adults in the U.S., or 8.3% of the population, have diabetes mellitus, and about 5% of these cases are T1DM. In 2010, clinicians diagnosed 1.9 million new cases of all types of diabetes in U.S. people aged 20 years or older. T1DM treatment requires a lifelong commitment to regular exercise, healthy weight, excellent nutrition, frequent monitoring of blood sugar, and taking various formulations of insulin by either injection or an infusion pump. DV-0100 is an autologous dendritic cell immunotherapy intended to treat T1DM by halting the body's autoimmune reaction against pancreatic islet cells, thus enabling the pancreas to produce insulin normally. According to the developer, dendritic cells are collected from the patient's blood, modified through use of interfering oligonucleotides to develop a "diabetes-suppressive" capability and tested for potency and sterility. The patient then is vaccinated with the cells, which are purportedly absorbed, and travel to the pancreatic lymph nodes to induce tolerance. DiaVacs, Inc., Edgewater, NJ Phase II trial ongoing; FDA granted orphan drug status	Insulin modifications Islet cell transplantation Pancreas transplantation	Increased beta cell function Improved glycemic control Reduced or eliminated need for exogenous insulin
Combination metformin-microbiome modulator (NM505) for treating type 2 diabetes mellitus	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	Metformin is effective 1st-line therapy for T2DM, but as many as 40% of patients with newly diagnosed T2DM may withdraw from therapy within the 1st year or combine it with another drug because of metformin's gastrointestinal side effects, such as diarrhea and abdominal cramps and pain. NM505 combines metformin and proprietary microbiome modulators with the goal of improving metformin tolerability while further reducing blood glucose levels in patients with T2DM. The company's plant-based microbiome modulators are intended to correct the microbial imbalances in the gut associated with high blood glucose levels and excess weight in T2DM and prediabetes. NM505 is formulated for oral administration; no information is available on dosing. MicroBiome Therapeutics™, LLC, New Orleans, LA May 2015, received FDA authorization to pursue 505(b)(2) expedited pathway; company plans new drug application submission in 2017	Metformin (alone)	Improved metformin tolerance Improved treatment adherence Reduced complications

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Degludec ultra-long-acting insulin (Tresiba) and degludec plus aspart (Ryzodeg) for treatment of type 1 or 2 diabetes	Patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) who require insulin or insulin and oral medication	Nearly 26 million children and adults in the U.S., or 8.3% of the population, have diabetes mellitus, and about 5% of these are cases of T1DM. In about 7.0 million of all those with diabetes, the disease remains undiagnosed. In 2010, clinicians diagnosed 1.9 million new cases of diabetes in U.S. people aged 20 years or older. Treatment requires a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and for T1DM and some cases of T2DM, taking insulin. Degludec (Tresiba®) is an ultra-long-acting insulin that releases over several days—its action extends beyond 42 hours, according to the company. The flexible dosing regimen allows 8–40 hours between dosing, which could lead to thrice-weekly dosing, or dosing once in the evening. Novo Nordisk a/s, Bagsværd, Denmark Phase III trials (BEGIN and BOOST) completed for degludec and degludec plus aspart; Nov 2012, FDA advisory committee voted 8-4 to recommend approval of both formulations; FDA panel unanimously also recommended a cardiovascular outcomes trial be conducted; FDA issued complete response letter in Feb 2013 for both drugs requesting additional cardiovascular data from a dedicated cardiovascular outcomes trial; company resubmitted to FDA and application was accepted for review Apr 2015; approved Sept 2012 in Japan; submitted for approval in Europe	Diet and lifestyle changes Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sodium glucose co-transporter 1 and/or 2 inhibitors (in development) Sulfonylurea drugs (glimepiride)	Achieved target glycated hemoglobin (HbA_{1c}) levels Reduced progression of complications Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Exenatide continuous subcutaneous delivery (ITCA 650) for treatment of type 2 diabetes	Patients with type 2 diabetes mellitus (T2DM) who have not achieved desired blood glucose goals with metformin	Nearly 26 million children and adults in the U.S., or 8.3% of the population, have diabetes mellitus, and about 5% of these are cases of type 1 diabetes mellitus (T1DM). In about 7.0 million of all those with diabetes, the disease remains undiagnosed. In 2010, clinicians diagnosed 1.9 million new cases of diabetes in U.S. people aged 20 years or older. Treatment requires a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and for T1DM and some cases of T2DM, taking insulin. Despite available treatments and blood glucose monitoring devices for T2DM, achieving adequate glycemic control remains a prominent issue for patients. ITCA 650 is a proprietary form of exenatide (a glucagon-like peptide-1 [GLP-1] mimetic) delivered subcutaneously and continuously through a tiny implanted stick-shaped pump. It purportedly remains stable at body temperature for as long as a year, according to the most recently presented data. The delivery system is a semipermeable, osmotic mini-pump that a physician or physician assistant implants into the patient's arm or abdomen during an outpatient procedure that takes about 5 minutes. The device is intended to deliver a steady dose for up to 12 months (after which it must be reimplanted), potentially providing a more convenient dosing option for patients. The system is also designed to minimize the nausea associated with twice-daily dosing. Amylin Pharmaceuticals subsidiary of Bristol-Myers Squibb, New York, NY (drug) Intarcia Therapeutics, Inc., Hayward, CA (device) Phase III trials ongoing; ITCA 650 technology FDA approved for drug delivery; exenatide formulation for use with pump is under study; Nov 2011, Eli Lilly and Co. (Indianapolis, IN) returned all development rights of exenatide to Amylin	Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sodium glucose co-transporter 1 and/or 2 inhibitors (in development) Sulfonylurea drugs (glimepiride)	Delayed insulin dependence in T2DM Improved target glycated hemoglobin (HbA_{1c}) levels Reduced glycemic excursions Improved quality of life
Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema	Patients in whom diabetic macular edema (DME) has been diagnosed	DME affects an estimated 560,000 patients in the U.S. Only a single FDA-approved drug therapy (ranibizumab) is available for treating DME. Iluvien® is a tube-shaped implant that releases a steady flow of the corticosteroid fluocinolone acetonide (FAc) into the ocular space for up to 3 years. FAc is a corticosteroid that has both anti-inflammatory and anti-VEGF (vascular endothelial growth factor) activity and has a history of effectiveness in treating ocular disorders. Alimera Sciences, Inc., Alpharetta, GA FDA approved Sept 2014 for treating DME	Intravitreal triamcinolone acetonide with or without laser photocoagulation Laser photocoagulation Pharmacotherapy (e.g., VEGF antagonists)	Increased visual acuity Increased contrast sensitivity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Implantable bioartificial pancreas (ßAir) for treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus (T1DM) has been diagnosed	Nearly 26 million children and adults in the U.S., or 8.3% of the population, have diabetes mellitus, and about 5% of these are cases of T1DM. In about 7.0 million of all those with diabetes, the disease remains undiagnosed. In 2010, clinicians diagnosed 1.9 million new cases of diabetes in U.S. people aged 20 years or older. Treatment requires a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and for T1DM and some cases of type 2 diabetes, taking insulin. Artificial pancreas device systems typically consist of an insulin pump, a real-time glucose monitor, and a sensor to detect glucose levels and automatically adjust and deliver appropriate insulin doses. The ßAir bioartificial pancreas is a macroencapsulation system consisting of islets of Langerhans (pancreatic islet cells) subcutaneously implanted in the abdomen, which purportedly controls the body's insulin and glucagon production. The system consists of a hockey puck–sized implant, which also contains an oxygen reservoir to maintain cell viability. It is implanted in a 30–60 minute inpatient procedure with external ports for daily oxygen replacement. Patients treated with the bioartificial pancreas do not require immunosuppressive drug therapy, which is indicated for life in traditional islet cell transplantation. The manufacturer is currently sourcing cells from human cadavers, but has plans to use porcine, stem cell, and live human donation cells. Beta-O2 Technologies, Ltd., Rosh-Haayin, Israel Uppsala University Hospital, Uppsala, Sweden Phase I/II trial ongoing	Insulin modifications Islet cell transplantation Pancreas transplantation	Increased beta cell function Improved glycemic control Reduced or eliminated need for exogenous insulin

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Implantable glucose monitoring system (GlySens system) for blood glucose monitoring	Patients with type 1 diabetes mellitus (T1CM) or type 2 diabetes mellitus (T2DM) who require regular glucose monitoring	Continuous glucose monitoring (CGM) systems are used by patients with diabetes to check their blood glucose levels. Because available CGM devices are purportedly not as accurate as standard blood glucose meters, patients must confirm glucose levels with a meter before changing their treatment on the basis of a CGM measurement alone. Also, traditional CGM sensors need to be replaced after several days or a week. The GlySens implantable CGM is intended as a long-term CGM purported to work continuously for up to 1 year or longer. The system consists of 2 components: a fully implantable sensor and an external receiver with monitor that displays “continuous, at-a-glance” glucose status and provides alerts if hypo- or hyperglycemic excursions occur. The sensor is implanted subcutaneously in the abdomen during a brief outpatient procedure and purportedly requires minimal calibration. The device does not need the needle insertion or skin-adhered components that other CGMs do. GlySens, Inc., San Diego, CA Unphased safety and feasibility/tolerance study ongoing under FDA investigational device exemption; Aug 2015, FDA approved change in ongoing implanted device evaluation duration from 6 to 12 months	Conventional blood-based glucose monitors Standard blood glucose testing	Improved compliance with glucose testing Improved management of blood glucose levels Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Metabolic surgery for treatment of type 2 diabetes mellitus regardless of body mass index	Obese and nonobese patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	Nearly 26 million children and adults in the U.S., or 8.3% of the population, have diabetes mellitus, and about 5% of these are cases of type 1 diabetes mellitus (T1DM). In about 7.0 million of all those with diabetes, the disease remains undiagnosed. In 2010, clinicians diagnosed 1.9 million new cases of diabetes in U.S. people aged 20 years or older. Treatment requires a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and for T1DM and some cases of T2DM, taking insulin. Metabolic surgery (i.e., gastric bypass, lap banding, sleeve gastrectomy) has been observed to restore metabolic imbalances in morbidly obese patients who have undergone bariatric surgery for weight loss. This led to interest in the surgery for patients with diabetes who are not morbidly obese, but are overweight or even normal weight, because researchers have observed that metabolic abnormalities have resolved independent of weight loss, and some think weight is not the only factor contributing to the metabolic abnormalities observed in patients with T2DM. Some researchers suggest that metabolic surgery could be used to possibly “cure” T2DM regardless of body mass index (BMI) and independent of weight loss. Multiple U.S. academic research centers Mid- to late-phase trials completed and ongoing	Behavior and lifestyle modifications Various approved drugs for treating T2DM G-protein coupled receptor 40 agonists (in development) Sitagliptin Sodium glucose co-transporter 1 and/or 2 inhibitors (in development) Sulfonylurea drugs (glimepiride)	Reduced use of diabetes medications Reduced secondary complications Resolution of diabetes Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Noninvasive glucose monitoring device (GlucoTrack) for monitoring blood glucose levels	Patients with diabetes who require regular blood glucose monitoring	Nearly 26 million children and adults in the U.S., or 8.3% of the population, have diabetes mellitus, and about 5% of these are cases of type 1 diabetes mellitus (T1DM). In about 7.0 million of all those with diabetes, the disease remains undiagnosed. In 2010, clinicians diagnosed 1.9 million new cases of diabetes in U.S. people aged 20 years or older. Treatment requires a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and for T1DM and some cases of type 2 diabetes (T2DM), taking insulin. Options to improve patients' self blood-glucose monitoring are needed to improve adherence to treatment and management of diabetes. GlucoTrack® is a noninvasive blood glucose monitoring device that obtains glucose measurements from an ear lobe clip. It is intended for use by patients with T1DM or T2DM. The system uses ultrasonic, electromagnetic, and thermal technology purportedly to detect glucose levels in the blood. It consists of a battery-operated main unit with display and control features. The main unit also houses a transmitter, receiver, and processor. The system includes a personal ear clip that contains sensors and calibration electronics to obtain glucose measurements in less than 1 minute. Integrity Applications, Inc., Ashkelon, Israel Pilot trials completed; Aug 2015, company submitted presubmission documents to FDA for guidance on U.S. clinical trial protocol and U.S. regulatory pathway; has CE mark	Conventional skin-prick blood-based glucose monitors	Improved compliance with glucose testing Improved management of blood glucose levels Reduced monitoring costs

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Noninvasive skin measurement test (Diab-spot) for screening for type 2 diabetes	Patients at risk of developing type 2 diabetes mellitus (T2DM)	About 7 million of the 25.8 million people in the U.S. with diabetes have not been screened and had the disease diagnosed. Late detection typically leads to secondary complications (e.g., cardiovascular disease, nephropathy, neuropathy) that could be prevented or delayed with earlier diagnosis and treatment. Late diagnosis may occur for many reasons, including patient nonadherence with recommended screening that involves a blood sample. The Diab-spot® device is a portable tabletop unit that measures skin fluorescence to detect biologic markers associated with cumulative glycemic exposure, oxidative stress, and microvascular changes. Using an algorithm that adjusts for skin-tone variations, skin fluorescence measurements are indicated by a color: red for increased likelihood of T2DM; orange for increased likelihood of cardiovascular pathology; or green for low risk of either T2DM or impaired glucose tolerance. This device is intended for individuals 18 years or older who are at risk of prediabetes and/or T2DM. DiagnOptics, B.V., Groningen, the Netherlands Unphased trials completed; has CE mark and Health Canada License approval	Noninvasive glucose screening tests in development (i.e., GlucoTrack) Standard blood glucose testing	Delayed or prevented secondary complications Increased screening adherence Increased rate of early diagnosis Improved quality of life
Noninvasive skin measurement test (Scout DS) for screening for type 2 diabetes	Patients at risk of type 2 diabetes mellitus (T2DM)	About 7 million of the 25.8 million people in the U.S. with diabetes have not been screened and had the disease diagnosed. Late detection typically leads to secondary complications (e.g., cardiovascular disease, nephropathy, neuropathy) that could be prevented or delayed with earlier diagnosis and treatment. Late diagnosis may occur for many reasons, including patient nonadherence with recommended screening that involves a blood sample. The Scout DS® is a noninvasive portable tabletop unit that measures skin fluorescence to detect biologic markers associated with cumulative glycemic exposure, oxidative stress, and microvascular changes. Using an algorithm that adjusts for skin-tone variations, the skin fluorescence measurement is said to be converted into a Scout Diabetes Score in less than 4 minutes. This device is intended for individuals 18 years or older who are at risk of prediabetes and/or T2DM. Miraculins, Inc., Winnipeg, Manitoba, Canada Apr 2015, based on consultation with FDA, company announced tentative plans to submit application for FDA clearance under de novo regulatory pathway for Scout DS for identifying prediabetes; Health Canada cleared; CE marked	Standard blood glucose testing	Delayed or prevented secondary complications Increased screening adherence Increased rate of early diagnosis Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pexiganan cream (Locilex) for treatment of mild diabetic foot ulcer infections	Patients in whom mild diabetic foot ulcer infection (DFI) has been diagnosed	An estimated 3 million patients with diabetes have DFIs, and about 60% of all amputations are preceded by a DFI. Antibiotic resistance in DFIs is becoming increasingly more common, making treatment more difficult. Additionally, because patients with DFIs have impairments in their microvascular circulation, the effectiveness of systemic anti-infectives can be compromised because only low concentrations reach the infection. Topical anti-infectives that are effective against antibiotic-resistant bacteria would be an attractive treatment option for DFIs; however, no topical anti-infectives have been proved effective. Pexiganan acetate cream 1% (Locilex™) is a novel, topical, broad-spectrum antimicrobial peptide that is being investigated as a topical anti-infective agent for treating mild DFIs. It is purportedly effective against multidrug-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *enterococcus*, as well as other antibiotic-resistant bacteria. In clinical trials, pexiganan acetate 1% cream is applied twice daily. Dipexium Pharmaceuticals, LLC, New York, NY 2 phase III trials ongoing (OneStep 1 and OneStep2); company plans new drug application filing with FDA in 2016	Carbapenems Cephalosporins Clindamycin Fluoroquinolones Linezolid Lipopeptides Metronidazole Penicillins Topical antibiotics Topical antiseptics Vancomycin	Decreased systemic therapy–related side effects Decreased antibiotic resistance Improved quality of life
Pyridoxamine (Pyridorin) for treatment of diabetic nephropathy	Patients with type 2 diabetes mellitus who have been given a diagnosis of diabetic nephropathy	Treatments exist to manage symptoms of diabetic nephropathy, but none of these address the underlying cause, and few can slow disease progression. Pyridorin™ is an oral pharmaceutical that targets pathogenic oxidative chemistries, including advanced glycation end-products, toxic carbonyls, and reactive oxygen species, which develop in patients with diabetes and are considered a principal cause of diabetic microvascular disease. In clinical trials, the drug was given twice daily, 150 or 300 mg, for 1 year. NephroGenex, Inc., Research Triangle Park, NC Phase III trial ongoing; Jun 2014, FDA granted fast-track status	Dialysis (end-stage renal failure) Kidney transplantation (end-stage renal failure) Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors)	Reduced disease progression (as measured by serum creatinine and biomarkers) Improved renal function Reduced complications of diabetic nephropathy Increased survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Relamorelin for treatment of diabetic gastroparesis	Patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) and gastroparesis	Gastroparesis causes delayed gastric emptying in up to 30% of patients with T1DM or T2DM. Available treatments for diabetic gastroparesis treat only symptoms, work with varying degrees of efficacy, and subject patients to moderate adverse events, warranting a need for new treatments. Relamorelin (RM-131) is a ghrelin agonist purported to stimulate gastrointestinal (GI) motility. This compound is naturally derived from ghrelin, a GI hormone that stimulates GI motility, regulates feeding and absorption, and inhibits GI inflammatory responses. This drug will be administered subcutaneously with dosing regimens ranging from 10 to 100 mcg, daily, for 1 month. Rhythm, Boston, MA Phase II trial ongoing; FDA granted fast-track status	Antiemetics Botulinum toxin Dietary modifications Domperidone Erythromycin Gastric electrostimulation Metoclopramide Other antibiotics Parenteral nutrition	Decreased GI bacterial overgrowth Decreased bezoar development and intestinal obstruction Improved blood glucose control Improved gastric emptying
Ultra-rapid-acting inhaled insulin (Technosphere Insulin Inhalation System with Afrezza) for treating diabetes that requires insulin	Patients with type 1 or type 2 diabetes mellitus (T1DM or T2DM) who require insulin injections	Nearly 26 million children and adults in the U.S., or 8.3% of the population, have diabetes mellitus, and about 5% of these are cases of T1DM. In about 7.0 million of all those with diabetes, the disease remains undiagnosed. In 2010, clinicians diagnosed 1.9 million new cases of diabetes in U.S. people aged 20 years or older. Treatment requires a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and for T1DM and some cases of T2DM, taking insulin. Afrezza® is a combination drug/device product that combines powdered insulin and the Technosphere Technology Platform inhaler. Premeasured, single-use insulin cartridges are inserted a pocket-size inhaler. The insulin enters systemic circulation by rapidly dissolving in the lungs after being inhaled. Afrezza is categorized as an ultra-rapid-acting insulin therapy to be taken at mealtime by individuals with T1DM or T2DM who require exogenous insulin. The inhaled insulin is said to be able to reach maximum blood insulin concentration within 12–14 minutes and has a 2–3 hour duration of action. It is purportedly cleared from the body within 12 hours. The technology would not eliminate injection therapy, but would supplement it, reducing the number of daily injections needed. The inhaler device is small and fits within the palm of the user's hand. MannKind Corp., Valencia, CA (manufacturer) Sanofi, Paris, France (global marketing partner) FDA approved Jun 2014 for improving glycemic control in adult patients with diabetes; the approval included a risk evaluation and mitigation strategy requiring a plan to inform professionals about the serious risk of acute bronchospasm associated with Afrezza	Other ultra-rapid-acting insulin formulations and delivery modes	Improved target glycated hemoglobin (HbA_{1c}) levels Reduced glycemic excursions related to meals Delayed insulin dependence in T2DM Improved quality of life

Table 8. AHRQ Priority Condition: 08 Functional Limitations and Disability: 135 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
3-D printed bioresorbable trachea for treatment of tracheobronchomalacia	Patients in whom tracheobronchomalacia has been diagnosed	Tracheobronchomalacia is a congenital condition in which babies are born with weak cartilage in the airways, making them prone to collapsing. Most children grow out of it, except for about 10% with severe cases. When breathing is seriously comprised, clinicians perform a tracheotomy; however, this requires intensive care management and increases risk of infection. Stents and surgical mesh can be inserted for additional support but may require multiple surgeries. 3-dimensional (3-D) printing has been used to create an implantable, customized, bioresorbable implant using a computer-aided design based on a computed tomographic image that shows the patient's anatomy. The implant is fabricated with the biopolymer polycaprolactone using laser-based 3-D printing, which allows health care providers to create implants that are tailored to the individual patient. The implant is designed to expand as the patient grows and provide scaffolding for the patient's own cells to grow. It dissolves about 3 years after implantation. University of Michigan Health System, Ann Arbor Pilot study completed after FDA granted emergency use exemption	Tracheobronchial airway stent Tracheobronchoplasty Tracheotomy	Improved health outcomes Increased survival Improved quality of life
5-hydroxymethyl-furfural for treatment of sickle cell disease	Patients in whom sickle cell disease (SCD) has been diagnosed	SCD is an autosomal recessive disorder that affects about 100,000 people in the U.S. and Europe and can present as sickle cell anemia or sickle beta-0 thalassemia. Increased disease prevalence is seen in people of African and Mediterranean descent; about 1 in 500 African American children born have sickle cell anemia. In SCD, sickled red blood cells are more susceptible to oxidative damage and inappropriate adhesion, which can lead to vaso-occlusive crisis (VOC). VOC causes severe pain by obstructing vasculature; it requires hospitalization. Patients may progress to thromboembolic events, stroke, organ failure, or early death. The only FDA-approved treatment for SCD, hydroxyurea, can reduce VOC incidence but is not effective in about 1/3 of adult patients. 5-hydroxymethylfurfural, called BAX 555, purportedly binds to hemoglobin, increasing its oxygen affinity and stabilizing it. It may prevent blood cells from sickling. It administered orally, 1,000 mg, 4 times daily, as a liquid formulation. Baxalta, Inc., Bannockburn, IL Phase II trial terminated for unknown reasons; FDA granted orphan drug status	Blood transfusion Bone marrow transplant Hydroxyurea	Decreased pain Fewer hospitalizations Shorter hospitalizations Reduced incidence of VOCs Reduced organ damage Reduced mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Acellular biologic scaffold and targeted rehabilitation for treatment of volumetric muscle loss	Patients who have volumetric muscle loss in a leg after trauma	Patients who have experienced a severe trauma (e.g., improvised explosive device, skiing accident) to a leg may be debilitated from lost muscle. While some muscle regrowth is possible, it does not occur on a large scale. Researchers have developed a procedure that combines intensive physical therapy with a commercially available acellular biologic scaffold (porcine extracellular matrix) in the damaged muscle. As the scaffold degrades over several months, it releases biochemical signals that recruit stem cells. Physical therapy puts tension on the spot where stem cells are growing to help form muscle cells instead of scar tissue. Patients undergo intensive physical therapy before and after surgery to implant the scaffold. University of Pittsburgh Medical Center, PA, with funding from U.S. Department of Defense Unphased trials ongoing	Physical therapy	Improved function Muscle regrowth Improved quality of life
Alipogene tiparvovec (Glybera) for lipoprotein lipase deficiency	Patients in whom lipoprotein lipase deficiency (LPLD) has been diagnosed	LPLD is a rare genetic disorder, affecting about 1 in 1 million individuals, in whom the development of chylomicronemia leads to hypertriglyceridemia and acute pancreatitis. No treatments exist to address the underlying cause of the disease (loss of function of the lipoprotein lipase [*LPL*] gene). Alipogene tiparvovec (Glybera®) is an adeno-associated viral vector–based, gene-therapy product that encodes an LPL isoform intended to complement the genetic deficiency in patients with LPLD. Glybera is administered at a dose of $1x10^{12}$ genome copies/kg, in a single series of intramuscular injections. uniQure, N.V., Amsterdam, the Netherlands Phase III trial completed; Aug 2015, uniQure announced that FDA requires data from at least 1 additional trial to support a biologics license application; May 2007, FDA granted orphan drug status; Nov 2012, EU granted marketing approval for Glybera, under exceptional circumstances and subject to annual review, as the 1st approved gene-therapy drug in the EU	Standard of care, including low-fat diet	Improved plasma triglyceride levels Improved chylomicron (lipoprotein particle) levels

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Allosteric GABA-A receptor modulator (SAGE-547) for treatment of super-refractory status epilepticus	Patients in whom super-refractory status epilepticus (SRSE) has been diagnosed	Status epilepticus (SE) is a rare, potentially fatal condition in which patients' brains are in an acute, prolonged seizure state. In the U.S., SE has a prevalence of approximately 40 cases per 100,000 persons; an estimated 42,000 of these patients die within 30 days of their 1st SE seizure. Clinically, 2 types of SE are recognized; both can be diagnosed using blood tests, electroencephalography, imaging, and urinalysis. Standard SE treatment involves aggressively applying benzodiazepine, anticonvulsants, barbiturates, or anesthetics; 1 or more of these medications is often successful in eliminating seizures. However, in unresponsive patients with SRSE, continuously administered general anesthesia is required, and these patients face increased risks of infection and death. An unmet need exists for effective interventions for patients with this condition. SAGE-547 is an allosteric gamma aminobutyric acid A (GABA-A) receptor modulator that purportedly reduces seizures in patients with SRSE. In clinical trials, SAGE-547 is administered intravenously, as an adjunct to other therapies. SAGE Therapeutics, Cambridge, MA Pivotal phase III trial and expanded access trial ongoing; in 2014, FDA granted fast-track and orphan drug statuses; SAGE-547 is also being investigated for treating essential tremor and postpartum depression	Continuous intravenous general anesthesia (medically induced coma)	Reduced treatment-related infection rate Reduced mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Amifampridine (Firdapse) for treatment of Lambert-Eaton myasthenic syndrome	Patients in whom Lambert-Eaton myasthenic syndrome (LEMS) has been diagnosed	LEMS is a rare autoimmune disorder that disrupts electrical signalling at the neuromuscular junction. Because of this disruption, symptoms arise, including muscle weakness and tingling sensations at affected areas; patients with LEMS may also exhibit vision difficulty, fatigue, and dry mouth. More than half of patients with LEMS develop small cell lung cancer, with LEMS diagnoses preceding cancer diagnoses by up to 3 years. No cure exists for LEMS; common treatment options attempt to decrease the associated autoimmune response or improve electrical impulse transmission. Amifampridine (Firdapse®) is a potassium channel blocker and phosphate salt of 3,4-diaminopyridine, purported to treat LEMS by delaying nerve terminal repolarization; 3,4-diaminopyridine, through compassionate use and clinical trial expanded access allowances, has been used to treat LEMS. Investigators hypothesize that amifampridine's activity extends repolarization times, allowing calcium accumulation at nerve junctions and directly alleviating LEMS symptoms. In clinical trials, amifampridine tablets are orally administered 3–4 times daily, up to a daily dose of 80 mg, with a maximum single dose of 20 mg; it is intended as a chronic medication. If approved, amifampridine may potentially increase treatment costs among this patient population, with some speculation that comparable per-unit prices could be 100 times higher than reported for 3,4-diaminopyridine. BioMarin Pharmaceutical, Inc., San Rafael, CA (manufacturer) Catalyst Pharmaceutical Partners, Inc., Coral Gables, FL (U.S. licensee / primary clinical trial designee) Phase III and expanded access trials ongoing; Jul 2015, Catalyst initiated rolling new drug application; Aug 2013, FDA granted breakthrough therapy and orphan drug statuses; EU granted approval in 2010 for treating LEMS. In the U.S., amifampridine (as 3,4-diaminopyridine/DAP) is available on a compassionate-use basis through application to Catalyst or Jacobus Pharmaceutical Co., Princeton, NJ; amifampridine is also under investigation for treating congenital myasthenia gravis and other neuromuscular junction disorders	4-aminopyridine (not recommended because of side effects) Guanidine (not recommended because of side effects) Intravenous immunoglobulin (IVIG) Plasmapheresis Pyridostigmine Steroids	Increased mobility Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Antisense molecule (ISIS-SMNRx) for treatment of spinal muscular atrophy	Children in whom spinal muscular atrophy (SMA) has been diagnosed	SMA is an inherited neuromuscular disorder in which muscles atrophy and weaken, often resulting in death of infants born with the most severe form of the disorder. The disorder is caused by mutations to *SMN1,* a gene that normally encodes the survival motor neuron 1 (SMN) protein; abnormally low levels of SMN protein are a hallmark of SMA. SMA occurs in an estimated 1 in 10,000 live births worldwide. Affected infants typically appear normal at birth, and symptoms develop within several months after birth. Available SMA treatments only address disease symptoms. An unmet need exists for disease-modifying therapies for this patient population. ISIS-SMNRx is an antisense molecule that purportedly boosts levels of SMN protein by addressing an RNA splicing irregularity. In an ongoing trial enrolling children aged 2–14 years who are medically stable, ISIS-SMNRx is administered during a single injection of 1 of 4 dose levels into the spinal cord fluid. In clinical trials for infant patients, ISIS-SMNRx is administered as a single 6 mg or 12 mg injection. Biogen, Cambridge, MA Isis Pharmaceuticals, Inc., Carlsbad, CA 2 phase III trials ongoing investigating ISIS-SMNRx for treating adolescent patients; 1 phase II trial ongoing investigating ISIS-SMNRx for treating presymptomatic infants with genetically confirmed SMA; in 2011, FDA granted fast-track and orphan drug statuses	ChariSMA gene therapy (investigational) Supportive therapy	Reduced SMA symptoms Improved motor function Improved quality of life
Apical sodium-dependent bile acid transporter (SHP625) for treatment of cholestatic liver diseases	Patients in whom cholestatic liver disease has been diagnosed	Cholestatic liver diseases, including Alagille syndrome, progressive familial intrahepatic cholestasis, primary biliary cirrhosis, and primary sclerosing cholangitis, cause impaired bile acid flow and retention of bile acids in the liver. This can progress to severe liver damage and failure. Available treatment options have limited efficacy, and many patients eventually require surgical intervention or liver transplant. SHP625 is an apical sodium-dependent bile acid transporter inhibitor that purportedly cycles intestinal bile acids back into circulation. Trials are testing doses of 5, 10, and 20 mg, once daily, orally. Lumena Pharmaceuticals subsidiary of Shire, plc, Dublin, Ireland Phase II trials ongoing; FDA granted orphan drug status Sept 2013	Antipruritics Bile duct surgery Dietary changes Liver transplant Ursodeoxycholic acid	Improved health outcomes Improved liver function Improved symptoms (e.g., pruritus) Reduced serum bile acid levels Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Apremilast (Otezla) for treatment of Behçet's disease	Patients in whom Behçet's disease has been diagnosed	Behçet's disease is characterized by oral ulcers, genital ulcers, and eye disorders including uveitis, retinitis, and iritis. More than half of patients develop blurred vision, pain, redness, and eventually blindness. Apremilast purportedly inhibits phosphodiesterase type 4 (PDE-4), and increases intracellular cAMP, which modulates multiple inflammatory mediators and relieves the inflammatory symptoms of Behçet's disease. In clinical trials, it is administered at 30 mg, twice daily, orally. Celgene Corp., Summit, NJ Phase III trial ongoing; FDA granted orphan drug status; approved for treating psoriatic arthritis	Corticosteroids Immunosuppressants (e.g., azathioprine, cyclosporine) Nonsteroidal anti-inflammatory drugs (NSAIDs)	Improved visual symptoms Reduced pain and frequency of oral/genital ulcers Slowed disease progression Improved quality of life
Asfotase alfa (Strensiq) for treatment of hypophosphatasia in infants and children	Infants and children in whom hypophosphatasia has been diagnosed	Hypophosphatasia is a rare metabolic disorder caused by deficiency of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP). TNSALP is a phosphomonoesterase that plays a key role in regulating bone mineralization. Alterations in the *TNSALP* gene result in extracellular accumulation of inorganic pyrophosphate, leading to inhibited bone mineralization and resultant rickets or osteomalacia or both. Incidence has been estimated at 1 per 100,000 births. Asfotase alfa (Strensiq®) is an enzyme, a form of recombinant human TNSALP. This enzyme is fused to the Fc portion of human immunoglobulin G and attaches to a deca-aspartate bone-targeting peptide derived from osteopontin and bone sialoprotein. The enzyme has a high affinity for bone, allowing it to exert its effects with limited systemic effects and at a half-life 30% longer in bone than in serum. In clinical trials, asfotase alfa is administered as daily, subcutaneous injection of 0.3 or 0.5 mg/kg. Alexion Pharmaceuticals, Inc., Cheshire, CT Phase II and II/III trials ongoing; Mar 2015, FDA accepted Alexion's biologics license application for priority review, covering proposed infant- and juvenile-onset hypophosphatasia; in 2013, FDA granted breakthrough therapy, fast-track, and orphan drug statuses; asfotase alfa is approved in Canadian, European, and Japanese markets for treating hypophosphatasia	Cortisone Nutritional supplements: Magnesium Vitamin B_6 Zinc	Decreased risk of rickets and osteomalacia Restored bone mineralization Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ataluren (Translarna) for treatment of nonsense mutation dystrophinopathies	Patients in whom a nonsense mutation dystrophinopathy or nonsense mutation Duchenne muscular dystrophy (DMD) has been diagnosed	Dystrophinopathies are a class of muscle diseases caused by dystrophin genes that function abnormally or not at all. Dystrophinopathies have an X-linked inheritance pattern and almost exclusively affect males; of the various dystrophinopathies, the most common form is DMD, affecting 1 in 3,300 boys. About 13% of DMD cases are caused by a nonsense mutation that creates premature stop codons in transcribed mRNA, leading to nonfunctional dystrophin protein products. Ataluren (Translarna™) is a small-molecule compound purported to treat dystrophinopathies, including DMD caused by nonsense mutations; the manufacturer hypothesizes that ataluren interacts directly with ribosomes, decreasing sensitivity to premature stop codons. This decreased sensitivity purportedly enables ribosomes to read through nonsense mRNA stop codons and produce functional dystrophin protein. In clinical trials, adolescent male patients are administered 40 mg/kg ataluren in 3 daily doses (10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening) for about 96 weeks. PTC Therapeutics, Inc., South Plainfield, NJ Phase III trial ongoing; rolling new drug application submission to FDA initiated in Dec 2014; Mar 2015, manufacturer expanded ataluren access to affected siblings of patients enrolled in clinical trials; Jan 2005, FDA granted orphan drug status; ataluren (as Translarna) has marketing approval in 12 countries, and is also under investigation for treating nonsense mutation cystic fibrosis, aniridia, and mucopolysaccharidosis type I	Beta-2 agonists Corticosteroids Orthotic devices Physical therapy Respiratory support devices	Improved 6-minute walk test scores Reduced muscle weakness Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous adipose-derived stem cell therapy system (ECCS-50, Celution System) for treatment of impaired hand function in systemic sclerosis	Patients in whom systemic sclerosis with impaired hand function has been diagnosed	Systemic sclerosis is an autoimmune connective tissue disease marked by vasculopathy; skin thickening, due to collagen accumulation; auto-antibody formation; and inflammation leading to fibrosis in skin and internal organs. In the U.S., systemic sclerosis has an estimated prevalence of 2.4 patients per 10,000 persons; incidence rates are increased among women in mid-to-late childbearing years, African Americans, and Choctaw Native Americans. Patients with sclerosis-related hand impairment may experience reduced functional independence and significant focal pain. A cure for systemic sclerosis has not been found, and conventional therapies for related motor impairment have side effects and limited therapeutic efficacy. The Celution® system is an experimental intervention that purportedly rapidly and automatically processes viable adipose-derived stromal vascular fraction contents, including mesenchymal stem cells, mast cells, and preadipocytes. Researchers hypothesize that introduction of 1 or more of these biologics can alleviate inflammation and other symptoms underlying hand impairment in systemic sclerosis. In clinical trials, patients are treated with autologous stromal vascular fractions, obtained via lipoaspiration and processed within 2 hours, using a proprietary automatic system (Celution system); patients receive about 40 million adipose-derived stem cells per finger, delivered in 2 subcutaneous injections. Assistance Publique Hôpitaux de Marseille, Marseille, France (clinical trial investigators) Cytori Therapeutics, Inc., San Diego, CA (manufacturer and clinical trial investigator) Phase III trial ongoing; Jan 2015, FDA granted investigational device exemption for use in a pivotal trial	Cyclophosphamide Methotrexate	Reduced hand impairment Reduced systemic sclerosis-related pain Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous bone marrow mesenchymal stem cells (NurOwn) for treating amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	ALS is a progressive disorder marked by neurodegeneration of nerve cells in the brain and spinal cord. A 2014 report calculated that ALS prevalence is about 3.9 cases per 100,000 Americans. The average life expectancy of a patient with ALS is 3–5 years after diagnosis, and only 10% of patients survive for more than 10 years. Only 1 agent (riluzole) is FDA approved for treating ALS, and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function; novel therapies are urgently needed. NurOwn™ is a differentiated autologous adult mesenchymal stem cell (MSC) therapy intended to slow or halt ALS disease progression by regenerating damaged tissue and cells. The company terms the therapy MSC-NTF ("neuron-supporting cells") and collects MSCs from the patient's own bone marrow. The MSCs are processed in vitro using a proprietary process intended to differentiate the cells into astrocyte-like cells capable of releasing neurotrophic factors, including glial-derived neurotrophic factor, to repair and regenerate diseased tissue. The processed cells are reinfused through either a single intrathecal injection into the cerebrospinal fluid or multiple intramuscular injections into the patient's biceps or triceps. BrainStorm Cell Therapeutics, Inc., New York, NY (developer) Dana-Farber Cancer Institute Connell O'Reilly Cell Manipulation Core, Boston, MA (U.S. clinical trial collaborator) Massachusetts General Hospital, Boston (U.S. clinical trial collaborator) Mayo Clinic Human Cellular Therapy Laboratory, Rochester, MA (U.S. clinical trial collaborator) University of Massachusetts Memorial Hospital, Worcester (U.S. clinical trial collaborator) Phase II U.S. trial ongoing; phase IIa Israeli trial ongoing; Oct 2014, FDA granted fast-track status; Feb 2011, FDA granted orphan drug status	Physical therapy and assistive technology (e.g., speaking tubes, motored chairs) Riluzole (Rilutek®)	Slowed disease progression Maintained independence and activities of daily living Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous peripheral blood stem cell therapy for medically refractory inflammatory multiple sclerosis	Patients in whom an inflammatory form of multiple sclerosis (MS) has been diagnosed	Available treatments for MS may slow disease progression, but they are not effective in all patients, and the disease has no cure. An unmet need exists for safe, effective treatments for patients with treatment-refractory forms of inflammatory MS. Peripheral blood stem cell therapy purportedly addresses this need by preventing motor disability symptoms associated with MS. Autologous unmanipulated blood stem cells are obtained, conditioned with a regimen of cyclophosphamide and rabbit antithymocyte globulin (rATG), then infused back into the patient; research has suggested that this technique yields more hematopoietic stem cells than other methods, increasing treatment efficiency. In ongoing clinical trials, investigators hypothesize that this stem cell treatment will prevent further disability and may improve patients' performance on standard measures of MS symptom severity and functional limitation, including Expanded Disability Status Scale (EDSS) scores, timed walk, ambulation index, and relapse rates. European Group for Blood and Marrow Transplantation, Leiden, the Netherlands Northwestern University, Evanston, IL (study sponsor) Rush University Medical Center, Chicago, IL (research collaborator) University of São Paulo, São Paulo, Brazil (research collaborator) Uppsala University, Uppsala, Sweden (research collaborator) Sheffield Teaching Hospitals NHS Foundation Trust, Yorkshire, England (research collaborator) Phase II and III trials ongoing	Dimethyl fumarate (Tecfidera®) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Improved ambulation Improved EDSS scores Improved timed walk scores Reduced functional limitations Reduced relapse rates Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Avoralstat for prophylaxis of acute hereditary angioedema attacks	Patients in whom acute hereditary angioedema (HAE) has been diagnosed	HAE is a genetic disorder caused by dysfunction or deficiency of the plasma protein C1 inhibitor (C1INH). C1INH inhibits the C1 protease that is responsible for activating the complement pathway in the immune system. If C1INH is deficient, the immune system reacts with an inflammatory response that leads to swelling due to uncontrolled levels of bradykinin, a mediator of acute swelling. Infusions of C1INH concentrate or fresh frozen plasma may be given prophylactically but only for short-term use (e.g., before a dental procedure). Danazol is an oral androgen used prophylactically but has significant side effects that increase in frequency and severity the longer the drug is used. An unmet need exists for long-term prophylaxis. Avoralstat (BCX4161) is a selective plasma kallikrein inhibitor that purportedly suppresses bradykinin production. In clinical trials, it is administered orally, 300 or 500 mg, thrice daily. BioCryst Pharmaceuticals, Inc., Durham, NC Phase II/III trial ongoing; Jan 2015, FDA granted fast-track status after granting orphan drug status Dec 2014	C1INH (concentrate from donor blood) Danazol Fresh-frozen plasma	Improved symptoms Reduced mortality Improved quality of life
Beloranib for treatment of obesity related to Prader-Willi syndrome	Patients with Prader-Willi syndrome (PWS) in whom comorbid obesity has been diagnosed	PWS is a congenital chromosomal disorder characterized by compulsive overeating and the early development of obesity. The disorder typically causes low muscle mass and function, short stature, incomplete sexual development, a chronic feeling of hunger, and metabolism that uses drastically fewer calories than normal. This leads to excessive eating and life-threatening obesity. PWS occurs in males and females equally and in all races. Worldwide prevalence estimates range from 1 in 8,000 to 1 in 50,000. Obesity is identified as the main cause of morbidity and mortality in PWS; thus, weight reduction is important for prolonged survival. Beloranib is under development for this patient population; it inhibits methionine aminopeptidase 2 (MetAp2), which purportedly reduces hunger and blood flow to fatty tissues, starving them, and increasing metabolism of fat as an energy source. Researchers purport that this can induce weight loss. In clinical trials for treating PWS, beloranib is injected subcutaneously at dosages of 1.8 or 2.4 mg, twice weekly, for up to 28 weeks. Zafgen, Inc., Cambridge, MA Phase III trial ongoing; Jan 2013, FDA granted orphan drug status for treating PWS; beloranib is also under investigation for treating other obesity indications	Diet and lifestyle modifications Various obesity drugs on the market and under development Surgical interventions ZGN-433 (MetAp2 inhibitor)	Weight loss Decreased comorbidities Fewer adverse events Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bimagrumab for treatment of sporadic inclusion body myositis	Patients in whom sporadic inclusion body myositis (sIBM) has been diagnosed	sIBM is the most common acquired myopathy in patients older than 50 years and accounts for 16% to 28% of inflammatory myopathies in the U.S. In sIBM, inclusion bodies accumulate in muscle tissue and cause degeneration. The primary affected muscles are the wrist, finger, thigh, and calf muscles. sIBM progresses slowly, and patients may have limited mobility requiring a cane or wheelchair. Investigators have not found a definitive treatment. Bimagrumab (BYM338) is a monoclonal antibody that purportedly binds to type II activin receptors to prevent natural ligands (including myostatin and activin) from binding, thereby stimulating muscle growth. Bimagrumab is administered by intravenous infusion. Novartis International AG, Basel, Switzerland Phase II/III trials ongoing; FDA granted breakthrough therapy status; also studied for sarcopenia and cachexia associated with chronic obstructive pulmonary disease	No approved therapies exist	Improved motor function symptoms Reduced muscle loss Improved quality of life
Blisibimod for treatment of IgA nephropathy	Patients in whom immunoglobulin A (IgA) nephropathy has been diagnosed	IgA nephropathy is characterized by IgA accumulation in a patient's kidneys, which causes blood and protein to leak into urine. After 10–20 years, from 25% to 50% of adult patients and 5% to 10% of pediatric patients develop total kidney failure and require dialysis or a kidney transplant. Available treatments target symptom management and slow progression. Blisibimod (A-623) is a peptibody and selective antagonist of B-cell activating factor (BAFF) cytokine that potentially reduces production of IgA. If approved, blisibimod would be the 1st treatment intended to halt IgA nephropathy. Blisibimod is administered by subcutaneous injection. Anthera Pharmaceuticals, Hayward, CA, in collaboration with Zenyaku Kogyo Co., Ltd., Tokyo, Japan Phase III trial (BRIGHT-SC) ongoing	Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers Corticosteroids Dialysis Kidney transplant	Decreased creatinine levels Decreased IgA levels Decreased protein in urine Delayed or prevented end-stage renal failure Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Blood protein marker test for diagnosis of traumatic brain injury	Patients being evaluated for a suspected traumatic brain injury who are characterized as having a mild to moderate head injury (Glasgow coma scale score between 9 and 15)	Mild traumatic brain injury (i.e., concussion) can be difficult to diagnose with available methods, and the lack of a quantitative diagnostic test hampers the process of identifying the condition, estimating prognosis, and tracking improvement. Research has indicated that certain brain-specific proteins may cross the blood-brain barrier when traumatic injury is present, and these proteins could serve as blood-based biomarkers for traumatic brain injury. A point-of-care diagnostic test based on 2 proteins (ubiquitin carboxy-terminal hydrolase L1 [UCHL1] and glial fibrillary acidic protein [GFAP]) is under study as a test for traumatic brain injury. Abbott Laboratories, Abbott Park, IL (licensee) Banyan Biomarkers, Inc., Alachua, FL (principal developer) U.S. Department of Defense, Arlington, VA (development collaborator) Unphased trial completed; Aug 2014, Banyan licensed its intellectual property to Abbott for validation and verification	Clinical neurologic evaluation Computed tomography Magnetic resonance imaging	Improved sensitivity Improved specificity
Caspase 2 siRNA (QPI-1007) for treatment of nonarteritic anterior ischemic optic neuropathy	Patients in whom nonarteritic anterior ischemic optic neuropathy (NAION) has been diagnosed	NAION is characterized by a loss of blood flow to the optic nerve, causing the death of retinal ganglion cells. It has a sudden onset and leads to mild to total vision loss in the affected eye. Its cause is unknown, but some patients may have anatomical variations of the optic nerve that contribute to it. NAION causes irreversible vision loss and has no approved treatments. QPI-1007 is a synthetic siRNA that temporarily inhibits expression of caspase 2. It purportedly has neuroprotective properties that may preserve retinal ganglion cells and vision. It is administered by intravitreal injection at an unspecified dose. Quark Pharmaceuticals, Inc., Fremont, CA Phase II/III trial ongoing; FDA granted orphan drug status	No treatments are available	Improved visual acuity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cenicriviroc for treatment of nonalcoholic steatohepatitis	Patients in whom nonalcoholic steatohepatitis (NASH) with liver fibrosis has been diagnosed	NASH is a liver disease characterized by fatty deposits, inflammation, and hepatocyte damage. It affects an estimated 2% to 5% of Americans, although it is asymptomatic for most patients. As NASH progresses over several years, it may lead to cirrhosis and permanent liver damage. In the most severe cases, patients require a liver transplant to survive. NASH's cause is unknown. People who are middle-aged, obese, or glucose intolerant are at higher risk of the disease, although some patients have none of these risk factors. For patients who alter their diets and exercise, NASH may be reversible. No other treatments exist. Cenicriviroc (CVC) is a dual inhibitor of the CCR2 and CCR5 pathways, which have roles in inflammation and fibrosis. It is administered at a dose of 150 mg, once daily, orally. Tobira Therapeutics, Inc., South San Francisco, CA Phase IIb trial (CENTAUR) ongoing; Jan 2015, FDA granted fast-track status	Improved diet and exercise	Decreased liver fat Decreased liver inflammation and damage Reduced rates of cirrhosis and liver failure Fewer liver transplantations Improved quality of life
Cholbam for treatment of bile acid synthesis disorders and peroxisomal disorders	Patients in whom bile acid synthesis disorders due to single-enzyme defects have been diagnosed Patients in whom peroxisomal disorders have been diagnosed	Certain bile acid synthesis disorders and peroxisomal disorders are caused by single-enzyme mutations resulting in deficiencies in enzymes that synthesize cholic acid or enzymes that produce abnormal, toxic cholic acid derivatives. Nationwide, these rare, often autosomal recessive disorders have a collective prevalence of 1 in every 50,000–70,000 live births. Patients who have any of these disorders display symptoms including enlarged spleens, jaundice, liver bleeds, and cirrhosis, malabsorption of fats, and poor growth; central nervous system symptoms can also occur when toxic cholic acid derivatives are transported from the liver. In severe cases, a liver transplant is required. Cholbam treats these disorders by downregulating cholesterol 7-alpha-hydroxylase, the rate-limiting enzyme in bile acid synthesis. This action inhibits production and accumulation of bile acid precursors, stimulates bile flow and secretion, and can facilitate fat absorption; Cholbam administration has also been reported to prevent production of toxic bile acid derivatives. It is administered as 50 or 250 mg capsules, in dosages of 10–15 mg/kg per day. Retrophin, Inc., San Diego, CA (manufacturer) Asklepion Pharmaceuticals, LLC, Baltimore, MD (developer and clinical trial sponsor) Mar 2015, FDA approved for treating pediatric and adult patients with bile acid synthesis disorders due to single-enzyme defects and for patients with peroxisomal disorders	Liver transplant Nutrient and vitamin supplements	Decreased rates of liver transplantation Improved liver function Reduced bile acid precursors Reduced toxic bile acid derivatives Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cholic and arachidic acid conjugate (Aramchol) for treatment of nonalcoholic steatohepatitis	Patients with nonalcoholic steatohepatitis (NASH), obesity, and glucose intolerance	NASH is a liver disease characterized by fatty deposits, inflammation, and hepatocyte damage. It affects an estimated 2% to 5% of Americans, although it is asymptomatic for most patients. As NASH progresses over several years, it may lead to cirrhosis and permanent liver damage. In the most severe cases, patients require a liver transplant to survive. NASH's cause is unknown. People who are middle-aged, obese, or glucose intolerant are at higher risk of the disease, although some patients have none of these risk factors. For patients who alter their diets and exercise, NASH may be reversible. No other treatments exist. Aramchol is a synthetic conjugate of cholic acid (a bile acid) and arachidic acid (a fatty acid) that purportedly affects liver fat metabolism by inhibiting stearoyl coenzyme A desaturase 1 (SCD1) activity. SCD1 inhibition results in decreased hepatic storage of triglycerides and fatty acid esters. Aramchol is administered orally, 400 or 600 mg, daily for 3 months. Galmed Pharmaceuticals, Ltd., Tel Aviv, Israel Phase II/III trial ongoing; FDA granted fast-track status	Improved diet and exercise	Decreased liver fat Decreased liver inflammation and damage Reduced rates of cirrhosis and liver failure Fewer liver transplantations Improved quality of life
Conestat alfa (Ruconest) for treatment of acute hereditary angioedema	Patients in whom acute hereditary angioedema (HAE) has been diagnosed	HAE is a genetic disorder caused by dysfunction or deficiency of the plasma protein C1 inhibitor (C1INH). C1INH inhibits the C1 protease that is responsible for activating the complement pathway in the immune system. If C1INH is deficient, the immune system reacts with an inflammatory response that leads to swelling. Conestat alfa (Ruconest®) is purportedly the 1st recombinant replacement therapy for C1INH deficiency. It consists of human recombinant C1-esterase inhibitor purified from the milk of transgenic rabbits, and it is intended to treat acute attacks of swelling by restoring functional plasma levels. The drug is administered at 50 IU/kg up to 4200 IU, by self injection. Pharming Group NV, Leiden, the Netherlands (manufacturer) Salix Pharmaceuticals, Inc., Raleigh, NC (distributor) FDA approved Jul 2014 for treating acute HAE attacks; trials ongoing in children and for preventing acute attacks	Bradykinin inhibitors (e.g., ecallantide, icatibant) C1INH (concentrate from donor blood) Fresh-frozen plasma Pain relievers and fluids given intravenously	Reduced mortality Reduced symptom severity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Corneal collagen cross-linking (VibeX/KXL System) for treatment of progressive keratoconus	Patients in whom progressive keratoconus has been diagnosed	Keratoconus is a degenerative disease of the eye. Progressive keratoconus requires invasive interventions, such as corneal transplants and insertion of corneal rings, and it is the leading cause in corneal transplants in the U.S. These invasive surgical interventions may present unfavorable complications, such as graft rejection, persistent visual problems, permanent vision loss, and prolonged surgical recovery. If accepted, corneal collagen-crosslinking (CCL) would provide a procedure that is less invasive, requires a shorter recovery time, and generates more optimal clinical outcomes to improve quality of life. CCL is performed by removing the corneal epithelium and applying riboflavin drops to the eye; the eye is then exposed to ultraviolet (UV) light, which interacts with the riboflavin. The interaction produces reactive oxygen molecules that cause chemical bonds to form between and within the corneal collagen fibrils, making them stiffer. The riboflavin soak and UV crosslinking take about 6 minutes. Avedro, Inc., Waltham, MA Phase III trials ongoing; FDA granted orphan drug status and priority review; new drug application submitted Sept 2014; FDA sent complete response letter to application requiring additional information Mar 2015; CE marked	Corneal ring segment inserts Surgical therapy	Improved corneal structure Improved vision Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cyclic pyranopterin monophosphate enzyme cofactor replacement (ALXN1101) for treatment of molybdenum cofactor deficiency type A	Patients in whom molybdenum cofactor deficiency (MoCD) type A has been diagnosed	MoCD type A is a rare autosomal recessive metabolic disorder caused by homozygous or compound heterozygous mutation in the *MOCS1* gene on chromosome 6p21, leading to a lack of molybdenum cofactor. The resulting deficiency causes toxic levels of sulphite to accumulate and neurologic damage to occur, which can often lead to death in early infancy from a critical lack of active sulfite oxidase. MoCD type A is characterized by poor feeding in the affected infant, intractable seizures, and severe psychomotor disabilities. MoCD type A is also known as molybdenum cofactor deficiencies of complementation group A (MOCODA) to distinguish it from molybdenum cofactor deficiencies of complementation group B and group C, phenotypically similar disorders caused by mutations on 2 different genes. As of 2010, fewer than 200 patients with MoCD type A had been identified worldwide. No approved treatments exist for patients with MoCD type A. ALXN1101, a synthetic formulation of cyclic pyranopterin monophosphate (cPMP) derived from recombinant *Escherichia coli*, is under study to treat MoCD type A by alleviating molybdenum cofactor deficiencies. cPMP is a precursor of molybdenum cofactor experimentally demonstrated to be more stable than its end-product enzyme. In clinical trials, patients with MoCD type A receive daily intravenous infusions with dosages increased monthly as tolerated. Alexion Pharmaceuticals, Inc., Cheshire, CT Phase II trial and unphased observational followup study of treated patients ongoing; Oct 2013, FDA granted breakthrough therapy status; Nov 2009, FDA granted orphan drug status	No comparators or approved treatments are available	Decreased mortality Increased molybdenum cofactor activity Reduced MoCD type A symptomology Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Daclizumab (Zinbryta) for treatment of multiple sclerosis	Patients in whom multiple sclerosis (MS) has been diagnosed	Available treatments for MS may slow disease progression, but they are not effective in all patients, and the disease has no cure. Daclizumab (Zenapax®) is a humanized monoclonal antibody against the CD25 alpha subunit of the high affinity interleukin-2 receptor. It is intended to bind the receptor and inhibit T-cell activation, thus slowing disease progression and degradation of the axon-protecting myelin sheath. In clinical trials, daclizumab is administered by subcutaneous injection, 150 mg, once every 4 weeks. Biogen, Cambridge, MA AbbVie, North Chicago, IL Phase III trials ongoing; Apr 2015, FDA accepted biologics license application for review; FDA granted fast-track status for this indication; Dec 1997, FDA approved an intravenous daclizumab formulation as part of an immunosuppressive regimen for preventing organ transplant rejection	Dimethyl fumarate (Tecfidera®) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Delayed disease progression Decreased demyelination Fewer relapses Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Deferiprone (Ferriprox) for treatment of pantothenate kinase–associated neurodegeneration	Patients in whom pantothenate kinase–associated neurodegeneration (PKAN) has been diagnosed	PKAN is a rare autosomal recessive inherited neurodegenerative disorder in which the brain accumulates iron; the disorder has an estimated worldwide incidence of 1 to 3 cases per million persons. PKAN is caused by mutations to the PANK2 gene, which normally encodes pantothenate kinase 2, a key enzyme involved in mitochondrial coenzyme A production. In affected persons, PKAN usually manifests in early childhood (before age 10 years) and is characterized by progressive dystonia and basal ganglia iron deposition. Common PKAN symptoms include dysarthria, rigidity, and pigmentary retinopathy; in approximately 25% of patients, PKAN onset occurs after 10 years of age, and is marked by prominent speech defects, psychiatric disturbances, and more gradual disease progression. Presently, no cure exists for PKAN, and standard treatment is palliative and primarily focused on treating dystonia symptoms. Deferiprone (Ferriprox®) is an iron chelator under investigation as a potential PKAN therapy. Researchers hypothesize that deferiprone's chelation properties will reduce excess iron accumulating in patients' brains, addressing an underlying biochemical cause of PKAN's most severe symptoms. In clinical trials for treating PKAN, deferiprone is administered as an oral solution at dosages between 5 and 15 mg/kg bodyweight, taken twice daily for 18 months. ApoPharma, Inc., Toronto, Ontario, Canada (manufacturer) Ente Ospedaliero Ospedali Galliera, Genoa, Italy (clinical trial sponsor) Phase II and III trials ongoing; Oct 2011, FDA approved deferiprone for treating thalassaemia major.	Iron chelators	Improved motor-skill functions and movement control Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Deflazacort for treatment of Duchenne muscular dystrophy	Patients in whom Duchenne muscular dystrophy (DMD) has been diagnosed	DMD is an X-linked recessive disorder and is the most common of the 9 recognized types of muscular dystrophy, with an estimated worldwide prevalence of 1 in 3,600 males. Available treatments for DMD are limited to reducing symptoms without addressing their underlying cause. Patients experience a shortened lifespan and require additional support from orthotic devices. Deflazacort is a glucocorticoid prodrug of desacetyl deflazacort, marketed outside the U.S. as an anti-inflammatory and immunosuppressant for treating multiple indications, including DMD. Its mechanism of action is undetermined for treating DMD, but studies have demonstrated that, for patients with DMD, deflazacort is effective in maintaining and improving muscle strength, independent ambulation, and pulmonary function; delaying onset of cardiomyopathy symptoms; and reducing rates of scoliosis. In American clinical trials, deflazacort is administered as an oral tablet, at a daily dose of 0.75 mg/kg, for up to 60 months; previous trials have investigated deflazacort at daily doses of up to 0.9 mg/kg, as a monotherapy or in combination with vitamin regimens. Marathon Pharmaceuticals, LLC, Northbrook, IL (FDA orphan drug and fast-track status sponsor) National Institute of Neurological Disorders and Stroke (NINDS), Bethesda, MD (named U.S.-based phase III trial collaborator) Newcastle University, Newcastle upon Tyne, UK (named U.S.-based phase III trial international collaborator) University of Rochester, Rochester, NY (U.S.-based phase III clinical trial sponsor) University Medical Center Freiburg (Universitätsklinikum Freiburg), Freiburg, Germany (named U.S.-based phase III trial international collaborator) U.S.-based phase III trial ongoing; deflazacort is widely used internationally for treating DMD but is unavailable in the U.S; Aug 2015, Marathon announced initiation of new drug application submission; Jan 2015, FDA granted fast-track status; Aug 2013, FDA granted orphan drug status	Beta-2 agonists Corticosteroids Orthotic devices Physical therapy Respiratory support devices	Delayed DMD progression Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Delayed-release cysteamine capsule (RP103) for treatment of Huntington's disease	Patients in whom Huntington's disease (HD) has been diagnosed	More than 15,000 Americans have HD, and another 150,000 people have a 50% risk of developing the disease. As a genetic, inherited disorder, HD arises from genetically programmed degeneration of neurons in the brain. The degeneration results in uncontrolled movements, loss of cognitive abilities, and emotional disturbance. Affected cells include the basal ganglia, which coordinate movement. Also affected is the brain's cortex, which controls thought, perception, and memory. No cure exists for HD, and available therapies help only to manage the emotional and motor symptoms associated with the disease. Cysteamine capsule (RP103) is a delayed-release, cystine-depleting drug being investigated as a potential disease-modifying therapy for HD. RP103 purportedly inhibits multiple intracellular enzymes, increases brain-derived neurotropic factor (BDNF), and chelates metals; these properties potentially address protein aggregation, BDNF deficiencies, and copper accumulation characteristic in HD. In clinical trials, patients are administered 16 oral capsules, daily. Raptor Pharmaceutical Corp., Novato, CA (manufacturer) University Hospital, Angers (Centre Hospitalier Universitaire [CHU] d'Angers), Angers, France (clinical trial sponsor) Phase II/III trial ongoing; May 2008, FDA granted orphan drug status; Apr 2013, FDA approved RP103 (as Procysbi®) for managing nephropathic cystinosis in patients aged 6 years or older; RP103 is also under investigation for treating nonalcoholic fatty liver disease in children and mitochondrial diseases including Leigh syndrome	No FDA-approved treatments exist to simultaneously treat multiple symptoms of HD. Existing treatments for various HD symptoms include: Nonpharmaceutical interventions (e.g., occupational therapy, physical therapy, psychotherapy, speech therapy) Treatments for motor dysfunction: Antipsychotic drugs (e.g., haloperidol, clozapine) Antiseizure drugs (e.g., clonazepam, diazepam) Tetrabenazine (Xenazine®; FDA approved to suppress chorea associated with HD) Treatments for psychiatric disorders: Antidepressants (e.g., escitalopram, fluoxetine, sertraline) Antipsychotic drugs Mood-stabilizing drugs	Delayed or reversed HD progression Improved motor and psychiatric symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Delayed-release cysteamine (Procysbi) for treatment of Leigh syndrome and non-Friedreich's ataxia inherited mitochondrial diseases	Patients in whom Leigh syndrome (SNEM) or a non-Friedreich's ataxia inherited mitochondrial disease has been diagnosed	Inherited mitochondrial diseases are a group of rare neurometabolic disorders caused by dysfunctional mitochondria inherited from 1 or both parents. In a subgroup of these diseases, including Leigh syndrome (also known as subacute necrotizing encephalomyelopathy, or SNEM), respiratory chain functioning is affected, leading to dystonia, ataxia, and failure to thrive. Many of these diseases are fatal, with the majority patients experiencing 1 or more symptoms within 10–13 years of birth. No approved treatments exist for Leigh syndrome or similar, inherited mitochondrial diseases such as non-Friedreich's ataxia. Delayed-release cysteamine (Procysbi®) is a cystine-depleting capsule that purportedly helps deplete toxic reactive oxygen species in cells. Abnormally increased levels of these oxygen species are found in patients with Leigh syndrome and similar diseases. In clinical trials, patients are administered increasing oral dosages of the drug, daily, dependent on tolerance. Raptor Pharmaceutical Corp., Novato, CA Phase II/III trial ongoing; May 2013, FDA approved Procysbi for managing nephropathic cystinosis in adults and children 6 years or older	No treatments are approved for Leigh syndrome and similar diseases Treatments for symptoms (e.g., coenzyme Q10, dichloroacetate, sodium bicarbonate or sodium citrate [for treatment of lactic acidosis]) High-fat, low carbohydrate diet Thiamine	Increased lifespan Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Deutetrabenazine for treatment of Huntington's disease chorea	Patients in whom Huntington's disease (HD) has been diagnosed	More than 15,000 Americans have HD and another 150,000 people have a 50% risk of developing the disease. As an inherited disorder, HD arises from genetically programmed degeneration of neurons in the brain. Neuronal degeneration results in symptoms including uncontrolled movements known as chorea, observed in up to 90% of HD patients and thought to arise from basal ganglia cell degeneration. No cure exists for HD, and only 1 medication, tetrabenazine, is FDA approved for its treatment; additional pharmacotherapies are needed. The drug deutetrabenazine (SD-809) purportedly functions as a vesicular monoamine transporter type 2 (VMAT-2) inhibitor. Investigators hypothesize that deutetrabenazine, which is synthesized by substituting deuterium at specific positions of tetrabenazine's structure, regulates dopamine levels underlying involuntary movement disorders. This compound potentially will provide symptom relief with minimal side effects and reduced drug-drug interactions. In clinical trials, SD-809 tablets are administered orally for up to 8 weeks, 6–12 mg, daily. Auspex Pharmaceuticals, Inc., La Jolla, CA (original developer) Teva Pharmaceutical Industries, Ltd., Petah Tikva, Israel (manufacturer) Phase III trial ongoing; FDA accepted new drug application Aug 2015; Nov 2014, FDA granted orphan drug status; deutetrabenazine is also under investigation for treating tardive dyskinesia and tics associated with Tourette's syndrome	Off-label antipsychotic drugs (e.g., haloperidol, clozapine) Off-label antiseizure drugs (e.g., clonazepam, diazepam) Tetrabenazine (Xenazine®)	Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Deutetrabenazine for treatment of tardive dyskinesia	Patients in whom tardive dyskinesia has been diagnosed	Tardive dyskinesia, involuntary movement of face or trunk muscles, can develop in patients taking long-term dopaminergic antagonist medications and is potentially debilitating. Although lowered doses of dopamine antagonists or alternative antipsychotic drugs may reduce or stop the symptoms of tardive dyskinesia, in some patients movements may persist or worsen when medications are altered. No standard treatment exists for this disorder. Deutetrabenazine (SD-809) is an investigational drug that purportedly inhibits vesicular monoamine transporter type 2 (VMAT-2). Investigators hypothesize that deutetrabenazine, which is synthesized by substituting deuterium at specific positions of tetrabenazine's structure, regulates dopamine levels underlying involuntary movement disorders. This compound potentially will provide symptom relief with minimal side effects, reduced drug interactions, and reduced need for individual patient drug genotyping. In clinical trials, deutetrabenazine tablets are administered orally for up to 54 weeks; doses are titrated to optimal levels during the 1st 6 weeks, with levels maintained for the duration of the trial. Auspex Pharmaceuticals subsidiary of Teva Pharmaceutical Industries, Ltd., Petah-Tikva, Israel Phase III trials ongoing; also under investigation for treating Huntington disease-related chorea	Anticholinergics (e.g., benztropine) Benzodiazepines (e.g., clonazepam, lorazepam) Botulinum toxin injection Cessation of dopamine antagonists Clozapine Deep brain stimulation Dopamine-depleting agents Stress reduction (e.g., psychotherapy) Supplements (e.g., ginkgo biloba, vitamin E) Valbenazine (investigational)	Reduced medication administration (relative to other interventions) Reduced abnormal involuntary movement Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Drisapersen for treatment of Duchenne muscular dystrophy	Ambulatory patients 5 years of age or older who have Duchenne muscular dystrophy (DMD) and a dystrophin gene mutation (deletions of exons 50, 52, 45–50, 48–50, or 49–50)	DMD is an X-linked recessive disorder and is the most common of the 9 recognized types of muscular dystrophy, with an estimated worldwide prevalence of 1 in 3,600 males. Available treatments for DMD are limited to reducing symptoms without addressing their underlying cause. Patients experience a shortened lifespan and require additional support from orthotic devices. Drisapersen (GSK-2402968, PRO-051) is an antisense oligonucleotide that induces exon skipping of exon 51. Antisense oligonucleotides skip defective exons (small RNA sequences that code for sections of protein), purportedly treating DMD by correcting the errant reading frame and allowing normal protein to be produced. In clinical trials, drisapersen is injected subcutaneously, at dosages up to 9 mg/kg, weekly. BioMarin Pharmaceutical, Inc., San Raphael, CA (manufacturer) Prosensa Therapeutics, Leiden, the Netherlands (original developer) Phase III trials ongoing; Jun 2015, FDA accepted new drug application for priority review with a decision date of Dec 27, 2015; Aug 2015, FDA granted rare pediatric disease status; Jun 2013, FDA granted breakthrough therapy status; Jan 2013, FDA granted orphan drug status	Beta-2 agonists Corticosteroids Orthotic devices Physical therapy Respiratory support devices	Decreased muscle degeneration Improved symptoms Decreased need for supportive devices Increased survival Improved quality of life
Eculizumab (Soliris) for prevention of delayed graft function after kidney transplantation	Patients who have undergone kidney transplantation using a cadaveric donor with a delayed graft function (DGF) risk	DGF is a form of acute renal failure most commonly defined as the use of dialysis within 1 week of kidney transplantation. It is likely due to ischemia or reperfusion injury when a cadaveric donor organ is used. DGF is associated with an inflammatory reaction that can be debilitating and life threatening because it increases the risk of organ loss. DGF incidence has increased in recent years, likely because of increased organ donations after cardiac death instead of just brain death. Eculizumab is a monoclonal antibody directed against C5 complement protein. It inhibits complement activation, potentially preventing DGF. Eculizumab is administered at a dosage of 1,200 mg by intravenous infusion over 25–45 minutes on the day of transplantation and 900 mg, 18–24 hours later. Alexion Pharmaceuticals, Inc., Cheshire, CT Phase II/III trial ongoing; FDA granted orphan drug status; FDA approved for treating atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria	No treatments are available	Faster kidney function after transplantation Reduced risk of kidney loss Reduced use of dialysis Improved survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Eculizumab (Soliris) for treatment of myasthenia gravis	Patients in whom severe or refractory myasthenia gravis has been diagnosed	Myasthenia gravis is a chronic autoimmune disease with an estimated U.S. prevalence of about 20 per 100,000 population. In myasthenia gravis, uncontrolled complement activation causes antibodies to block or destroy acetylcholine receptors at neuromuscular junctions. The result is decreased muscle contractions, manifesting physically as transient weakening of the skeletal muscles that peaks during activity and improves with sufficient rest. The most commonly affected muscles are in the mandibular and extraocular groups, controlling eye movement, facial expression, chewing, talking, and swallowing; in patients with severe forms of the disease, muscles involved in breathing and neck movement may also be affected. Eculizumab (Soliris®) is a recombinant humanized monoclonal immunoglobulin (Ig) IgG2/IgG4 antibody that selectively binds to terminal complement component C5. This binding prevents cleavage of C5 into C5a and C5b and also disrupts downstream generation and activation of C5b-9; preventing C5b-9 generation purportedly directly affects symptoms and progression of diseases reliant on uncontrolled complement activation. In preliminary clinical trials, patients received eculizumab intravenously at dosages of 600 mg, weekly, for 4 doses, followed by 900 mg, every 2 weeks, for 7 doses. Alexion Pharmaceuticals, Inc., Cheshire, CT Phase III trials ongoing; Jun 2014, FDA granted orphan drug status for this indication; since Mar 2007, FDA has approved eculizumab for treating both paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome	Anticholinesterase agents (e.g., Mestinon®) Corticosteroids (e.g., prednisone) and immunosuppressants Plasmapheresis Thymectomy	Improved disease severity scores Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Elafibranor for treatment of nonalcoholic steatohepatitis	Patients in whom nonalcoholic steatohepatitis (NASH) has been diagnosed	NASH is a liver disease characterized by fatty deposits, inflammation, and hepatocyte damage. It affects an estimated 2% to 5% of Americans, although it is asymptomatic for most patients. As NASH progresses over several years, it may lead to cirrhosis and permanent liver damage. In the most severe cases, patients require a liver transplant to survive. NASH's cause is unknown. People who are middle-aged, obese, or glucose intolerant are at higher risk of the disease, although some patients have none of these risk factors. For patients who alter their diets and exercise, NASH may be reversible. No other treatments exist. Elafibranor (GFT505) is a peroxisome proliferator activated receptor (PPAR) alpha and delta agonist. PPAR alpha regulates fatty acid transport, beta oxidation, gluconeogenesis, and inflammatory responses; PPAR delta regulates hepatic glucose utilization, lipoprotein metabolism, and inflammatory responses. Elafibranor is administered orally, 80 or 120 mg, once daily. GENFIT, Loos, France Phase II trial ongoing; Feb 2014, FDA granted fast-track status	Improved diet and exercise	Decreased liver fat Decreased liver inflammation and damage Improved cardiometabolic risk profile Reduced rates of cirrhosis and liver failure Fewer liver transplantations Improved quality of life
Electrode-embedded garment (Mollii) for treatment of muscle spasms and pain from traumatic brain injury	Patients with muscle spasms and pain due to traumatic brain injury (TBI)	Patients who experience TBI can have lasting brain damage that causes involuntary muscle spasms and tension throughout the body. The muscle spasms and tension can cause severe pain and limit mobility. Available treatments include surgery and muscle relaxants. The Mollii garment is an electrode-embedded elastic garment that works as a noninvasive alternative to available medical treatments. The full-body garment has 58 electrodes that can target up to 42 muscles. It is powered by a control box worn at the waist. Patients are expected to wear the garment a few hours at a time to receive transcutaneous electrical nerve stimulation to affected muscles, 3 times a week. Relief reportedly lasts up to 2 days. The garment's estimated cost is $7,600. Royal Institute of Technology (KTH), Stockholm, Sweden CE marked; expanded launch in the U.S. and other countries was anticipated but not seen in 2014	Muscle relaxants Surgery	Decreased pain and muscle spasms Increased mobility Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Eliglustat tartrate (Cerdelga) for treatment of Gaucher's disease type 1	Patients in whom Gaucher's disease type 1 has been diagnosed	Gaucher's disease is caused by a hereditary deficiency of glucocerebrosidase, which leads to enlarged and malfunctioning organs, skeletal disorders, and painful neurologic complications. 1st-line treatment is intravenous therapy. Eliglustat tartrate (Cerdelga) is a glucocerebroside synthase inhibitor that purportedly decreases the amount of glucocerebroside in major organs such as the spleen and liver by slowing production. In clinical trials, eliglustat tartrate has been administered twice daily; however, the manufacturer intends to ultimately market the drug as a once-daily treatment. Eliglustat tartrate is the 1st available 1st-line oral treatment option for patients with Gaucher's disease type 1. Eliglustat tartrate cannot be used in patients who are ultra-rapid metabolizers of the enzyme CYP2D6 because adequate levels of the drug cannot be maintained. Dosing is based on the rate at which patients metabolize CYP2D6, but most patients in trials took 84 mg, twice daily. Genzyme subsidiary of Sanofi, Paris, France Phase III trials completed and ongoing; FDA approved Aug 2014 "... for the long-term treatment of adult patients with Gaucher['s] disease type 1 who are CYP2D6 extensive metabolizers (EM), intermediate metabolizers (IM), or poor metabolizers as detected by an FDA-cleared test."	Blood transfusions Bone marrow transplant Enzyme replacement therapy (e.g., imiglucerase, taliglucerase alfa) Joint replacement surgery Miglustat (Zavesca®) Splenectomy	Decreased liver volume Decreased spleen volume Improved quality of life
Elosulfase alfa (Vimizim) for treatment of Morquio A syndrome	Patients in whom Morquio syndrome type A has been diagnosed	Morquio syndrome type A is a rare autosomal recessive genetic disorder. It results from a deficiency in *N*-acetylgalactosamine-6-sulfate sulfatase activity and leads to the accumulation of keratan sulfate and various developmental defects. The estimated U.S. prevalence is between 1,000 and 1,500 patients. No treatments exist to address the underlying cause of the disease; only palliative treatments are available. Elosulfase alfa (Vimizim®) is an enzyme replacement therapy (*N*-acetylgalactosamine-6-sulfate sulfatase, encoded by the *GALNS* gene) intended to treat the underlying disorder. Elosulfase alfa is infused at a dose of 2 mg/kg over a period of about 4 hours once a week or once every other week. BioMarin Pharmaceutical, Inc., San Rafael, CA Feb 2014, FDA approved for treating Morquio syndrome type A	No other treatments are available to resolve the underlying disease	Disease regression Improved bone growth as measured by radiograph Improved activities of daily living Increased physical endurance (6-minute walk test) Improved respiratory function Reduced urine keratan sulfate levels

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Eltrombopag (Promacta) for treatment of severe or very severe aplastic anemia	Patients with severe aplastic anemia (SAA) or very severe aplastic anemia (VSAA) whose disease has not responded to immunosuppressive therapy	Aplastic anemia is a bone marrow disease in which bone marrow cells are damaged, resulting in deficiencies in white and red blood cells and platelets. SAA and VSAA can be caused by exposure to toxins, radiation, or infection. It can also be hereditary or arise from an unknown origin. Standard treatment is immunosuppressive therapy, but about 30% of patients do not respond. Among patients who do not respond, about 40% die from infection or bleeding within 5 years. Eltrombopag (Promacta) is a thrombopoietin receptor agonist that potentially stimulates the growth of platelets to enable clotting. Dosage is 50 mg, once daily, orally. The dose is adjusted to maintain platelet count greater than $50x10^9$/L, not to exceed 150 mg, daily. GlaxoSmithKline, Middlesex, UK FDA approved Aug 2014; phase II and III trials ongoing	Blood transfusion for symptom relief Bone marrow transplant Immunosuppressive therapy	Blood transfusion independence Improved hemoglobin levels Increased neutrophil, eosinophil, and platelet counts
Epratuzumab for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	Investigators have not found a permanent cure for SLE, and available treatments provide only partial relief of symptoms. Epratuzumab is a fully humanized monoclonal antibody that purportedly binds and modulates the activity of B cell CD22 antigen. Research indicates that CD22 may prevent autoreactive B cell responses that may play a major role in SLE pathogenesis; by modulating these responses, epratuzumab may reduce SLE severity and delay disease progression. In clinical trials, the drug is administered as a monthly subcutaneous injection. UCB, S.A., Brussels, Belgium (licensee) Immunomedics, Inc., Morris Plains, NJ (original developer) Phase III trial ongoing; Jul 2015, UCB announced that 2 completed phase III trials failed to meet primary endpoints; Jan 2005, FDA granted fast-track status; epratuzumab is also under investigation for treating several other inflammatory autoimmune disorders and oncology indications	Belimumab Rituximab Rontalizumab	Delayed disease progression Improved biologic markers of disease activity Fewer disease flares Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Eprodisate disodium (Kiacta) for treatment of amyloid A amyloidosis	Patients at risk of amyloid A (AA) amyloidosis, especially those who have rheumatoid arthritis or chronic infection	AA amyloidosis is a disorder marked by abnormal deposits of serum amyloid A (SAA) protein in the extracellular space of tissues and organs; worldwide, it is the most common form of systemic amyloidosis. The U.S. prevalence of AA amyloidosis is unknown, but it is more common in females than males. Because SAA levels are often elevated during inflammation, AA amyloidosis can manifest in patients with a variety of inflammatory conditions, including Crohn's disease, rheumatoid arthritis, and tuberculosis. No curative treatment for AA amyloidosis is available. Eprodisate disodium (Kiacta™) is designed to interfere with the formation of AA fibrils that can accumulate in organs and tissues; specifically, it is purported that eprodisate disodium indirectly protects renal function in patients with AA amyloidosis. In clinical trials, eprodisate disodium is administered orally, at dosages of 400, 800, or 1,200 mg, twice daily. Auven Therapeutics, St. Thomas, U.S. Virgin Islands (worldwide licensee) Bellus Health, Inc. (formerly Neurochem), Laval, Quebec, Canada (original developer) Pivotal phase III trial ongoing; new drug application submitted to FDA in 2006; FDA requested more data; manufacturers initiated phase III confirmatory trial in 2010 to address this concern; company expects phase III study completion in 2016	Biologics Colchicine for familial Mediterranean fever Immunosuppressants Kidney transplantation for kidney failure Supportive care Surgical excision of infected tissue and antibiotics for chronic infection	Reduced risk of organ failure (especially kidneys, liver, spleen) Reduced mortality
Erythropoietin analogue (ARA 290) for treatment of sarcoidosis-associated small fiber neuropathy	Patients in whom sarcoidosis-associated small fiber neuropathy (SFN) has been diagnosed	Sarcoidosis-associated SFN is a type of peripheral neuropathy that arises in some patients with sarcoidosis. SFN is characterized by disabling peripheral pain that may have a burning or shooting sensation. It is differentiated from other types of pain by a loss of small fiber nerves, seen with a skin biopsy. Sarcoidosis and SFN have no cures; limited treatments focus on symptom management. ARA 290 is a nonhematopoietic erythropoietin analogue that acts at the innate repair receptor and inhibits cytokines. It has anti-inflammatory and tissue protective properties. Administered at a 1, 4, or 8 mg dose by subcutaneous injection, daily, for 28 days. Araim Pharmaceuticals, Inc., Tarrytown, NY Phase IIb trial completed; FDA granted orphan drug and fast-track statuses	Anticonvulsants Antidepressants Corticosteroids Immunosuppressants Prolonged-release opioids	Improved functional capacity Improved sensory function Increased nerve fiber density Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Eteplirsen for treatment of Duchenne muscular dystrophy	Patients in whom Duchenne muscular dystrophy (DMD) has been diagnosed	DMD is an X-linked recessive disorder and is the most common of the 9 recognized types of muscular dystrophy, with an estimated worldwide prevalence of 1 in 3,600 males. Available treatments for DMD are limited to reducing symptoms without addressing their underlying cause. Patients experience a shortened lifespan and require additional support from orthotic devices. Eteplirsen (AVI-4658) is intended for patients who have a mutation in the dystrophin gene; the eteplirsen splice-switching oligomer is intended to skip exon 51 of the dystrophin gene (which codes a protein that plays a key structural role in muscle fiber function) during translation. This restores the gene's ability to make a shorter form of dystrophin that is not perfect, but is functional. In clinical trials, eteplirsen is intravenously infused, at dosages of 30 or 50 mg/kg, once weekly. Sarepta Therapeutics, Inc., Cambridge, MA Phase III trial ongoing; Aug 2015 FDA accepted Sarepta's new drug application and granted priority review, with a decision date set for Feb 26, 2016; FDA previously granted fast-track, orphan drug, and rare pediatric disease statuses	Beta-2 agonists Corticosteroids Orthotic devices Physical therapy Respiratory support devices	Delayed or halted muscle degeneration Improved symptoms Increased survival Improved quality of life
External trigeminal nerve stimulation (Monarch) for treatment of epilepsy	Patients in whom epilepsy has been diagnosed	An estimated 3 million people in the U.S. have some form of epilepsy, with about 1 million cases resistant to medical therapy. Pharmacological therapies have helped treat epilepsy, but it commonly recurs. Surgical procedures such as craniotomy may be performed, but they may leave the brain susceptible to unintended injury and resultant neurological complications. External trigeminal nerve stimulation (eTNS) using the Monarch device is a noninvasive therapy in which mild electrical signals pass through electrodes placed on the patient's forehead. eTNS is intended to transcutaneously stimulate the various branches of the trigeminal nerve (the largest cranial nerve), which projects to the amygdala. The stimulation is controlled by an external pulse generator worn by patients during sleep. NeuroSigma, Inc., Los Angeles, CA (manufacturer), in collaboration with Olive View-UCLA Education and Research Institute, Sylmar, CA; Boston Scientific Corp., Natick, MA; and the Epilepsy Foundation, Landover, MD (investigators) Phase II study completed; Jan 2015, FDA also granted humanitarian use device exemption to eTNS for treating Lennox-Gastaut syndrome (severe pediatric-onset epilepsy); eTNS is approved in Canada, Europe, and Mexico for treating various epilepsy indications	Pharmacotherapy (e.g., ezogabine, lamotrigine, levetiracetam, perampanel, tiagabine, tricyclics, valproate)	Reduced frequency of seizure Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fingolimod for treatment of chronic inflammatory demyelinating polyneuropathy	Patients in whom chronic inflammatory demyelinating polyneuropathy (CIDP) has been diagnosed	CIDP is a neurologic disorder characterized by progressive weakness and impaired sensory function in the legs and arms; it is closely related to Guillain-Barré syndrome. In the U.S., about 40,000 people have CIDP. It is caused by damage to the myelin sheath of peripheral nerves. CIDP is most common in young adult men, with symptoms including tingling or numbness in appendages, weakness of the arms and legs, areflexia, and fatigue. Treatments for CIDP, including immunoglobulin medications, attempt to alleviate symptoms or prevent further loss of peripheral nerve myelin. However, about 20% of CIDP cases do not respond to available treatments. Fingolimod (Gilenya®), an immunomodulating drug, is purportedly an effective treatment for CIDP, possibly acting by decreasing demyelination of sciatic nerves. In planned trials, patients with CIDP will receive daily oral administrations of 0.5 mg. Novartis International AG, Basel, Switzerland Mitsubishi Tanabe Pharma Corp., a subsidiary of Mitsubishi Chemical Holdings Corp., Tokyo, Japan Phase III trial ongoing and new phase III trials planned; Apr 2010, FDA granted orphan drug status for treating CIDP; Sept 2010, FDA approved fingolimod (as Gilenya) for treating multiple sclerosis	Corticosteroids (e.g., prednisone), alone or with immunosuppressant drugs Lower-dosage intravenous immunoglobulin (IVIG) therapy (e.g., 10% formulations) Physiotherapy Plasmapheresis	Decreased demyelination Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Focused ultrasound (ExAblate Neuro) for treatment of essential tremor	Patients in whom essential tremor (ET) has been diagnosed	ET is a slowly progressive neurologic disorder that affects approximately 10 million people in the U.S. and has no cure. This disease is characterized by a tremor of the arm during voluntary movements. Existing treatments are invasive and often ineffective. The ExAblate Neuro focused ultrasound device consists of a unique helmet-like apparatus containing phased array focused ultrasound transducers. Computed tomography images can be used to reconstruct the skull and configure the ultrasound beams to focus on the targeted area (the ventral intermediate nucleus of the thalamus). Magnetic resonance (MR) imaging or MR thermography can be used to track the delivery of ultrasound beams. Purported benefits of focused ultrasound therapy include noninvasive transcranial treatment; absence of ionizing radiation, allowing for repeated treatment without long-term toxicity; immediate bio-physical tissue response from thermal ablation; and precise tissue targeting with 1 mm accuracy. University of Virginia (UVA) Focused Ultrasound Center, Charlottesville (partnership of UVA, Charlottesville; Commonwealth of Virginia; Focused Ultrasound Foundation, Charlottesville; and InSightec, Ltd., Tirat Carmel, Israel) Unphased trials ongoing; CE marked Jun 2010	Antiepileptics Beta blockers Deep brain stimulation Stereotactic thalamotomy	Improved contralateral tremor as assessed on the Clinical Rating Scale for Tremor (CRST) Improved functional activities score as assessed on disabilities section of CRST Improved quality of life
Fostamatinib for treatment of chronic immune thrombocytopenia	Patients in whom chronic immune thrombocytopenic purpura (ITP) has been diagnosed	Chronic ITP is an autoimmune disease affecting otherwise healthy adults, in which the platelets are destroyed. The age-adjusted prevalence is estimated to be 9.5 per 100,000 persons in the U.S. Platelet destruction can cause chronic bleeding and potentially fatal intracranial hemorrhage. ITP has no cure, and relapses can occur years after seemingly successful medical or surgical management. Patients with chronic ITP may need to undergo splenectomy, thus increasing the risk for further complications. Fostamatinib disodium (R788) is a spleen tyrosine kinase inhibitor that interrupts lymphocyte signaling involved in platelet destruction in ITP. It is intended for treating patients with chronic ITP whose disease does not respond to 1st-line medical therapy (i.e., corticosteroids). In clinical trials, the dosage is 100 or 150 mg, twice daily, for 24 weeks; administered orally. Rigel Pharmaceuticals, Inc., South San Francisco, CA Phase III trials ongoing; FDA granted orphan drug status Sept 2015	Corticosteroids Immunosuppressants Intravenous immune globulin *Helicobacter pylori* treatment Rituximab Splenectomy Thrombopoietin receptor agonists	Improved blood clotting Increased platelet count Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Galectin-3 inhibitor (GR-MD-02) for treatment of nonalcoholic steatohepatitis	Patients in whom nonalcoholic steatohepatitis (NASH) with advanced liver fibrosis has been diagnosed	NASH is a liver disease characterized by fatty deposits, inflammation, and hepatocyte damage. It affects an estimated 2% to 5% of Americans, although it is asymptomatic for most patients. As NASH progresses over several years, it may lead to cirrhosis and permanent liver damage. In the most severe cases, patients require a liver transplant to survive. NASH's cause is unknown. People who are middle-aged, obese, or glucose intolerant are at higher risk of the disease, although some patients have none of these risk factors. For patients who alter their diets and exercise, NASH may be reversible. No other treatments exist. GR-MD-02 inhibits galectin-3, which binds to glycoproteins and is involved in liver fibrosis. It is administered by intravenous infusion, 2 or 8 mg/kg; 28 days after the 1st dose, 3 weekly doses are given. Galectin Therapeutics, Inc., Norcross, GA Phase II trial ongoing; Aug 2013, FDA granted fast-track status	Improved diet and exercise	Decreased liver fat Decreased liver inflammation and damage Reduced rates of cirrhosis and liver failure Fewer liver transplantations Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gene therapy (SPK-RPE65) for Leber congenital amaurosis	Patients with *RPE65* gene mutation–associated Leber congenital amaurosis (LCA) who have nyctalopia	LCA is an early onset, inherited eye disorder with estimated prevalence of 2–3 cases per 100,000 births. It is marked by pronounced retinal dystrophy leading to severe visual impairment. LCA is the most common cause of inherited blindness in childhood and is the primary cause of blindness in more than 20% of children who attend schools for the blind. Symptoms include photophobia, nystagmus, and extreme farsightedness (hyperopia). Patients' pupils are unresponsive to light, and retinal tissues have little to no function, evidenced by electroretinogram readings. Untreated, all patients with LCA progress to total blindness from loss of retinal photoreceptor cells. To date, mutations in at least 17 different genes are known to cause LCA, including *RPE65*, a gene on locus LCA2 that may cause 16% of LCA cases. No cure is available, and supportive treatment focuses on lifestyle management to address the impact of vision limitations. Adeno-associated viral vector gene therapy purportedly cures LCA or significantly improves visual impairment, by delivering nonmutated *RPE65* gene copies to patients' retinas. The functional gene is delivered to surviving photoreceptor cells. In clinical trials, patients with LCA receive a single subretinal, surgical administration of gene therapy vector AAV2-hRPE65v2, at a dose of $1.5x10^{11}$ vector genomes per eye; eyes are dosed on separate days. Spark Therapeutics, Inc., Philadelphia, PA, collaborating with Children's Hospital of Philadelphia, Philadelphia, PA Phase III trial ongoing; FDA granted orphan drug and breakthrough therapy statuses	Corrective vision equipment (e.g., glasses, contact lenses) and low-vision aids Lifestyle modifications Other accommodative equipment for low vision	Reduced need for caregiver interventions Restored or improved visual functioning Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Human embryonic stem cell–derived retinal pigment epithelium cells for treatment of Stargardt macular dystrophy	Patients in whom Stargardt macular dystrophy has been diagnosed	Stargardt macular dystrophy is a genetic eye disorder affecting a small area near the center of the retina, called the macula. It is most often caused by mutations in ABCA4, which encodes Rim protein. Rim transports vitamin A to be recycled. In Stargardt macular dystrophy, Rim is absent and vitamin A dimers accumulate in the eye causing damage. It progresses to central and color vision loss and difficulty transitioning from light to dark. Disease prevalence is an estimated 1 in 8,000–10,000 individuals, and no treatment is available. Subretinal transplantation of retinal pigment epithelial cells derived from human embryonic stem cells (also called MA09-hRPE) to replace damaged cells is under study to determine its safety and tolerability for halting or preventing the disease. Treatment is administered by subretinal injection of 50,000, 100,000, 150,000, or 200,000 cells. Ocata Therapeutics, Inc., Marlborough, MA Phase I/II trials ongoing; FDA granted orphan drug status	No treatment is available	Improved functional status Improved vision Reversed loss of central vision Improved quality of life
Human spinal cord–derived neural stem cells for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	ALS is a progressive disorder marked by neurodegeneration of nerve cells in the brain and spinal cord. A 2014 report calculated that ALS prevalence is about 3.9 cases per 100,000 Americans. The average life expectancy of a patient with ALS is 3–5 years after diagnosis, and only 10% of patients survive for more than 10 years. Only a single agent (riluzole) is FDA approved for treating ALS, and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function; novel therapies for ALS are urgently needed. Stem cell therapy can potentially repair neurologic damage, including damage associated with ALS. Human spinal cord–derived neural stem cells (NSI-566RSC) is an investigational therapy, developed from human spinal cord–derived neural stem cells. In clinical trials, NSI-566RSC is injected into a patient's lumbar spinal cord. Neuralstem, Inc., Rockville, MD Phase II trial ongoing; Feb 2011, FDA granted orphan drug status	Riluzole (Rilutek®) Supportive care	Improved symptoms Slowed or halted disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Humanized immunoglobulin G1 monoclonal antibody (NEOD001) for treatment of systemic light chain (AL) amyloidosis	Patients in whom systemic light chain (AL) amyloidosis has been diagnosed	AL amyloidosis is the most common form of a group of plasma cell disorders characterized by abnormal amyloid deposits in body tissues. Among Americans, 1,200–3,200 new cases of AL amyloidosis are diagnosed each year; approximately 2/3 of cases occur in males, and 95% of these patients are older than 40 years. In AL amyloidosis, amyloid deposits are composed of excess amyloidogenic monoclonal immunoglobulin light chains produced by bone marrow clonal plasma cells. Severe symptoms of AL amyloidosis include congestive cardiomyopathy, sensorimotor or autonomic peripheral neuropathy, and nephritic syndrome. In 20% of cases, plasma cells replicate more aggressively and can lead to myeloma. Various chemotherapies targeting the underlying bone marrow disorder are 1st-line treatments for AL amyloidosis, but an unmet need exists for effective interventions for patients who do not respond to chemotherapy or who experience relapsing symptoms. NEOD001 is a humanized immunoglobulin G1 monoclonal antibody purported to treat AL amyloidosis by 2 mechanisms: neutralizing circulating excess amyloid, and clearing amyloid deposits in affected tissues. NEOD001 is also hypothesized to directly target misfolded light chain proteins that underlie this disorder. In clinical trials, 24 mg/kg (maximum dose of 2,500 mg) of NEOD001 is infused once every 28 days, for patients with treatment-naïve or treatment-refractory AL amyloidosis. Prothena Corp., plc, Dublin, Ireland Phase III trial (VITAL) and open-label phase I/II trial ongoing; Feb 2012, FDA granted orphan drug status for treating AL and amyloid A amyloidoses	Chemotherapy	Reduced amyloid deposition Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Humanized monoclonal antibody (NKTT120) for treatment of sickle cell disease	Patients in whom sickle cell disease (SCD) has been diagnosed	SCD is an autosomal recessive disorder that affects about 100,000 people in the U.S. and Europe and can present as sickle cell anemia or sickle beta-0 thalassemia. Increased disease prevalence is seen in people of African and Mediterranean descent; about 1 in 500 African-American children born have sickle cell anemia. In SCD, sickled red blood cells are more susceptible to oxidative damage and inappropriate adhesion, which can lead to vaso-occlusive crisis (VOC). VOC causes severe pain by obstructing vasculature; it requires hospitalization. Patients may progress to thromboembolic events, stroke, organ failure, or early death. The only FDA-approved treatment for SCD, hydroxyurea, can reduce VOC incidence but is not effective in about 1/3 of adult patients. A humanized monoclonal antibody that specifically depletes invariant natural killer T cells, a mediator of organ damage in SCD, is in development. Appropriate dosing is under study. It is administered intravenously. NKT Therapeutics, Inc., Waltham, MA Phase Ib trial completed; FDA granted orphan drug and fast-track statuses	Blood transfusion Bone marrow transplant Hydroxyurea	Decreased pain Fewer hospitalizations Shorter hospitalizations Reduced organ damage Reduced mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Hypercaloric diet for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	ALS is a progressive disorder marked by neurodegeneration of nerve cells in the brain and spinal cord. A 2014 report calculated that ALS prevalence is about 3.9 cases per 100,000 Americans. The average life expectancy of a patient with ALS is 3–5 years after diagnosis, and only 10% of patients survive for more than 10 years. Only a single agent (riluzole) is approved for treating ALS, and it is associated with limited efficacy in improving survival time; additional effective therapies are needed. Research in human and animal models suggests that high-calorie diets may improve survival among patients with ALS. Controlled hypercaloric diets purportedly provide a potential nonpharmaceutical treatment that delays ALS disease progression; in clinical trials, patients were tube-fed diets consisting of 125% of their daily energy requirements, with excess calories provided by either Jevity 1.5 (high-carbohydrate hypercaloric diet) or Oxepa (high-fat hypercaloric diet). Harvard NeuroDiscovery Center, Cambridge, MA (cosponsor and primary investigator affiliation) Massachusetts General Hospital, Boston (clinical trial sponsor) Muscular Dystrophy Association, Chicago, IL (advertising and recruiting coordinator) National Institutes of Health, Bethesda, MD (cosponsor) Multicenter phase II trial completed	Fingolimod (Gilenya®; experimental) Riluzole (Rilutek®)	Delayed disease progression Decreased mortality rate Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Idebenone (Catena) for treatment of Duchenne muscular dystrophy	Patients in whom Duchenne muscular dystrophy (DMD) has been diagnosed	DMD is an X-linked recessive disorder and is the most common of the 9 recognized types of muscular dystrophy, with an estimated worldwide prevalence of 1 in 3,600 males. Available treatments for DMD are limited to reducing symptoms without addressing their underlying cause. Patients experience a shortened lifespan and require additional support from orthotic devices. Idebenone is a small molecule that purportedly facilitates electron transport within mitochondria. The developer asserts that maintaining correct electron balance is essential for normal energy metabolism, particularly in nerve and muscle cells, which demand more energy, making them more prone to rapid cell damage or death from mitochondrial dysfunction. Preserving mitochondrial function and protecting cells from oxidative stress might prevent cell damage and increase energy production within impaired nerve and muscle tissue in patients with DMD. Published data suggest that idebenone primarily improves respiratory symptoms of DMD, with limited efficacy for ambulatory and functional mobility deficits. In clinical trials, idebenone was administered 900 mg daily, as two 150 mg tablets, taken 3 times a day, with meals. Santhera Pharmaceuticals Holding AG, Liestal, Switzerland Phase III trial completed; manufacturer has begun meetings with FDA before a new drug application filing; Aug 2015, FDA granted rare pediatric disease status; Apr 2015, FDA granted fast-track status; Feb 2007, FDA granted orphan drug status	Beta-2 agonists Corticosteroids Respiratory support devices	Delayed or halted muscle degeneration Improved symptoms Increased survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Implanted electrical nerve block system (Altius) for treatment of chronic amputation pain	Patients who have had an amputation and experience ongoing chronic amputation pain	No treatment is approved for chronic amputation pain, and many patients do not experience pain relief with available treatment options. The Altius system uses very high frequency stimulation of peripheral nerves to prevent transmission of pain signals to the central nervous system. The system consists of a pacemaker-like implanted device that transmits electrical pulses through an electrode attached to a peripheral nerve. The device delivers the current at 10,000 Hz per second for 30 minutes. Neuros Medical, Inc., Willoughby, OH Pivotal trial ongoing	Medications (e.g., tricyclic antidepressants, anticonvulsants, narcotics) Minimally invasive therapies (e.g., narcotic injections, electrical spinal cord stimulation, intrathecal catheter delivered drugs) Noninvasive therapies (e.g., transcutaneous electrical nerve stimulation, mirror box visual therapy, acupuncture) Surgery (e.g., deep brain stimulation, stump revision/neurectomy)	Reduced pain Reduced pain-medication use Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interferon gamma-1b (Actimmune) for treatment of Friedreich's ataxia	Patients in whom Friedreich's ataxia (FRDA) has been diagnosed	FRDA is an autosomal recessive disorder caused by a defect in the frataxin gene, leading to signs and symptoms including ataxia, diabetes, sensorimotor deficiencies, muscle weakness, and heart failure. FRDA is an increasingly debilitating disease, severely limiting patients' ability to function independently; disease-related symptoms, particularly cardiac and respiratory symptoms, are often fatal. No FDA-approved interventions exist for this indication; consequently, an unmet need exists for effective treatments. Interferon gamma-1b (Actimmune®) has been shown to increase cellular frataxin protein levels. It is hypothesized that this activity addresses an underlying cause of FRDA, providing viable protein in the absence of a normally functioning frataxin gene. In completed clinical trials, interferon gamma-1b is subcutaneously injected, thrice weekly. at escalating doses of up to 50 mcg/m^2, for 12 weeks. Horizon Pharma, plc, Dublin, Ireland (manufacturer and U.S. clinical trial sponsor) University of Rome's Azienda Policlinico Umberto I, Italy (independent clinical trial investigator) Phase III trial ongoing; Apr 2015, FDA granted fast-track status; Oct 2014, FDA granted orphan drug status; Feb 1999, FDA approved Actimmune for reducing the frequency and severity of serious infections associated with chronic granulomatous disease and for delaying time to disease progression for patients with severe, malignant osteopetrosis	Physical therapy (palliative) Speech therapy (palliative) Vatiquinone (investigational) Wheelchair use (palliative)	Increased cellular frataxin levels Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Intravenous patisiran for treatment of transthyretin familial amyloid polyneuropathy	Patients in whom transthyretin familial amyloid polyneuropathy (TTR-FAP) has been diagnosed	TTR-FAP is a genetic neurodegenerative disease that can also affect the heart and kidneys. The disease is usually fatal by age 10 years if no liver transplant is available. Transthyretin (TTR) is a potentially amyloidogenic transport protein for thyroxine and retinol. Mutation of the *TTR* gene can lead to the development of unstable TTR, which forms amyloid fibrils that are deposited in various organs. Patisiran (ALN-TTR02) is an RNAi therapeutic that targets and inhibits the expression of the mutated *TTR* gene. Patisiran is purported to treat TTR-FAP by silencing the *TTR* gene and reducing serum levels of TTR; it is hypothesized that these actions prevent pathogenic TTR deposition in peripheral tissues, including dorsal root ganglia, sciatic nerve, stomach, and intestines. In clinical trials, patisiran is intravenously infused for up to 18 months; dosing may be titrated upward based on patient tolerance. Alnylam Pharmaceuticals, Inc., Cambridge, MA Phase III and long-term dosage phase II trials ongoing; Nov 2013, FDA granted fast-track status; Jun 2012, FDA granted orphan drug status	Supportive therapy	Improved Neuropathy Impairment Scores Stabilized TTR Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Intravenous trehalose (Cabaletta) for treatment of oculopharyngeal muscular dystrophy	Patients in whom oculopharyngeal muscular dystrophy (OPMD) has been diagnosed	OPMD is a form of muscular dystrophy that affects eyelid and throat muscles; patients also commonly experience symptoms affecting facial and limb muscles. OPMD is caused by mutations to polyadenylate binding protein (PABPN1), that lead to excess amino acid production and subsequent aggregation in muscle cell nuclei. Nationwide OPMD prevalence is unknown, but studies show that symptoms are 1st observed between ages of 40 and 60 years and that people of French-Canadian, Ashkenazi Jewish, or Spanish-American background are disproportionately affected. An unmet need exists for interventions treating underlying causes of OPMD. The disease primarily causes difficulty swallowing and controlling eyelids, and as the disorder progresses, patient mobility may also be affected. No pharmacotherapies are available for treating OPMD; standard of care is palliative treatment, including surgeries to treat severe eyelid drooping (blepharoplasty) or difficulty swallowing (cricopharyngeal myotomy), and orthopedic support devices for patients experiencing mobility symptoms. Cabaletta® is an intravenous formulation of trehalose, an alpha-linked disaccharide shown to induce autophagy and promote removal of aggregated proteins. Investigators hypothesize that an intravenous form of trehalose can reach muscle cells, improving trehalose's efficacy for treating OPMD. In clinical trials, Cabaletta is administered intravenously, weekly, at a dose of 30 g. BioBlast Pharma, Ltd., Tel Aviv, Israel Phase III trial ongoing; Apr 2015, FDA granted fast-track status; Mar 2015, FDA allowed BioBlast to proceed with an investigational new drug application; Oct 2013, FDA granted orphan drug status	Palliative care (including surgeries and orthopedic support devices)	Improved independent functioning Reduced muscle cell amino acid aggregation Improved symptoms (e.g., visual symptoms, swallowing, vocalization) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Intravenous trehalose (Cabaletta) for treatment of spinal cerebellar ataxia type 3	Patients in whom spinal cerebellar ataxia type 3 (SCA 3) has been diagnosed	SCA 3 is a rare neurodegenerative disorder caused by a mutation leading to abnormal CAG trinucleotide repeats in the *ATXN3* gene; it is the most common cause of autosomal-dominant ataxia. *ATXN3* mutations lead to accumulation of ataxin-3 protein in pons and striatum, among other brain areas. Patients with 1 of 5 identified SCA 3 subtypes exhibit cerebellar ataxia, manifesting in multiple symptoms such as motor difficulties, spasticity, memory declines, speech and swallowing problems, and visual dysfunction (including gaze-evoked nystagmus and slow saccades); disease progression can lead to paralysis and death. U.S. SCA 3 prevalence is undetermined; the highest worldwide prevalence rates are found in persons of Azorean (Portuguese island) heritage, and the average age of onset is in the 30s. Presently, no cure exists for SCA 3, and standard care focuses on treating patients' most pronounced symptoms using medications, orthopedic assistance devices, and physical and speech therapy. An unmet need exists for therapies targeting underlying causes of SCA 3. Cabaletta® is an intravenous formulation of trehalose, an alpha-linked disaccharide shown to induce autophagy and promote removal of aggregated proteins. Investigators hypothesize that an intravenous form of trehalose can effectively treat SCA 3 by preventing ataxin-3 aggregation and subsequent neuronal degeneration. In clinical trials, Cabaletta is administered intravenously, weekly, at a dose of 15 g, for 24 weeks. BioBlast Pharma, Tel Aviv, Israel Phase II trial ongoing; Nov 2014, FDA granted orphan drug status	Palliative care (including antispasticity medications, orthopedic devices, and physical and speech therapy)	Improved independent functioning Reduced SCA 3 symptoms (e.g., dysarthria, motor dysfunction, spasticity) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ixazomib in combination with oral dexamethasone for treatment of recurrent or refractory systemic light chain (AL) amyloidosis	Patients with recurrent or refractory systemic light chain (AL) amyloidosis after 1 or 2 1st-line chemotherapies	AL amyloidosis is the most common form of a group of plasma cell disorders characterized by abnormal amyloid deposits in body tissues. Among Americans, 1,200–3,200 new cases of AL amyloidosis are diagnosed each year; approximately 2/3 of cases occur in males, and 95% of patients with AL amyloidosis are older than 40 years. In AL amyloidosis, amyloid deposits are comprised of excess amyloidogenic monoclonal immunoglobulin light chains produced by the bone marrow clonal plasma cell population. Severe symptoms include congestive cardiomyopathy, sensorimotor or autonomic peripheral neuropathy, and nephritic syndrome. In 20% of cases, plasma cells replicate more aggressively and can lead to myeloma. Chemotherapy regimens targeting the underlying bone marrow disorder are 1st-line treatments for AL amyloidosis, but an unmet need exists for effective interventions for patients who do not respond to chemotherapy or who experience relapsing symptoms. Ixazomib is a small-molecule, 2nd-generation proteasome inhibitor purported to induce apoptosis in cancerous cells by disrupting essential protein synthesis. In clinical trials, 4 mg ixazomib is administered in oral tablet form, once every 7 days, in combination with alternating 4-day cycles of 20 or 40 mg dexamethasone; this combination can also be administered with cycles of melphalan, cyclophosphamide, thalidomide, or lenalidomide, based on a primary clinician's recommendation. Millennium Pharmaceuticals subsidiary of Takeda Pharmaceutical Co., Ltd., Osaka, Japan Phase III trial ongoing; FDA granted breakthrough therapy status in 2014 and orphan drug status in 2012	Additional chemotherapy regimens	Reduced amyloid deposition Reduced disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lamazym for treatment of alpha-mannosidosis	Patients in whom alpha-mannosidosis has been diagnosed	Alpha-mannosidosis is an autosomal recessive inherited lysosomal storage disorder caused by mutations in the *MAN2B1* gene, which encodes the enzyme alpha-mannosidase. Patients with alpha-mannosidosis exhibit symptoms including intellectual disability, distinctive facial features, and skeletal abnormalities. Patients with type III alpha-mannosidosis develop symptoms in infancy, including hearing loss, respiratory infections, splenomegaly, and profound mental impairment; these patients often do not survive childhood. Across all types in humans, alpha-mannosidase is a very rare disorder, with a worldwide prevalence of 1 in 500,000. Most standard treatments are palliative; hematopoietic stem cell transplantation is viable only for patients who receive a diagnosis before age 2 and has been used experimentally in only a single patient. An unmet need exists for effective alternative interventions that address underlying genetic causes of this disorder. Recombinant human alpha-mannosidase (Lamazym) is an intravenously administered enzyme-replacement therapy for patients with alpha-mannosidosis. In clinical trials, Lamazym is infused weekly. Chiesi, Ltd., Cheadle, UK (manufacturer) Zymenex A/S, Hillerød, Denmark (original developer and clinical trial sponsor) 2 phase III trials ongoing and 2 phase III trials completed; Feb 2006, FDA granted orphan drug status	Hematopoietic stem cell transplantation (HSCT) before age 2 years Palliative treatment	Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lampalizumab for treatment of dry age-related macular degeneration	Patients in whom advanced, dry age-related macular degeneration (AMD) has been diagnosed	Dry AMD is an inherited autosomal dominant disease affected by nutrition and environmental factors (e.g., smoking). It may slowly progress to geographic atrophy and central vision loss over decades; however, no treatments are available to halt progression or restore lost vision. If neovascularization develops (i.e., wet AMD), vision loss occurs more rapidly, over months. Dry AMD is the most common cause of vision loss in the developed world. Vitamin and mineral supplements (AREDS formulation) may prevent later progression in some people, but no treatments are available. Lampalizumab is an antigen-binding fragment of an antibody targeted at complement factor D. It purportedly works by inhibiting the hyperactive alternate complement pathway, which has been implicated in AMD. It potentially reduces the area of geographic atrophy. Lampalizumab is administered at a dose of 10 mg, as an intravitreal injection, every 4 or 6 weeks. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials (CHROMA and SPECTRI) ongoing	AREDS formulation (high levels of antioxidants and zinc) Implanted telescopic lens	Improved visual acuity Reduced area of geographic atrophy Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Laquinimod for treating Huntington's disease	Patients in whom Huntington's disease (HD) has been diagnosed	More than 15,000 Americans have HD, and another 150,000 people have a 50% risk of developing the disease. As a genetic, inherited disorder, HD arises from genetically programmed degeneration of neurons in the brain. The degeneration results in uncontrolled movements, loss of cognitive abilities, and emotional disturbance. Affected cells include the basal ganglia, which coordinate movement. Also affected is the brain's cortex, which controls thought, perception, and memory. No cure exists for HD, and available therapies help only to manage the emotional and motor symptoms of the disease. Laquinimod is a synthetic immunomodulator, with anti-inflammatory properties, being investigated for treating HD and other neurodegenerative disorders. Although this drug's exact mechanism of action has not yet been elucidated, it may exert its effect by modulating the immune system from a proinflammatory to an anti-inflammatory response and by preventing damaging immune-system cells from entering central nervous system. Recent research also suggests that laquinimod functions as a novel inhibitor of microglial activation that lowers microglia-induced neuronal death in culture and axonal injury and loss; these properties may also contribute to its potential efficacy in treating HD. In clinical trials for treating HD, laquinimod is administered orally, at dosages up to 1.5 mg, daily, for up to 12 months. Active Biotech AB, Lund, Sweden (developer) Teva Pharmaceutical Industries, Ltd., Petah-Tikva, Israel (commercial in-licenser) Phase II trial ongoing; Dec 2005, FDA granted orphan drug status; laquinimod is also under investigation for treating multiple sclerosis	No FDA-approved treatments exist to simultaneously treat multiple symptoms of HD. Existing treatments for various HD symptoms include: Nonpharmaceutical interventions (e.g., occupational therapy, physical therapy, psychotherapy, speech therapy) Treatments for motor dysfunction: Antipsychotic drugs (e.g., haloperidol, clozapine) Antiseizure drugs (e.g., clonazepam, diazepam) Tetrabenazine (Xenazine®) Treatments for psychiatric disorders: Antidepressants (e.g., escitalopram, fluoxetine, sertraline) Antipsychotic drugs Mood-stabilizing drugs	Delayed or reversed HD progression Reduced motor and psychiatric symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lentiviral-based gene therapy (LentiGlobin BB305) for treatment of beta-thalassemia	Patients in whom beta-thalassemia has been diagnosed	Patients with beta-thalassemia have a mutation in the gene that encodes beta-globin. Patients who are homozygous for mutated beta-globin have thalassemia major, which causes severe anemia. They rely on chronic blood transfusions for survival. To combat the effects of iron overload due to chronic transfusions, patients must also undergo nightly iron chelation. A cure for beta-thalassemia—an allogeneic hematopoietic stem cell transplant from a matched sibling donor—is available only to children. About 75% of patients do not have this option, and those who do face significant risk of morbidity and mortality. LentiGlobin BB305 is a lentiviral-based gene therapy that inserts a functional human beta-globin gene into a patient's ex vivo stem cells. A patient is then transplanted with the altered stem cells. Because it is an autologous stem-cell transplant, patients do not need immunosuppressive therapy. Bluebird Bio, Cambridge, MA Phase I/II trials ongoing; FDA granted orphan drug and breakthrough therapy statuses	Allogeneic stem cell transplant Chronic blood transfusions	Improved organ function Reduced dependence on blood transfusions Reduced incidence of iron overload Improved quality of life
Levoketoconazole for treatment of endogenous Cushing's syndrome	Patients in whom endogenous Cushing's syndrome has been diagnosed	Endogenous Cushing's syndrome is caused by the body's production of high levels of cortisol or a cortisol precursor, adrenocorticotrophic hormone (ACTH), typically by pituitary, adrenal, or ectopic endocrine tumors. ACTH stimulates the production and release of the stress hormone cortisol, which controls the body's use of carbohydrates, fats, and proteins and helps reduce inflammatory responses. Too much ACTH results in too much cortisol. Not all patients respond to surgery or radiotherapy and limited medical treatments are available. Levoketoconazole (COR-003) is being developed as single 2S, 4R enantiomer of ketoconazole for treating endogenous Cushing's syndrome. It purportedly affects the downregulation of cortisol synthesis by targeting multiple points in the synthetic pathway. Clinical trial using dose titration to determine minimum and maximum effective doses. Cortendo AB, Partille, Sweden Phase III trial (SONICS) ongoing; Mar 2012, FDA granted orphan drug status	Mifepristone (Korlym) Off-label pharmacotherapy agents (ketoconazole, mitotane) Radiotherapy Surgery	Improved symptoms Reduced ACTH levels Reduced morbidity from excess cortisol Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
L-glutamine for prevention of vaso-occlusive crises in sickle cell disease	Patients in whom sickle cell anemia or sickle beta-0 thalassemia has been diagnosed	Sickle cell disease (SCD) is an autosomal recessive disorder that affects about 100,000 people in the U.S. and Europe and can present as sickle cell anemia and sickle beta-0 thalassemia. Increased disease prevalence is seen in people of African and Mediterranean descent; about 1 in 500 African-American children born have sickle cell anemia. In SCD, sickled red blood cells are more susceptible to oxidative damage and inappropriate adhesion, which can lead to vaso-occlusive crisis (VOC). VOC causes severe pain by obstructing vasculature and requires hospitalization. Patients may progress to thromboembolic events, stroke, organ failure, or early death. VOC is typically managed with hydration and pain medication but cannot be halted. The only FDA-approved treatment for SCD, hydroxyurea, can reduce VOC incidence but is not effective in about 1/3 of adult patients. Pharmaceutical grade L-glutamine might have a role in managing SCD because it is a precursor of natural antioxidants in red blood cells, which may be deficient in SCD. In clinical trials, L-glutamine is mixed in with food or beverage at 0.3 g/kg in 5 g increments, up to 30 g, daily. Emmaus Medical, Inc., Torrance, CA Phase III trial completed; FDA granted orphan drug and fast-track statuses; manufacturer intends to submit new drug application to FDA in 2015	Allogeneic hematopoietic stem cell transplantation Analgesics Blood transfusion Hydroxyurea Statins Supplemental oxygen	Fewer hospitalizations Reduced frequency of VOCs Reduced health disparities (African Americans) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Macrophage regulator (NP001) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	ALS is a progressive disorder marked by neurodegeneration of nerve cells in the brain and spinal cord. A 2014 report calculated that ALS prevalence is about 3.9 cases per 100,000 Americans. The average life expectancy of a patient with ALS is 3–5 years after diagnosis, and only 10% of patients survive for more than 10 years. Only a single agent (riluzole) is FDA approved for treating ALS, and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function; novel therapies for ALS are urgently needed. NP001 is a small-molecule regulator of macrophage activation; aberrant macrophage activation is believed to be a primary contributor to the pathology underlying ALS and other neurodegenerative diseases. NP001 is intended to restore normal functioning of macrophages in central nervous system, reducing inflammation and normalizing the cellular environment. In clinical trials, NP001 is administered intravenously, at dosages of 1 mg/kg or 2 mg/kg, for up to 6 months. Neuraltus Pharmaceuticals, Inc., Palo Alto, CA Phase II trial completed; Aug 2011, FDA granted fast-track and orphan drug statuses	Riluzole (Rilutek®) Supportive care	Improved biomarker levels Restoration of macrophages to their neuroprotective state Improved activities of daily living Delayed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Masitinib for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	ALS is a progressive disorder marked by neurodegeneration of nerve cells in the brain and spinal cord. A 2014 report calculated that nationwide ALS prevalence is about 3.9 cases per 100,000 Americans. The average life expectancy of a patient with ALS is 3–5 years after diagnosis, and only 10% of patients survive for more than 10 years. Only 1 agent (riluzole) is FDA approved for treating ALS, and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function; novel therapies are urgently needed. Masitinib is an investigative medication that purportedly inhibits tyrosine kinases c-Kit, Fyn, and Lyn. C-Kit inhibition is hypothesized to reduce mast cell–mediated neuroinflammation, a protective function that potentially makes masitinib a viable ALS pharmacotherapy. In clinical trials for treating early stage ALS, masitinib is administered orally at doses of up to 200 mg; the manufacturer has not announced a dosing regimen for this indication. AB Science S.A., Paris, France European phase II/III trial ongoing; Mar 2015, FDA granted orphan drug status; masitinib is also under investigation for treating a wide variety of cancers and other indications, including multiple sclerosis, Alzheimer's disease, and severe asthma	Riluzole (Rilutek®) Supportive care	Delayed disease progression Improved cognitive and motor-degeneration symptoms Improved quality of life
Masitinib for treatment of multiple sclerosis	Patients in whom multiple sclerosis (MS) has been diagnosed	Treatments for MS may slow disease progression, but they are not effective in all patients, and the disease has no cure. Masitinib is a tyrosine kinase inhibitor purportedly targets the activity of mast cells, which are involved in triggering local inflammatory reactions in tissues. Masitinib purportedly selectively inhibits KIT, platelet-derived growth factor receptor, Lyn, and to a lesser extent, fibroblast growth factor receptor 3. In clinical trials, masitinib is administered orally at a daily dosage of 6 mg/kg. AB Science S.A., Paris, France Phase IIb/III trial ongoing; masitinib is also under investigation for treating a wide variety of cancers and other indications, including amyotrophic lateral sclerosis, Alzheimer's disease, severe asthma, and rheumatoid arthritis	Dimethyl fumarate (Tecfidera®) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Delayed disease progression Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mepolizumab (Nucala) for treatment of Churg-Strauss syndrome	Patients in whom Churg-Strauss syndrome has been diagnosed	Churg-Strauss syndrome is a rare (1 to 3 cases per 1 million population), currently incurable, autoimmune disorder marked by blood vessel inflammation, new or worsening asthma symptoms, hypereosinophilia, and vasculitis. Disease severity in patients can range from mild, with only skin lesions and polyps, to severe, with life-threatening heart disease, often caused by eosinophilic myocarditis. In the 2nd and 3rd stages of disease, patients may also present with peripheral nerve damage, skin scarring, and kidney damage. Churg-Strauss syndrome is also known as allergic granulomatosis or eosinophilic granulomatosis with polyangiitis (EGPA), in part due to the abnormally high number of eosinophils and elevated interleukin-5 (IL-5) levels during the 2nd stage of the disease. Interventions to treat primary symptoms include systemic corticosteroids, such as prednisone; immunosuppressive drugs, including azathioprine and methotrexate; and immune globulin, administered monthly. Each of these treatments has side effects and limited efficacy in all patients. Mepolizumab (Nucala), a humanized monoclonal antibody targeting IL-5, that may improve symptoms of Churg-Strauss syndrome and reduce reliance on corticosteroids by reducing eosinophil levels in patients. In a late-phase clinical trial, mepolizumab is administered to patients as a 300 mg subcutaneous injection, every 4 weeks. GlaxoSmithKline, Middlesex, UK Phase III trials ongoing; Jul 2011, FDA granted orphan drug status for this indication; mepolizumab is also under investigation for treating indications including severe chronic obstructive pulmonary disease and eosinophilic asthma	Corticosteroids (e.g., prednisone) Immune globulin Immunosuppressants (e.g., azathioprine, methotrexate)	Improved disease course (reduced hypereosinophilia in 2nd disease stage) Reduced corticosteroid reliance Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Metal protein attenuating compound (PBT2) for treatment of Huntington's disease	Patients in whom Huntington's disease (HD) has been diagnosed	More than 15,000 Americans have HD and another 150,000 people have a 50% risk of developing the disease. As an inherited disorder, HD's symptoms arise from genetically programmed degeneration of neurons in the brain. The degeneration results in uncontrolled movements, loss of cognitive abilities, and emotional disturbance. Affected cells include the basal ganglia, which coordinate movement. Also affected is the brain's cortex, which controls thought, perception, and memory. No cure exists, and current therapies help only to manage emotional and motor symptoms of the disease. PBT2 (5,7-dichloro-2-methylaminomethyl-8-hydroxyquinolone hydrochloride) is a metal protein attenuating compound that purportedly improves motor and cognitive symptoms associated with HD by preventing accumulation of huntingtin proteins and restoring copper and zinc levels affected by HD neurodegeneration. In clinical trials for treating HD, PBT2 is administered orally, once daily, for up to 26 weeks, at 100 and 250 mg doses. Prana Biotechnology, Melbourne, Australia Phase II trial completed; Sept 2014, FDA granted orphan drug status; PBT2 is also under investigation for treating Alzheimer's disease	Nonpharmaceutical interventions (e.g., occupational therapy, physical therapy, psychotherapy, speech therapy) Treatments for motor dysfunction: Antipsychotic drugs (e.g., haloperidol, clozapine) Antiseizure drugs (e.g., clonazepam, diazepam) Tetrabenazine (Xenazine; FDA approved to suppress HD-associated chorea) Treatments for psychiatric disorders: Antidepressants (e.g., escitalopram, fluoxetine, sertraline) Antipsychotic drugs Mood-stabilizing drugs	Reduced motor and psychiatric symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Methacetin breath test (BreathID) to monitor liver function in acute liver failure	Patients in whom acute liver failure has been diagnosed	BreathID® Methacetin Breath Test (MBT) is intended to monitor liver function in patients with acute liver failure by working in conjunction with a marker targeted to challenge hepatic metabolism. The marker purportedly can be measured in the breath of the patient and thus inform clinical decisionmaking regarding need for liver transplantation. The breath test could give additional liver function assessment information not available with blood tests. The company purports to provide a novel diagnostic option for this population. The test requires a patient to breathe into a device and is administered in a physician's office. After a patient fasts overnight for 8 hours, a physician gives 75 mg of 13C-labeled methacetin to the patient, orally in a small volume of water, and measures expired 13C-labeled carbon dioxide with a nasal cannula. Exalenz Bioscience, Inc., Modi'in, Israel (manufacturer) Virginia Commonwealth University, Richmond (investigator) Phase III trial completed; in Sept 2011, FDA granted humanitarian use device exemption for monitoring hepatic metabolism in patients with acute liver failure; Exalenz obtained a patent for BreathID use in assessing liver function Aug 2013; also under study for assessing liver function in chronic liver disease, non-alcoholic steatohepatitis, clinically significant portal hypertension, and hepatocellular carcinoma	Liver biopsy Liver function blood tests	Earlier detection of liver function problems Improved patient comfort Increased adherence with liver function testing

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Migalastat hydrochloride (Galafold) for treatment of Fabry disease	Patients with Fabry disease who either have migalastat-responsive mutations in alpha-galactosidase A or are receiving enzyme replacement therapy	Fabry disease is a genetic disorder characterized by cellular buildup of globotriaosylceramide, a type of fat, that causes a wide range of symptoms and can lead to heart attack, stroke, and kidney damage. Enzyme replacement therapies for the disease are expensive and have been subject to recent shortages. Migalastat hydrochloride (Galafold®) is a small-molecule drug that enhances the activity of alpha-galactosidase A, the enzyme that is deficient in Fabry disease. The drug could be used to enhance the activity of exogenously provided enzyme replacement therapy or to enhance the endogenous activity of certain alpha-galactosidase mutant isoforms that have been shown to be responsive to it. In trials, it is being tested as an oral monotherapy and in combination with enzyme replacement therapy. Dosage is 150 mg, every other day, or 250 mg, in cycles of 3 days on and 4 days off. It is taken orally. Amicus Therapeutics, Inc., Cranbury, NJ Phase III trials ongoing; FDA granted orphan drug status; manufacturer intends to file new drug application for accelerated approval in 2nd half 2015	Enzyme replacement therapy Palliative treatment	Decreased globotriaosylceramide (GL-3) levels Improved cardiac outcomes Improved renal function (e.g., glomerular filtration rate) Reduced mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Motoneuronotrophic factor oligopeptide analogue (GM6, GM604) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	ALS is a progressive disorder marked by neurodegeneration of nerve cells in the brain and spinal cord. A 2014 report calculated that ALS prevalence is about 3.9 cases per 100,000 Americans. The average life expectancy of a patient with ALS is 3–5 years after diagnosis, and only 10% of patients survive for more than 10 years. Only 1 agent (riluzole) is FDA approved for treating ALS, and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function; novel therapies are urgently needed. GM6 is a 6 amino acid motoneuronotrophic factor (MNTF) analogue, identified by in silico (computerized) analysis, under investigation as a novel ALS intervention. GM6 purportedly exhibits key properties of endogenous MNTF, including motor neuron differentiation, maintenance, and reinnervation; in animal models and early clinical trials, GM6 demonstrated neuroprotective activities, and chronic treatment was associated with sustained or recovered motor function. In ongoing clinical trials, GM6 is administered as a slow, 6.4 mL/dose intravenous bolus injection; 6 doses are administered over 2 weeks, on Monday, Wednesday, and Friday of each week. Genervon Biopharmaceuticals, LLC, Pasadena, CA Phase II trial completed; Apr 2015, FDA requested that manufacturer publicly release data from completed phase II trial; Feb 2014, FDA granted orphan drug status; Jun 2013, FDA granted fast-track status	Riluzole (Rilutek®) Supportive care	Delayed disease progression Decreased mortality rate Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multitargeted tyrosine kinase inhibitor (PLX3397) for treatment of pigmented villonodular synovitis and localized nodular tenosynovitis	Patients in whom pigmented villonodular synovitis (PVNS) or surgery-contraindicated localized nodular tenosynovitis has been diagnosed	PVNS and localized nodular tenosynovitis are rare joint disorders with an estimated prevalence of 2–9 cases per 1 million people, characterized by inflammation of the synovium and abnormal growth in joints or joint tendon sheaths. These disorders can occur at any age, but are most commonly identified in adults between age 20 and 50 years; localized nodular tenosynovitis is observed more frequently in women than in men. Symptoms can spontaneously manifest and are most commonly observed in hand, foot, knee, or hip joints. PVNS and localized nodular tenosynovitis are also marked by hemorrhagic synovial fluid and benign tumor growth on joint tendon sheaths, leading to pain, swelling, and decreased range of motion. To date, the pathology of these disorders is unknown but may be triggered by joint trauma before symptom occurrence. Surgery, including synovectomy or total joint replacement, is standard treatment for these disorders but is counterproductive for some patients; radiation therapy may also be considered. An unmet need exists for effective, nonsurgical interventions for PVNS and localized nodular tenosynovitis. PLX3397 is an investigational, small-molecule tyrosine kinase inhibitor of KIT, colony stimulating factor 1 receptor (CSF1R), and Fms-like tyrosine kinase 3 (*FLT3*). Of these kinases, CSF1R is known to play a key role in the development of advanced PVNS, while the other 2 may also be involved in disease etiology. PLX3397 also has potential antineoplastic activity, offering an additional mechanism of action against tumor growth. In clinical trials, it is administered as a 200 mg oral capsule, given in initial daily doses of 1,000 mg, tapered down to 800 mg or less after 2 weeks; doses are split over morning and evening administrations. Plexxikon subsidiary of Daiichi Sankyo Co., Ltd., Tokyo, Japan (original developer) Daiichi Sankyo Co., Ltd., Tokyo, Japan (clinical trial sponsor) Phase III trial ongoing; PLX3397 is also under investigation, as a monotherapy and combination regimen, for treating several oncologic indications including advanced ovarian cancer and metastatic breast cancer	Radiation therapy Surgery	Increased joint range of motion Reduced joint pain and inflammation Reduced tumor volume Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multitargeting neuroprotective agent (BN82451 / BN82451B) for treatment of Huntington's disease	Patients in whom Huntington's disease (HD) has been diagnosed	More than 15,000 Americans have HD, and another 150,000 people have a 50% risk of developing the disease. As a genetic, inherited disorder, HD arises from genetically programmed degeneration of neurons in the brain. The degeneration results in uncontrolled movements, loss of cognitive abilities, and emotional disturbance. Affected cells include the basal ganglia, which coordinate movement. Also affected is the brain's cortex, which controls thought, perception, and memory. No cure exists for HD, and available therapies help only to manage the emotional and motor symptoms of the disease. BN82451B is an investigational oral molecule that has displayed broad neuroprotective properties in animal models of disorders including amyotrophic lateral sclerosis, cerebral ischemia, and HD. This broad activity is purportedly due to BN82451B's antioxidant properties, cyclooxygenase inhibition, specific mitochondria-protecting activity, and sodium channel blockade activity; the latter 2 functions may directly underlie BN82451B's HD treatment efficacy. In clinical trials, BN82451B is administered as a capsule, twice daily, at doses of 40, 60, or 80 mg. Ipsen, Paris, France Phase II trial ongoing in Germany; Mar 2015, FDA granted orphan drug status	No FDA-approved treatments exist to simultaneously treat multiple symptoms of HD. Existing treatments for various HD symptoms include: Nonpharmaceutical interventions (e.g., occupational therapy, physical therapy, psychotherapy, speech therapy) Treatments for motor dysfunction: Antipsychotic drugs (e.g., haloperidol and clozapine) Antiseizure drugs (e.g., clonazepam and diazepam) Tetrabenazine (Xenazine®; FDA approved to suppress chorea associated with HD) Treatments for psychiatric disorders: Antidepressants (e.g., escitalopram, fluoxetine and sertraline) Antipsychotic drugs Mood-stabilizing drugs	Delayed or reversed HD progression Reduced motor and psychiatric symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mu-opioid agonist with small-molecule polymer conjugate technology (NKTR-181) for treatment of chronic pain	Patients experiencing chronic pain	Chronic use of opioid analgesics can lead to abuse and may increase risk of dangerous suppression of central nervous system (CNS) activity leading to sedation or respiratory distress. NKTR-181 is a novel mu-opioid agonist formulation that modifies the opioid by pegylation. Pegylation is intended to reduce the rate at which the drug enters the brain, thereby limiting high CNS concentrations that could lead to feelings of euphoria or respiratory distress. In clinical trials, NKTR-181 is administered at a dose of 100–400 mg, twice daily, orally. Nektar Therapeutics, San Francisco, CA Phase III trials ongoing; FDA granted fast-track status	Conventional mu-opioid agonists Opioids with abuse-deterrent properties (e.g,, crush-resistant or agonist-antagonist combined formulations)	Improved pain relief Reduced abuse liability Reduced adverse effects Improved quality of life
Nabiximols oromucosal spray (Sativex) for treatment of multiple sclerosis spasticity and neuropathic pain	Patients in whom multiple sclerosis (MS) has been diagnosed	Current treatments for MS may slow disease progression, but they are not effective in all patients, and the disease has no cure. Sativex® is a whole-plant medicinal cannabis extract that contains Tetranabinex® and Nabidiolex® (cannabidiol) as its main components. Delta-9-tetrahydrocannabinol (THC) in the extract acts as a partial agonist at both cannabinoid receptors, CB1 and CB2, mimicking the effects of the endocannabinoids, which may modulate the effects of neurotransmitters (e.g., reduce effects of excitatory neurotransmitters such as glutamate) to improve symptoms. Sativex is sprayed under the tongue, 100 mcL/dose, which contains 2.5 mg cannabidiol and 2.7 mg THC. Sativex is intended for use as an add-on treatment to current MS therapies. GW Pharmaceuticals, plc, Salisbury, UK Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan Phase III joint U.S./UK trial ongoing, with multiple international phase III trials completed. Sativex has marketing approval in UK, New Zealand, and Canada for treating MS spasticity and is also approved in Canada for relief of MS-related neuropathic pain.	Pharmacotherapy (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], opioids)	Reduced pain Reduced spasticity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nav1.7 sodium channel blocker (CNV1014802) for treatment of trigeminal neuralgia	Patients in whom trigeminal neuralgia has been diagnosed	Trigeminal neuralgia is a chronic pain condition characterized by intense pain in the face along the trigeminal nerve in response to mild stimuli (e.g., toothbrushing, applying makeup). The condition is progressive with bouts of pain becoming more intense and more frequent over time. Patients may experience pain relief with anticonvulsant and antispasmodic medications until the condition progresses. However, these drugs lose their effectiveness over time and cause significant side effects including fatigue and cardiac toxicity. Surgery provides relief to some patients. CNV1014802 is a selective sodium channel modulator that blocks the voltage-gated sodium channel Nav1.7, which has been implicated in multiple pain conditions. CNV1014802 is administered at 150 mg, thrice daily, or 350 mg, twice daily, orally. Convergence Pharmaceuticals, Cambridge, UK, a subsidiary of Biogen, Cambridge, MA Phase IIa trial completed; Jul 2013, FDA granted orphan drug status	Anticonvulsants (e.g., carbamazepine, clonazepam, gabapentin) Antispasmodics (e.g., baclofen) Rhizotomy (e.g., balloon compression, glycerol injection, radiofrequency thermal lesioning) Surgery (e.g., microvascular decompression, Gamma Knife® radiosurgery)	Decreased frequency of paroxysms Decreased severity of pain Improved quality of life
Obeticholic acid for treatment of nonalcoholic steatohepatitis	Patients in whom nonalcoholic steatohepatitis (NASH) has been diagnosed	NASH is a liver disease characterized by fatty deposits, inflammation, and hepatocyte damage. It affects an estimated 2% to 5% of Americans, although it is asymptomatic for most patients. As NASH progresses over several years, it may lead to cirrhosis and permanent liver damage. In the most severe cases, patients require a liver transplant to survive. NASH's cause is unknown. People who are middle-aged, obese, or glucose intolerant are at higher risk of the disease, although some patients have none of these risk factors. For patients who alter their diets and exercise, NASH may be reversible. No other treatments exist. Obeticholic acid (INT-747) is a 1st-in-class farnesoid X receptor (FXR) agonist derived from human bile. FXR is a nuclear hormone receptor that mediates bile acid signaling. Obeticholic acid purportedly decreases liver tissue scarring and fibrosis. Intercept Pharmaceuticals, Inc., New York, NY Phase II trial completed; FDA granted breakthrough therapy status Jan 2015	Improved diet and exercise	Decreased liver fat Decreased liver inflammation and damage Reduced rates of cirrhosis and liver failure Fewer liver transplantations Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Obeticholic acid for treatment of primary biliary cirrhosis	Patients in whom primary biliary cirrhosis (PBC) has been diagnosed	PBC is a chronic and progressive cholestatic liver disease, which results in destruction of small-to-medium bile ducts. Cirrhosis develops with disease progression and results in death unless a patient receives a liver transplant. Even after transplantation, PBC has a high recurrence rate. The standard care for earlier disease stages is to delay progression by using ursodeoxycholic acid, which is ineffective in up to 50% of patients. Obeticholic acid (OCA) is a 1st-in-class, bile acid–analogue agonist of the farnesoid X receptor (FXR), which is a negative feedback regulator of bile acid levels. OCA activation of FXR may delay progression in patients whose disease does not respond to ursodeoxycholic acid. In clinical trials, OCA is administered orally, at doses of 5–25 mg. Intercept Pharmaceuticals, Inc., New York, NY Phase III trials ongoing; Jun 2015, new drug application submitted; FDA granted priority review Aug 2015 with a decision date in Feb 2016; FDA granted orphan drug and fast-track statuses	Antipruritic therapy Colchicine Corticosteroids Cyclosporine Immunosuppressive therapy Liver transplant Methotrexate Ursodeoxycholic acid	Decreased risk of liver transplant or death Improved high-density lipoprotein metabolism Reduced bilirubin levels Reduced serum alkaline phosphatase levels Improved quality of life
Obeticholic acid for treatment of primary sclerosing cholangitis	Patients in whom primary sclerosing cholangitis (PSC) has been diagnosed	PSC is a cholestatic liver disease that causes scarring in bile ducts. It progresses slowly but may lead to liver failure, frequent infections, or tumors of the bile duct and liver. No treatments are available. Obeticholic acid (OCA) is a 1st-in-class, bile acid–analogue agonist of the farnesoid X receptor (FXR), which is a negative feedback regulator of bile acid levels. OCA activation of FXR may delay disease progression by reducing scarring and fibrosis. In clinical trials, OCA is administered orally, 1.5–10 mg, daily. Intercept Pharmaceuticals, Inc., New York, NY Phase II trial ongoing; Sept 2008, FDA granted orphan drug status	Antibiotics Antipruritics Liver transplant Nutrition support Surgery to correct bile duct obstruction Ursodiol	Decreased liver inflammation and damage Decreased risk of liver transplant or death Reduced rates of cirrhosis and liver failure Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ocrelizumab for treatment of relapsing-remitting and primary progressive multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) or primary progressive multiple sclerosis (PPMS) has been diagnosed	Available therapies for RRMS and PPMS provide unsatisfactory results for many patients. Ocrelizumab (RG1594) represents a novel mechanism of action for this disease. It is a human monoclonal antibody intended to target CD20-positive B cells (believed to play a role in multiple sclerosis), then interact with immune system to eliminate these CD20-positive B cells. In clinical trials, ocrelizumab is administered via infusion, once every 6 months. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Biogen, Cambridge, MA Pivotal phase III trials for RRMS (OPERA I and OPERA II) completed and pivotal phase III trial for PPMS (ORATORIO) ongoing; manufacturer plans to file new drug application in 2016	Dimethyl fumarate (Tecfidera®) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Decreased frequency of relapse Slowed disease progression Improved quality of life
Off-label etanercept (Enbrel) as an adjunctive therapy for treatment of Kawasaki disease	Patients in whom Kawasaki disease (KD) has been diagnosed	KD is the most common cause of acquired heart disease in U.S. children. In many patients, the disease is refractory to current standard of care; new treatment options are needed for refractory disease. Etanercept (Enbrel®) is a soluble, dimeric form of the p75 tumor necrosis factor (TNF) receptor purported to bind TNF alpha and beta molecules, thus inhibiting the binding of TNF molecules to cell surface receptors and preventing inflammation associated with KD. Etanercept may be administered immediately after intravenous immunoglobulin (IVIG) infusion, 0.8 mg/kg per dose, 2 times weekly. In ongoing clinical trials, etanercept is administered subcutaneously as an adjunct therapy to IVIG and aspirin, 0.8 mg/kg (with a maximum dose of 50 mg), once weekly, for 3 weeks. Amgen, Inc., Thousand Oaks, CA (manufacturer) Seattle Children's Hospital, Seattle, WA (clinical trial sponsor) Phase II trial ongoing; Nov 1998, FDA approved etanercept (as Enbrel) for treating moderate to severe rheumatoid arthritis, with subsequent expanded indications for other inflammatory conditions	Corticosteroids High-dose aspirin IVIG	Prevented increase in coronary artery diameter Prevented new coronary artery dilation/cardiac dysfunction Reduced fever Improved survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label isradipine for treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	Up to 1 million Americans have diagnosed PD, and about 60,000 new cases are diagnosed yearly. Worldwide, 7 million to 10 million patients have PD. The most frequently prescribed intervention for PD is L-dopa, which can be an effective treatment, but it can also have severe side effects such as dyskinesia and must have dosages consistently monitored and adjusted. Other pharmaceuticals, including pramipexole and rasagiline mesylate, have been prescribed but have demonstrated poor efficacy at low dosages. An unmet need exists for well-tolerated PD treatments that have fewer adverse side effects. Isradipine, a calcium channel blocker, is being investigated as a potential PD therapy. Isradipine purportedly prevents damage to calcium channels located in dopamine-producing brain cells; experts hypothesize that this neuroprotective activity can delay or prevent PD symptoms and disease progression. In clinical trials, isradipine is orally administered as a 5 mg tablet, taken twice daily for up to 36 months. Multiple universities including the University of Rochester, Rochester, NY (lead study sponsor) Michael J. Fox Foundation for Parkinson's Research, New York, NY (collaborator) National Institute of Neurological Disorders and Stroke, Bethesda, MD (collaborator) Phase III trial ongoing; Feb 1997, FDA originally approved isradipine for treating high blood pressure to reduce risk of stroke and heart attack	Adenosine A2A receptor antagonist (in development) Dopamine agonists Glutamate receptor 5 modulators (in development) Levodopa/carbidopa Monoamine oxidase-B inhibitors Nicotinic receptor agonist (in development) Tozadenant (in development)	Delayed disease progression Improved cognitive function Improved motor function Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label phosphodiesterase type 5 (PDE-5) inhibitors for treatment of muscular dystrophinopathies	Patients in whom Duchenne muscular dystrophy (DMD) or muscular dystrophinopathies have been diagnosed	Dystrophinopathies are a class of muscle diseases caused by dystrophin genes that function abnormally or not at all; DMD and Becker muscular dystrophies are among the more severe forms. Current treatments for these 2 diseases reduce symptoms but do not address their underlying cause. Research in human and mouse models has demonstrated that various proteins, including neuronal nitric oxide synthase, normally targeted by dystrophin may underlie the most pronounced muscular symptoms observed in severe dystrophies. Increased nitric oxide signaling by phosphodiesterase type 5 (PDE-5) inhibitor-class drugs, including tadalafil and sildenafil, is purported to effectively treat significant symptoms of muscular dystrophy, particularly muscle ischemia. In clinical trials, PDE-5 inhibitors are administered at various stable or escalating doses for up to 48 weeks. Cedars-Sinai Medical Center, Los Angeles, CA Eli Lilly and Co., Indianapolis, IN Parent Project Muscular Dystrophy, Hackensack, NJ National Institutes of Health's National Center for Advancing Translational Sciences, Bethesda, MD Phase III trial ongoing	Beta-2 agonists Corticosteroids Orthotic devices Physical therapy Respiratory support devices	Decreased mortality rate Delayed or halted muscle degeneration Reduced dystrophy-related symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label rituximab for treatment of pediatric nephrotic syndrome	Patients in whom pediatric nephrotic syndrome has been diagnosed	According to the National Kidney Foundation™, pediatric nephrotic syndrome affects an estimated 2–7 of 100,000 children in the U.S. It is characterized by massive renal losses of protein and is due to any number of diseases (e.g., postinfection glomerulonephritis, focal segmental glomerulosclerosis, congenital syphilis, systemic lupus erythematosus, malignancy, toxin exposure, diabetes mellitus). 1st-line treatment includes corticosteroids, to which some patients may develop resistance. Other treatment options are diuretic and antihypertensive therapies. Rituximab is a monoclonal antibody against CD20 antibody, which results in depletion of B cells. This drug therapy purportedly reduces the frequency of refractory cases of pediatric nephrotic syndrome. In clinical trials, rituximab is administered by infusion at a dose of 375 mg/m^2 up to 500 mg/day. 2nd and 3rd doses may be given at 1–3 week intervals if CD19 cells are not depleted. University of Tokyo, Japan (investigator) University Hospital, Limoges, France, (investigator) in collaboration with F. Hoffmann-La Roche, Ltd., Basel, Switzerland (manufacturer) Seoul National University Children's Hospital, South Korea (investigator) Phase III trial completed; FDA approved for treating non-Hodgkin's lymphoma and rheumatoid arthritis	Antihypertensives Corticosteroids Diuretics	Proteinuria with relapse of nephrotic syndrome Remission of refractory nephrotic syndrome Improved quality of life
Olesoxime for treatment of spinal muscular atrophy	Patients in whom spinal muscular atrophy (SMA) has been diagnosed	SMA is an inherited neuromuscular disease in which muscles atrophy and weaken, often resulting in death of infants born with the most severe form of the disorder. SMA occurs in an estimated 1 in 10,000 live births worldwide. Affected infants typically appear normal at birth, and symptoms develop within several months after birth. Available treatments address only disease symptoms. Treatments are needed that address the underlying cause of disease. Olesoxime (RG6083) potentially promotes neuroaxonal repair, remyelination, and neuroprotection by preserving mitochondrial integrity. It is administered in a 100 mg/mL liquid suspension at an oral dose of 10 mg/kg, once daily, with food, at dinner. TROPHOS SA, Marseille, France, a subsidiary of F. Hoffmann-La Roche. Ltd., Basel, Switzerland Phase II pivotal trial completed; company is pursuing regulatory pathway; Feb 2009, FDA granted orphan drug status	Supportive therapy (e.g., respiratory and nutrition support, physical therapy)	Improved motor function Increased progression-free survival Increased survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Palovarotene for treatment of fibrodysplasia ossificans progressiva	Patients in whom fibrodysplasia ossificans progressiva (FOP) has been diagnosed	FOP is a rare, autosomal dominant connective tissue disorder that affects fewer than 1 in 1 million people worldwide. In patients with FOP, soft connective tissue spontaneously swells and turns to bone (ossification) when damaged; these flare-ups can result in a "second skeleton," as any injuries spur new bone formation. Eventually, patients may be permanently immobilized. The disorder is caused by a mutation to the activin A receptor type-1 (*AVCR1*) gene, which normally encodes AVCR1 protein; the mutation causes abnormal AVCR1 activation, leading patients' endothelial cells to turn into mesenchymal stem cells and then into bone. A cure has not been found for FOP, and an unmet need exists for treatments that target underlying AVCR1 activation. Palovarotene is a retinoic acid receptor gamma (RAR-γ) agonist, originally developed as an investigational emphysema medication. In animal models, palovarotene blocks bone formation, and it is being studied as a potential FOP treatment. Palovarotene is administered orally and in clinical trials is taken as a powder mixed with foods; investigational dosages range from 2.5 to 15 mg, once daily. Clementia Pharmaceuticals, Inc., Montreal, Quebec, Canada (in-license developer) F. Hoffman-La Roche AG, Basel, Switzerland (original developer and manufacturer) 2 phase II trials ongoing; in 2014, FDA granted fast-track and orphan drug statuses and the European Medicines Agency granted orphan drug status	No approved comparator interventions exist	Improved symptoms (e.g., chronic pain, immobility) Reduced new bone growth Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Patiromer for treatment of hyperkalemia	Patients with chronic kidney disease (CKD) and hyperkalemia	A common condition, hyperkalemia is characterized by an excess of potassium in the blood. It may cause abnormal heart rhythms, and in severe cases, it can lead to cardiac arrest and death. In patients with CKD, hyperkalemia is a common consequence of renal dysfunction and medication side effects. Renin-angiotensin-aldosterone-system inhibitors used by patients with CKD to protect kidney and heart function may cause or worsen hyperkalemia. Patients are commonly treated with another ion-exchange resin, sodium polystyrene sulfonate; however, this drug may cause colonic necrosis and other serious gastrointestinal injuries. Patiromer for oral suspension (FOS) is a novel potassium binder that is intended to lower serum potassium, thereby treating hyperkalemia in patients with CKD and preventing recurrences. Patiromer FOS powder is administered twice daily, as an oral suspension in water, at dosages of 4.2 or 8.4 g. Relypsa, Inc., Redwood City, CA Phase III trial completed; Dec 2014, manufacturer submitted new drug application to FDA; decision date set for Oct 2015	Beta-2 adrenergic receptor stimulators (e.g., albuterol, epinephrine) Dialysis Diuretics Intravenous calcium Intravenous glucose and insulin Ion-exchange resins (e.g., sodium polystyrene sulfonate) Low-potassium diet	Decreased incidence of hyperkalemia Improved long-term cardiac outcomes Reduced serum potassium levels

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pediatric Vision Scanner for strabismus and amblyopia screening	Pediatric patients older than 2 years	The leading causes of preventable monocular vision loss in children are amblyopia ("lazy eye") and strabismus (misaligned eyes). Early detection of these conditions can be difficult because standard screening methods lack sufficient sensitivity and specificity, thereby missing cases of children who should be referred for further evaluation and possible treatment. If found early, amblyopia and strabismus are fully treatable, but as many as half of affected children are not identified until school age. The Pediatric Vision Scanner (PVS) purportedly improves screening for these conditions because it can be used in younger children, is easy to use, and is portable. It is intended as a screening tool for use in a pediatrician's office to identify children who should be referred to a specialist for further evaluation. The device uses proprietary technology called retinal birefringence scanning that detects eye fixation in screening for amblyopia and strabismus. The PVS scan takes about 2.5 seconds and can be performed in children older than 2 years. REBIScan, Inc., Cambridge, MA FDA classifies as nonsignificant risk device (Class I), which means it has abbreviated requirements for labeling, institutional review board approval, and trial and reporting rules; partnered with nonprofit organization VisionQuest 20/20 (Phoenix, AZ) to bring devices to pediatric offices and preschools nationwide; not yet commercially available	Photoscreening Standard vision examination	More appropriate referrals to ophthalmologists Reduced vision loss Improved quality of life
Pegvaliase (PEG-PAL) for treatment of severe phenylketonuria	Patients in whom severe phenylketonuria has been diagnosed	Phenylketonuria is an inherited disorder in which an enzyme, phenylalanine hydroxylase (PAH), needed to break down the essential amino acid phenylalanine is dysfunctional. Accumulated phenylalanine can damage the brain and lead to intellectual disabilities, behavioral abnormalities, seizures, and other neurologic complications. A drug that increases PAH activity (Kuvan®) is available to slow the progression of mild to moderate phenylketonuria for some patients, although its long-term efficacy is under study. Pegvaliase, also called PEG-PAL or BMN 165, might be a novel enzyme replacement; the drug is intended to reduce levels of phenylalanine in patients whose disease is unresponsive to Kuvan. Administered by self injection, daily. Trials are testing doses titrated up to 20 or 40 mg/day. BioMarin Pharma, Inc., Novato, CA Phase III trials ongoing; FDA granted orphan drug status	Kuvan (tetrahydrobiopterin or BH4) Specialized diet with limited phenylalanine	Decreased phenylalanine levels Fewer diet restrictions Improved cognitive and mood symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Phosphodiesterase 10 inhibitor (OMS824) for treatment of Huntington's disease	Patients in whom Huntington's disease (HD) has been diagnosed	More than 15,000 Americans have HD and another 150,000 persons have a 50% risk of developing the disease. As a genetic, inherited disorder, HD arises from genetically programmed degeneration of neurons in the brain. The degeneration results in uncontrolled movements, loss of cognitive abilities, and emotional disturbance. Affected cells include the basal ganglia, which coordinate movement. Also affected is the brain's cortex, which controls thought, perception, and memory. No cure exists for HD, and current therapies help only to manage emotional and motor symptoms associated with the disease. OMS824, a proprietary compound, purportedly treats the motor and psychiatric symptoms associated with HD by selective inhibiting phosphodiesterase 10. The drug is being administered orally for 28 days at 3 different dosages (not specified) in a phase II trial. Omeros Corp., Seattle, WA Phase II trial registered, but halted in Oct 2014 after abnormal medication blood concentrations were observed in a separate long-term mouse model study; in Feb 2014, FDA granted fast-track status	No FDA-approved treatments exist to simultaneously treat multiple symptoms of HD. Existing treatments for various HD symptoms include: Nonpharmaceutical interventions (e.g., occupational therapy, physical therapy, psychotherapy, speech therapy) Treatments for motor dysfunction: Antipsychotic drugs (e.g., haloperidol and clozapine) Antiseizure drugs (e.g., clonazepam and diazepam) Tetrabenazine (Xenazine) (FDA approved to suppress chorea associated with HD) Treatments for psychiatric disorders: Antidepressants (e.g., escitalopram, fluoxetine and sertraline) Antipsychotic drugs Mood-stabilizing drugs	Reduced HD-associated motor and psychiatric symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Phosphodiesterase 10 inhibitor (PF-02545920) for treatment of Huntington's disease	Patients in whom Huntington's disease (HD) has been diagnosed	More than 15,000 Americans have HD, and another 150,000 people have a 50% risk of developing the disease. As a genetic, inherited disorder, HD arises from genetically programmed degeneration of neurons in the brain. The degeneration results in uncontrolled movements, loss of cognitive abilities, and emotional disturbance. Affected cells include the basal ganglia, which coordinate movement. Also affected is the brain's cortex, which controls thought, perception, and memory. No cure exists for HD, and available therapies help only to manage the emotional and motor symptoms associated with the disease. PF-02545920 is a novel investigational drug that purportedly treats the motor and psychiatric symptoms associated with HD by selectively inhibiting phosphodiesterase 10, an enzyme associated with modulating basal ganglia functions, including motor control. In clinical trials, PF-02545920 is administered orally, twice daily, from 5 to 20 mg, for up to 26 weeks. Pfizer, Inc., New York, NY Phase II trials ongoing; Jun 2014, FDA granted orphan drug status	No FDA-approved treatments exist to simultaneously treat multiple symptoms of HD. Existing treatments for various HD symptoms include: Nonpharmaceutical interventions (e.g., occupational therapy, physical therapy, psychotherapy, speech therapy) Treatments for motor dysfunction: Antipsychotic drugs (e.g., haloperidol, clozapine) Antiseizure drugs (e.g., clonazepam, diazepam) Tetrabenazine (Xenazine®) Treatments for psychiatric disorders: Antidepressants (e.g., escitalopram, fluoxetine, sertraline) Antipsychotic drugs Mood-stabilizing drugs	Delayed or reversed HD progression Reduced motor and psychiatric symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pradigastat sodium (LCQ908) for treatment of lipoprotein lipase deficiency	Patients in whom lipoprotein lipase deficiency (LPLD) has been diagnosed	LPLD is a rare genetic disorder, affecting approximately 1 in 1 million individuals. The development of chylomicronemia leads to hypertriglyceridemia and acute pancreatitis. No treatment is approved in the U.S. Pradigastat sodium (LCQ908) is an oral medication intended to treat LPLD by inhibiting diglyceride acyltransferase-1 (DGAT-1), a late step in the triglyceride synthesis pathway hypothesized to underlie the disorder. In clinical trials, patients are administered 20 or 40 mg LCQ908, daily, for up 52 weeks; preliminary reports suggest that the drug may be positioned as an intervention taken continuously over a lifetime. Novartis International AG, Basel, Switzerland Phase III trial completed; extension trial ongoing	Alipogene tiparvovec (Glybera®; in development) Standard of care, including low-fat diet	Improved plasma triglyceride levels Improved chylomicron (lipoprotein particle) levels Improved symptoms (pancreatitis, neuropathy) Improved quality of life
Prosthetic arm with body-machine interface (DEKA Arm System) to restore natural arm functions after amputation	Patients with trauma-induced amputations of the upper limbs	The DEKA Arm System, an advanced prosthetic technology, comprises 2 major components, a prosthetic arm and a body-machine interface. The prosthetic arm is intended to produce near-normal movement, dexterity, and function; provide effortless and intuitive function via simple thoughts; and restore tactile sensation. Electromyogram electrodes implanted in the muscles are designed to improve the number of control sites available to manipulate the arms. Myoelectric and manual inputs control up to 10 powered movements. DEKA Integrated Solutions, Manchester, NH, in collaboration with Next Step Bionics & Prosthetics, Inc., Manchester, NH; Biodesigns, Inc., Westlake Village, CA; U.S. Defense Advanced Research Projects Agency, Arlington, VA; U.S. Department of Defense, Washington, DC; and U.S. Department of Veterans Affairs, Washington, DC FDA approved May 2014 under innovative device pathway, which is intended to move innovative devices to market within 4 years of start of trials; unphased trial ongoing; developers in search of manufacturing partner	Conventional prosthetic arms	Significant restoration of limb function compared with function of current prosthetic devices Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Purified plant-derived cannabidiol (Epidiolex) for treatment of Lennox-Gastaut and Dravet syndromes	Patients in whom Lennox-Gastaut syndrome (LGS) or Dravet syndrome has been diagnosed	LGS and Dravet syndrome are severe forms of epilepsy; seizures manifest early in life, often before age 5 years. Patients may experience multiple seizure types, including tonic, atonic, myoclonic, and atypical absence. Patients with Dravet syndrome, also known as severe myoclonic epilepsy of infancy (SMEI), experience frequent fever-related (febrile) seizures in the 1st year of life, followed by myoclonic seizures later in childhood. Both epilepsy forms result in developmental delays, socio-emotional difficulties, and cognitive impairments that may need permanent caregiver interventions. Investigators have not found cures for LGS or Dravet syndrome, although anticonvulsant drugs and ketogenic diets may provide temporary relief. Patients who are treated with anticonvulsants may develop tolerances to medications, limiting treatment options. Up to 70% of LGS cases are caused by brain malformations, perinatal asphyxia, central nervous system infection, or inherited degenerative conditions; genetic defects cause a similar percentage of Dravet syndrome cases. An unmet need exists for effective, long-term treatments. Epidiolex®, a purified plant-derived cannabidiol drug, is under study as an anticonvulsant for patients with LGS or Dravet syndrome. As of Apr 2014, Epidiolex clinical trial administration dosages had not been reported. GW Pharmaceuticals, plc, Wiltshire, UK Multiple phase III trials ongoing; in 2013 and 2014, FDA granted orphan drug status for treating LGS and Dravet syndrome; Jun 2014, FDA granted fast-track status for treating Dravet syndrome	Anticonvulsants Ketogenic diet	Fewer seizures Reduced cognitive and developmental delays Reduced reliance on caregiver interventions Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Quantitative susceptibility-based MRI for early diagnosis and progression tracking of multiple sclerosis	Patients in whom multiple sclerosis (MS) has been diagnosed Patients in whom early MS is suspected	Standard MRI techniques, including R2* mapping, are often used to identify and localize white matter lesions indicative of MS. These techniques, however, depend on transient visualization of lesions and do not provide information that correlates well to patients' clinical symptoms or predicts disease progression. This limitation prevents clinicians from rapidly addressing asymptomatic advances in disease state and from initiating early treatment. Quantitative susceptibility-based (QS) MRI is a technique that purportedly more accurately identifies areas of damaged white and gray matter, providing better MS progression tracking and advancing clinical early diagnostic capabilities. Additionally, QS MRI can be paired with standard MR imaging for supplemental patient analyses. In reported studies, QS MRI was conducted using a standard Siemens 3 tesla MRI system and is potentially reproducible in any clinical environment with similar equipment. University of Western Ontario, London, Canada Pilot study completed	Standard MRI white matter visualization	Potential advanced MS diagnosis Increased disease-progression monitoring accuracy
Real-time MRI-guided laser interstitial thermal therapy for treatment of medically refractory epilepsy	Patients in whom medically refractory epilepsy has been diagnosed Patients with epilepsy who have lesions identified by MRI	More than 2 million people in the U.S. have epilepsy, with nearly 1 million cases resistant to medical therapy. Pharmacological therapies have helped treat epilepsy, but it commonly recurs. Surgical procedures such as craniotomy may be performed, but they may leave the brain susceptible to unintended injury and resultant neurological complications. Laser ablation therapy would provide a minimally invasive, potentially curative therapy for patients who have epilepsy. Laser ablation surgery involves using MRI-guided laser technology to ablate lesions in specific and nearly inaccessible regions of the brain. The laser probe is inserted through a hole (diameter of a pen) created in the skull to map the brain and then ablate the confirmed affected area. To protect surrounding neurological tissue, an automatic system shuts the laser down when approaching such areas. In published reports, MRI-guided laser ablation surgery is associated with significant reductions in seizure frequency and shorter patient recovery times. Texas Children's Hospital, Houston Washington University School of Medicine, St. Louis, MO Mayo Clinic, Rochester, MN Phase I trial ongoing	Pharmacotherapy (e.g., lamotrigine, levetiracetam, tiagabine, tricyclics, valproate) Surgical procedures (e.g., craniotomy, Gamma Knife® radiosurgery)	Reduced or eliminated seizures Shortened comparative inpatient postoperative recovery periods

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
ReCell Spray-On Skin for treatment of burn wounds	Patients with severe skin burns	About 2.4 million burn injuries are reported each year in the U.S., with 75,000 patients being hospitalized for their burns. About 1 million will sustain substantial or permanent disabilities. Standard therapies have variable degrees of efficacy, warranting development of novel treatments. The ReCell® Spray-On Skin™ is a rapid, autologous cell-harvesting, processing, and delivery technology that uses epithelial cells from the patient in a regenerative process. Clinicians spray a suspension of these cultured cells (Regenerative Epithelial Suspension™) directly on the patient's wound, which purportedly accelerates healing, minimizes scarring, eliminates tissue rejection, and rehabilitates skin pigmentation. ReCell may be used with mesh grafts. Avita Medical, Ltd., Cambridge, UK Phase III trial ongoing	Cultured epithelial autograft Donor stem cell transplantation and skin printing Wound débridement	Decreased postsurgical blister and skin damage Improved skin regeneration Reduced area of donor site Shorter hospital stays Improved quality of life
Recombinant N-acetyl-alpha-D-glucosaminidase (SBC-103) for treatment of Sanfilippo syndrome type B	Patients in whom Sanfilippo syndrome type B has been diagnosed	Sanfilippo syndrome type B is a rare autosomal recessive lysosomal storage disorder, with a worldwide prevalence of less than 1 in 1 million. This disorder is caused by a mutation in the gene that codes *N*-acetyl-alpha-D-glucosaminidase (NAGLU), an enzyme that degrades the glycosaminoglycan heparan sulfate. As a result of the mutation, heparan sulfate accumulates; although physical symptoms are relatively mild, patients exhibit severe cognitive and behavioral symptoms that can prove difficult to manage. No medications are approved to treat the syndrome; an unmet need exists for effective interventions that address its underlying cause. SBC-103, a recombinant form of human NAGLU, is an enzyme replacement therapy intended to treat underlying NAGLU deficiencies. Based on preclinical models, SBC-103 can bypass the blood-brain barrier, and, in animal models, has been shown to reduce heparan sulfate storage in the brain and liver. In clinical trials, SBC-103 is intravenously infused at dosages of 0.3, 1.0, or 3.0 mg/kg, and administered every other week. Alexion Pharmaceuticals, Inc., Cheshire, CT (manufacturer) Synageva BioPharma Corp., Lexington, MA (original developer and clinical trial sponsor) Phase I/II trial ongoing; Apr 2013, FDA granted orphan drug status	Bone marrow replacement (restricted to earliest diagnosed cases) Gene therapy (in development) Genistein (in development) Palliative care	Reduced heparan sulfate accumulation Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Repurposed 3-drug combination therapy (PXT-3003) for treatment of Charcot-Marie-Tooth disease type 1A	Patients in whom Charcot-Marie-Tooth disease type 1A (CMT 1A) has been diagnosed	Charcot-Marie-Tooth disease is a group of rare, inherited peripheral nervous system disorders marked by systemic, progressive loss of muscle tissue and tactile perception. These disorders affect peripheral motor and sensory neurons, and common symptoms include muscle weakness in foot and lower leg muscles, leading to foot drop, tripping, and falling; foot deformities; fine motor skill problems; general or focal pain; and respiratory muscle weakness. CMT 1A is an autosomal dominant form of the disease, caused by duplication of a part of chromosome 17 that normally encodes peripheral myelin protein-22; it is the most common genetic subtype of Charcot-Marie-Tooth type 1 disorders. Like other forms of Charcot-Marie-Tooth disease, CMT 1A presently has no cure, and standard care focuses on maintaining patients' functional independence through therapies including orthotics, physical therapy, and orthopedic surgery. An unmet need exists for effective, nonpalliative therapies for CMT 1A. PXT-3003 is an investigational CMT 1A medication, identified via network pharmacology and formulated from a proprietary combination of 3 FDA-approved pharmaceuticals: (RS)-baclofen, naltrexone, and D-sorbitol. PXT-3003's developers hypothesize that this combination can safely improve functional mobility symptoms associated with CMT 1A. In clinical trials, PXT-3003 is administered orally as a liquid syrup, at varied dose concentrations, twice daily. Pharnext SAS, Paris, France Phase II trial completed; international phase III trial planned for 2015; Mar 2014, FDA granted orphan drug status	Orthopedic surgery Orthotic devices Physical therapy	Improved functional mobility Reduced pain Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Reveglucosidase alfa for treatment of Pompe disease	Patients in whom late-onset Pompe disease has been diagnosed	Late-onset Pompe disease results from a partial deficiency in alpha-glucosidase activity, which causes excessive amounts of lysosomal glycogen to accumulate everywhere in the body. It can cause muscle weakness and respiratory failure. Available enzyme replacement therapy (alglucosidase alfa) may have poor uptake in skeletal muscle, potentially due to low skeletal muscle expression of the key transporter required for cellular entry of the enzyme. Reveglucosidase alfa is an IGF-2 peptide conjugated alpha-glucosidase, an alternative enzyme replacement therapy. Reveglucosidase alfa purportedly circumvents low skeletal muscle uptake by adding the IGF-2 peptide, which directs the drug to lysosomes to degrade glycogen. Reveglucosidase alfa is administered at a dose of 20 mg/kg, every 2 weeks, by intravenous infusion. BioMarin Pharmaceuticals Inc., Novato, CA Phase III trial (INSPIRE) ongoing	Alpha-glucosidase enzyme replacement therapy (Lumizyme®)	Improved muscle strength, functional status, pulmonary function, and/or ventilation Improved quality of life
Revusiran for treatment of transthyretin-mediated amyloidosis	Patients in whom transthyretin-mediated amyloidosis and familial amyloid cardiomyopathy (FAC) has been diagnosed	FAC is characterized by a buildup of abnormal proteins in the heart and other tissues. It is the primary clinical manifestation of transthyretin-mediated amyloidosis and is a progressive disease caused by an inherited mutation in the transthyretin (*TTR*) gene. FAC is often fatal. Patients may recover after a heart transplant, but that option is not available for many patients. An effective pharmacologic treatment could reduce or postpone the need for transplantation. Revusiran (ALN-TTRsc) is a *N*-acetylgalactosamine-siRNA conjugate that is targeted to the liver and knocks down TTR. It purportedly prevents pathogenic TTR deposits in peripheral tissues, including dorsal root ganglia, sciatic nerve, stomach, and intestines, by silencing the *TTR* gene and reducing TTR serum levels. In clinical trials, revusiran is administered by subcutaneous injection, 500 mg, daily for 5 days and then weekly for 18 months. Alnylam Pharmaceuticals, Inc., Cambridge, MA Phase III trial ongoing; May 2015, FDA granted orphan drug status	Diuretics Heart transplantation	Improved function of cardiac and nervous tissues Improved symptoms of amyloidosis (variable) Increased survival Reduced need for heart transplant Reduced TTR deposits Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Rhopressa for treatment of glaucoma	Patients in whom glaucoma or ocular hypertension has been diagnosed	No cure exists for glaucoma, and if untreated or refractory to treatment, it leads to blindness. Available pharmaceuticals lower intraocular pressure (IOP) by redirecting aqueous outflow away from the diseased trabecular meshwork or by inhibiting fluid production. No pharmaceuticals target the underlying cause of IOP, which is an insufficiently permeable trabecular meshwork. Rhopressa™ is a rho kinase and norepinephrine transporter (ROCK/NET) inhibitor that purportedly increases outflow through the trabecular meshwork by promoting actomyosin contraction and relaxing cells in the trabecular meshwork. It has 3 effects: increased outflow through the trabecular meshwork, decreased fluid production, and reduced episcleral venous pressure. The drug is administered as a 0.02% ophthalmic solution, topically, once daily. Aerie Pharmaceuticals, Inc., Bedminster, NJ Phase III trials ongoing	Microstents Prostaglandin analogues Trabectome	Decreased IOP Reduced risk of progression Improved quality of life
Rigerimod (Lupuzor) for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	Investigators have not found a cure for SLE, and current treatments provide only partial relief of symptoms. Rigerimod (Lupuzor™), an investigational small peptide derived from the spliceosomal small nuclear ribonucleoprotein U1-70K, purportedly treats SLE via a unique mechanism of action, interfering with the chaperone-mediated autophagy pathway. Rigerimod is an injectable powder administered subcutaneously. In clinical trials, adult patients were administered rigerimod at dosages of 0.2 mg, once every 4 weeks, for 48 or 72 weeks. ImmuPharma, plc, London, UK Phase III trial ongoing; Nov 2011, FDA granted fast-track status	Belimumab Rituximab Rontalizumab	Improved biologic markers of SLE disease activity Reduced cutaneous manifestations of SLE Reduced SLE disease flare incidences Improved SLE responder index scores Reduced SLE-associated arthritic symptoms Reduced steroid administration frequency or dose Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Rintatolimod (Ampligen) for treatment of chronic fatigue syndrome	Patients in whom chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) has been diagnosed	CFS/ME is a debilitating condition of unknown cause characterized by pain and extreme fatigue. It has no cure, and no single therapy provides symptom relief in all patients. New therapies are needed. Rintatolimod (Ampligen®) is a synthetic double-stranded RNA that mimics viral proteins. It stimulates the innate immune response, which may be disrupted in CFS, through Toll-like receptor 3. It is administered by intravenous infusion, 200–400 mg, twice weekly. Hemispherx Biopharma, Inc., Philadelphia, PA Phase III trial ongoing; FDA granted orphan drug status; manufacturer submitted new drug application and FDA rejected it in 2013	Behavior and lifestyle changes Pharmacotherapy (e.g., antidepressants, sleeping aids) Psychotherapy	Improved cognition Improved global performance Increased exercise tolerance Increased independence and ability to perform activities of daily living Reduced use of other medications for symptom management Improved quality of life
Rivipansel for treatment of vaso-occlusive crisis in sickle cell disease	Patients with sickle cell disease (SCD) who are experiencing a vaso-occlusive crisis (VOC)	SCD is an autosomal recessive disorder that affects about 100,000 people in the U.S. and Europe and can present as sickle cell anemia or sickle beta-0 thalassemia. Increased disease prevalence is seen in people of African and Mediterranean descent; about 1 in 500 African-American children born have sickle cell anemia. In SCD, sickled red blood cells are more susceptible to oxidative damage and inappropriate adhesion, which can lead to VOC. VOC causes severe pain by obstructing vasculature and requires hospitalization. Patients may progress to thromboembolic events, stroke, organ failure, or early death. VOC is typically managed with hydration and pain medication but cannot be halted. The only FDA-approved treatment for SCD, hydroxyurea, can reduce VOC incidence but is not effective in about 1/3 of adult patients. Rivipansel (PF-06460031 or GMI-1070) is a synthetic glycomimetic, pan-selectin inhibitor that targets inflammatory and adhesion processes that may have a role in VOC. Rivipansel is intended to reduce the duration of VOC and hospital stays. It is infused intravenously every 12 hours for up to 15 doses. For patients older than 12 years and heavier than 40 kg, the 1st dose is 1,680 mg and subsequent doses are 840 mg. For patients 6–12 years or any patient weighing less than 40 kg, the 1st dose is 40 mg/kg up to 1,680 mg and subsequent doses are 20 mg/kg up to 840 mg. GlycoMimetics, Inc., Gaithersburg, MD, in partnership with Pfizer, Inc., New York, NY Phase III trials ongoing; FDA granted orphan drug and fast-track statuses	Analgesia (e.g., morphine, nonsteroidal anti-inflammatory drugs [NSAIDs], paracetamol) Hydration	Decreased amount and length of intravenous opioid use Decreased length of hospital stay Fewer rehospitalizations within 3 days of discharge Reduced health disparities (e.g., African Americans) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Roxadustat for treatment of anemia from chronic kidney disease	Patients with anemia due to chronic kidney disease (CKD)	Anemia, defined as low levels of erythrocytes or hemoglobin in the blood, impacts quality of life for more than 10% of patients with CKD. It can cause fatigue, depression, appetite loss, headaches, rapid heartbeat, and shortness of breath. Anemia is caused by low production of erythropoietin (EPO), which may result from damage to the kidney cells that produce EPO. Available treatments are given intravenously and can increase blood pressure and the risk of cardiovascular events. Roxadustat is a 1st-in-class hypoxia-inducible factor prolyl hydroxylase inhibitor. It purportedly increases hemoglobin using the body's own iron stores by stimulating EPO. Roxadustat is administered orally, 3 times a week, to achieve and maintain a hemoglobin level of 11 g/dL. AstraZeneca, London, UK, in collaboration with FibroGen, Inc., San Francisco, CA Phase III trials ongoing	EPO replacement therapy with erythropoiesis-stimulating agents Iron supplementation	Increased blood hemoglobin levels Reduced incidence of hospitalization Reduced risk of red blood cell transfusion Resolution of anemia Improved quality of life
Sebelipase alfa (Kanuma) for treatment of lysosomal acid lipase deficiency	Patients in whom lysosomal acid lipase (LAL) deficiency has been diagnosed	LAL deficiency is a rare genetic syndrome for which no treatment is FDA approved. The LAL enzyme breaks down cholesteryl esters and triglycerides; when it is lacking, these materials build up in the liver, the gut, other organs, and blood vessel walls. The deficiency occurs less often in infants than in children, adolescents, or adults, but the early onset form, also known as Wolman disease, is rapidly fatal, usually within the 1st year. Late-onset LAL is also known as cholesteryl ester storage disease and can lead to liver fibrosis, cirrhosis, liver failure, cardiovascular events, and premature death. Sebelipase alfa (Kanuma™) is a recombinant protein enzyme replacement therapy. If approved, it would be the 1st treatment cleared for use in LAL deficiency. In ongoing trials, it has been given in 4 once-weekly infusions (0.35, 1.0, or 3.0 mg/kg), followed by an infusion every other week (1 or 3 mg/kg) as part of a long-term, open-label extension study. Alexion Pharmaceuticals, Cheshire, CT Phase III trials ongoing in infants, children, and adults; FDA granted orphan drug status; FDA granted fast-track and breakthrough therapy statuses for infants; FDA granted priority review with a decision date set for Dec 2015	Bone marrow transplant Palliative treatments	Normalized alanine aminotransferase, cholesteryl, and triglyceride levels Reduced mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Self-complementary adeno-associated virus (ChariSMA) for treatment of spinal muscular atrophy	Patients in whom spinal muscular atrophy (SMA) has been diagnosed	SMA is an inherited neuromuscular disorder in which muscles atrophy and weaken, often resulting in death of infants born with the most severe form of the disorder. It is caused by mutations to *SMN1*, a gene that normally encodes the survival motor neuron 1 (SMN) protein; abnormally low levels of SMN protein are a hallmark of the disorder. SMA occurs in an estimated 1 in 10,000 live births worldwide. Affected infants typically appear normal at birth, and symptoms develop several months after birth. Available SMA treatments address only disease symptoms. ChariSMA is an investigational gene therapy for SMA, designed to treat the disorder by introducing functional copies of the *SMN1* gene. Researchers hypothesize that the presence of additional, nonmutated *SMN1* genes will supplement patients' current SMN production, addressing the underlying cause of SMA and potentially alleviating some of the most severe symptoms. In clinical trials, pediatric patients receive a single, intravenous dose of ChariSMA at 1 of 3 dosage levels. AveXis, Inc., Dallas, TX Phase I trials ongoing; Sep 2014, FDA granted orphan drug status; Sep 2013, FDA granted fast-track status	Supportive therapy	Increased systemic SMN1 protein levels Improved symptoms Reduced mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Smad-pathway activating peptide (THR-184) for treatment of acute kidney injury after cardiac surgery	Patients at risk of acute kidney injury (AKI) after cardiac surgery	AKI is characterized by a rapid, temporary loss of kidney function resulting in a failure to maintain fluid, electrolyte, and acid-base homeostasis. About 1 million patients receive an AKI diagnosis each year in the U.S., all of whom experience some permanent loss of kidney function. Causal factors for AKI include cardiac and/or vascular surgery, inflammatory disease, trauma, or the administration of contrast dye for imaging. AKI is common in hospitalized patients and also has a poor prognosis, with mortality ranging from 10% to 80%. Treatment options for AKI are limited, with no pharmacological therapy approved for its treatment. THR-184 is a small peptide that selectively activates the bone morphogenetic protein (BMP) type II receptor and Smad (small mothers against decapentaplegic) proteins (a family of signal transducers), responsible for regulating growth, differentiation, chemotaxis, and apoptosis of various cell types such as epithelial, mesenchymal, hematopoietic, and neuronal cells. By activating these receptors, this therapy may serve as a preventive and therapeutic option for patients in whom AKI has been diagnosed. THR-184 does not have bone morphogenetic activity. It is given by intravenous infusion at a high dose before surgery and a lower dose after surgery. Exact dosage is still under study. Thrasos, Inc., Montreal, Quebec, Canada Phase II trial ongoing; FDA granted fast-track status Feb 2014	Dialysis	Improved renal function Reduced incidence of AKI Reduced use of dialysis Reduced mortality Improved quality of life
Sodium zirconium cyclosilicate for treatment of hyperkalemia	Patients with chronic kidney disease (CKD) and hyperkalemia	Hyperkalemia is an excess of potassium in the blood. It may cause abnormal heart rhythms; in severe cases, it can lead to cardiac arrest and death. In patients with CKD, hyperkalemia is a common consequence of renal dysfunction and medication side effects. Renin-angiotensin-aldosterone-system inhibitors used by patients with CKD to protect kidney and heart function may cause or worsen hyperkalemia. Patients are commonly treated with an ion-exchange resin, sodium polystyrene sulfonate; however, this drug may cause colonic necrosis and other serious gastrointestinal injuries. Sodium zirconium cyclosilicate (ZS-9) is a novel selective potassium binder that is intended to lower serum potassium, thereby treating hyperkalemia in patients with CKD. ZS-9 is administered as an oral suspension or in tablets, at 5 or 10 g, once daily. ZS Pharma, Inc., Coppell, TX Phase III trials ongoing; manufacturer submitted a new drug application May 2015; FDA set decision date for May 2016	Beta-2 adrenergic receptor stimulators (e.g., albuterol, epinephrine) Dialysis Diuretics Intravenous calcium Intravenous glucose and insulin Ion-exchange resins (e.g., sodium polystyrene sulfonate) Low-potassium diet	Decreased incidence of hyperkalemia Improved long-term cardiac outcomes Reduced serum potassium levels

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Subretinal implant (Alpha IMS) to restore visual function in retinitis pigmentosa	Patients in whom retinitis pigmentosa (RP) has been diagnosed	No medications or devices can restore lost vision or halt progression of vision loss that occurs with the inherited disorder RP. 1 device (Argus II) recently became available in the U.S. to assist in some aspects of visual perception for RP. The Alpha IMS system, another system in development, consists of a 3-by-3 mm wireless microchip implant containing an array of electrodes. The developer indicates that the system uses light captured by the eye to stimulate the optic nerve, which delivers visual information to the brain. The developer notes that unlike the recently FDA-approved retinal prosthetic device implant, Argus II, the Alpha IMS system does not rely on an external camera. The purported benefit of this system is that it enables wearers to look around by moving their eyes rather than their heads; it purportedly has a higher resolution grid and is implanted under the retina to enable the middle layer of the retina to process the input before it is sent to the visual cortex. Retina Implant AG, Reutlingen, Germany Unphased trials ongoing; CE marked Jul 2013	Argus II retinal prosthesis system	Improved visual acuity Improved quality of life and independence

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tafamidis (Vyndaqel) for treatment of hereditary transthyretin-related amyloidoses	Patients in whom a transthyretin familial amyloidosis has been diagnosed Patients in whom familial amyloid cardiomyopathy (FAC) has been diagnosed	Transthyretin (TTR) is a transport protein for thyroxine and retinol. Mutation of the *TTR* gene can lead to unstable TTR and generate amyloid fibrils that are deposited in various organs, causing organ failure. TTR-related amyloidosis is a genetic neurodegenerative disease that can affect the heart and kidneys. It is a systemic disorder resulting in polyneuropathy, autonomic neuropathy, and cardiomyopathy. The disease is usually fatal within a decade in the absence of a liver transplant; patients with FAC require combined heart and liver transplants. Tafamidis (Vyndaqel®) purportedly binds to the TTR protein to stabilize functional tetrameric molecules. This binding is hypothesized to slow formation of misfolded amyloid fibrils and their deposit in organs. In clinical trials, patients with transthyretin familial amyloidoses and familial polyneuropathy are administered 20 mg oral tafamidis tablets, daily, for up to 18 months. In clinical trials investigating tafamidis for treating familial amyloid cardiomyopathy, patients are administered 20 or 80 mg oral tafamidis tablets, daily, for up to 30 months. Pfizer, Inc., New York, NY Phase III trials completed for treating familial amyloid polyneuropathy; as of Dec 2014, phase IV trial ongoing by invitation only; global phase III trial ongoing for treating familial amyloid cardiomyopathy; May 2006, FDA granted orphan drug status for treating familial amyloid polyneuropathy; Feb 2012, FDA granted orphan drug status for treating FAC. Tafamidis is approved in Europe and Japan; FDA did not approve Pfizer's new drug application for treating familial amyloid polyneuropathy when submitted in 2012	Organ transplant Supportive therapy	Decreased organ failure Increased TTR stabilization Reduced transthyretin amyloidoses patient transplant rate Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tasimelteon (Hetlioz) for treatment of non-24-hour sleep-wake disorder	Patients who are blind and have non-24-hour sleep-wake disorder	About 50% of patients with total blindness are affected by non-24-hour sleep-wake disorder, because they lack the light sensitivity necessary to synchronize the internal body clock with the day-night cycle. The disorder, also called hypernychthemeral syndrome, can cause disrupted nighttime sleep and excessive daytime sleep to a potentially debilitating degree. It affects between 65,000 and 95,000 people. Over-the-counter melatonin dietary supplement is sometimes used, though published data on efficacy are very limited. Tasimelteon (Hetlioz) is a melatonin receptor agonist thought to reset the internal body clock in a way similar to normal light-dependent resetting. The drug is taken before bedtime, at the same time every night, 20 mg, orally. Vanda Pharmaceuticals, Inc., Washington, DC FDA approved Jan 2014 with a requirement for postmarket followup studies; phase III trial ongoing	Melatonin Ramelteon	Higher quality uninterrupted nighttime sleep Less daytime sleep Improved quality of life
T-cell receptor peptide vaccine (NeuroVax) for treatment of secondary progressive multiple sclerosis	Patients in whom secondary progressive multiple sclerosis (MS) has been diagnosed	Available treatments for MS may slow disease progression, but are not effective in all patients, and the disease has no cure. Research has suggested that during the inflammatory phase of MS, an increase in pathogenic T cells directly contributes to disease progression. Also, researchers hypothesize that the increase in pathogenic T cells is caused by reduced suppression, normally mediated by a combination of T regulatory and T suppressor cells (including interleukin-10–secreting T regulatory 1 cells, CD4+ CD25+ regulatory T cells [Treg], and CD8+ T suppressor cells). NeuroVax™, a trivalent T-cell receptor (TCR) peptide vaccine, purportedly treats MS by inducing high frequencies of TCR-reactive T cells, subsequently inducing Foxp3+ Treg cells that can target pathogenic T cells. In clinical trials, patients with MS receive monthly injections of NeuroVax into the deltoid muscle, alternating arms each month; each dose of NeuroVax is a prepared in a mixture of the 3 peptides in aqueous solution in a 1:1 ratio with incomplete Freund's adjuvant, containing 100 mcg/mL of each peptide, with a nominal volume of 1.1±0.2 mL. Immune Response BioPharma, Inc., Atlantic City, NJ, in collaboration with Oregon Health and Science University, Portland Phase II/III trials ongoing; in 2014, FDA granted fast-track status for treating MS and orphan drug status for treating pediatric MS	Dimethyl fumarate (Tecfidera®) Fingolimod (Gilenya®) Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Decreased demyelination Decreased relapse rate Delayed disease progression Fewer MS-related lesions Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tirasemtiv for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	ALS is a progressive disorder marked by neurodegeneration of nerve cells in the brain and spinal cord. A 2014 report calculated that ALS prevalence is about 3.9 cases per 100,000 Americans. The average life expectancy of a patient with ALS is 3–5 years after diagnosis, and only 10% of patients survive for more than 10 years. Only a single agent (riluzole) is FDA approved for treating ALS, and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function; novel therapies for ALS are urgently needed. Tirasemtiv (CK-2017357) is purportedly a fast skeletal muscle troponin activator. It selectively activates the fast skeletal muscle troponin complex by increasing its sensitivity to calcium, leading to an increase in skeletal muscle force. In clinical trials, tirasemtiv is administered orally in 125 mg tablet form, in dosages of 125, 250, or 375 mg, daily for 14 days, alone or in combination with 50 mg riluzole. Cytokinetics, Inc., South San Francisco, CA Phase III trial ongoing; Mar 2010, FDA granted orphan drug status	Riluzole (Rilutek®)	Improved symptoms

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tocilizumab (Actemra) for treatment of giant cell arteritis	Patients in whom giant cell arteritis (GCA) is suspected or has been diagnosed	GCA, a generalized granulomatous arterial inflammation, is the most common primary vasculitis in adults. Based on U.S. census data from 2000, the prevalence is approximately 160,000. GCA most commonly affects head arteries, particularly in the temples. Patients with GCA often experience headaches, jaw pain, or vision problems from inflammation; these patients are frequently have comorbid polymyalgia rheumatica, a related inflammatory disorder. In severe cases, GCA can cause blood clots or arterial swelling leading to blindness, aortic aneurysm, or stroke. It is treated with high-dose corticosteroids to reduce the likelihood of severe symptoms; however, high doses of corticosteroids have side effects, including risk of osteoporosis, high blood pressure, glaucoma, and cataracts. Patients with GCA who have been placed on tapered doses of corticosteroids also often experience relapses. An unmet need exists for effective interventions. Tocilizumab (Actemra) is a humanized monoclonal antibody that targets interleukin-6 (IL-6) receptor. Elevated levels of IL-6 are hypothesized to indicate GCA. Tocilizumab purportedly reduces the dosage of corticosteroids needed to treat GCA and may reduce relapse rates in patients who are receiving tapered corticosteroid doses. In clinical trials, tocilizumab is given as an add-on treatment at monthly dosages of either 8 mg/kg or 162 mg for 12 months, along with corticosteroids; tocilizumab dosages are either consistent throughout the study or tapered. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials ongoing; Jun 2015, FDA granted breakthrough therapy status for treating systemic sclerosis; tocilizumab is also under study for treating polymyalgia rheumatica	Corticosteroids	Reduced corticosteroid doses Reduced corticosteroid-related side effects Reduced GCA relapse rates Improved quality of life
Topical Nav1.7 sodium channel blocker (TV-45070) for treatment of postherpetic neuralgia	Patients in whom postherpetic neuralgia (PHN) has been diagnosed	PHN is a painful condition that develops after shingles in a large portion of elderly patients. TV-45070, previously called XEN402, is a selective sodium channel modulator that blocks the voltage-gated sodium channel Nav1.7, which has been implicated in multiple pain conditions. TV-45070 is applied topically, twice daily. In clinical trials, formulations of 4% and 8% active ingredient are being tested. Teva Pharmaceutical Industries, Ltd., Petah Tikva, Israel Phase IIb trial ongoing; Nov 2012, FDA granted orphan drug status	Anticonvulsants (e.g., gabapentin, pregabalin) Lidocaine skin patches Opioid painkillers (e.g., morphine, oxycodone, tramadol) Tricyclic antidepressants	Reduced or eliminated pain Shorter recovery time Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Transthyretin antisense inhibitor (ISIS-TTRRx) for treatment of transthyretin familial amyloid polyneuropathy	Patients in whom transthyretin familial amyloid polyneuropathy (TTR-FAP) has been diagnosed	TTR-FAP is a genetic neurodegenerative disease that can also affect the heart and kidneys. The disease is usually fatal by age 10 years if no liver transplant is available. Transthyretin (TTR) is a transport protein for thyroxine and retinol. Amyloidogenic: mutation of the *TTR* gene can lead to the development of unstable TTR, which forms amyloid fibrils that are deposited in various organs. ISIS-TTRRx, a TTR antisense inhibitor, is under study to treat TTR-FAP by inactivating mutated *TTR*. In clinical trials, patients with TTR-FAP are administered 300 mg of ISIS-TTRRx subcutaneously, once daily, on 3 alternating days during the 1st week of treatment, followed by once-weekly treatments for 64 weeks. ISIS Pharmaceuticals, Carlsbad, CA, in collaboration with GlaxoSmithKline, Middlesex, UK 2 phase III trials ongoing; in 2012, FDA granted fast-track and orphan drug statuses	Supportive therapy	Improved neuropathy impairment score Improved quality of life TTR stabilization
Ultra-high dose biotin (MD1003) for treatment of progressive multiple sclerosis	Patients in whom primary or secondary progressive multiple sclerosis (MS) has been diagnosed	Treatments for MS may slow disease progression, but they are not effective in all patients, and the disease has no cure. Biotin is a water-soluble vitamin normally involved in energy metabolism and fatty acid synthesis. Experts estimate that, as a supplement, biotin intake of about 30 mcg daily is adequate. Biotin also activates acetylCoA carboxylase, an enzyme purported to play a key role in myelin synthesis. Researchers hypothesize that this latter activity underlies biotin's potential efficacy for treating MS. In completed pilot trials, ultra-high doses of biotin (100–600 mg/day) were associated with sustained disability improvement in patients with primary and secondary progressive MS. In a pivotal clinical trial, patients received 300 mg oral biotin (MD1003), daily, for up to 48 weeks. MedDay S.A.S., Paris, France Pivotal phase IIb/III trial completed and phase III trial ongoing; ultra-high dose biotin is also under investigation for treating adult forms of X-linked adrenoleukodystrophy	Dimethyl fumarate (Tecfidera®) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Reduced functional limitation Reduced optic neuritis–related vision loss Reduced disability Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Valbenazine for treatment of tardive dyskinesia	Patients in whom tardive dyskinesia has been diagnosed	Tardive dyskinesia, involuntary movement of face or trunk muscles, can develop in patients taking long-term dopaminergic antagonist medications and is potentially debilitating. Lowered doses of dopamine antagonists or alternative antipsychotic drugs may reduce or stop the symptoms of tardive dyskinesia. However, for some patients, the movements are permanent and may worsen when medications are altered. No standard treatment exists. Valbenazine (NBI-98854) is a vesicular monoamine transporter type 2 inhibitor that regulates levels of dopamine released during nerve communication while reducing the likelihood of "off-target" side effects. This compound provides sustained plasma and brain concentrations of the active drug to minimize side effects associated with excessive dopamine depletion. Trials are testing 40 and 80 mg doses, taken orally, every morning. Neurocrine Biosciences, Inc., San Diego, CA Phase III trials ongoing; FDA granted fast-track and breakthrough therapy statuses	Anticholinergics (e.g., benztropine) Benzodiazepines (e.g., clonazepam, lorazepam) Botulinum toxin injection Cessation of dopamine antagonists Clozapine Deep brain stimulation Deutetrabenazine (investigational) Dopamine-depleting agents Stress reduction (e.g., psychotherapy) Supplements (e.g., ginkgo biloba, vitamin E)	Reduced abnormal involuntary movement Improved quality of life
Vasoactive compound (MC-1101) for treatment of dry age-related macular degeneration	Patients in whom early stage, dry, age-related macular degeneration (AMD) has been diagnosed	Dry AMD is an inherited autosomal dominant disease affected by nutrition and environmental factors (e.g., smoking). It may slowly progress to central vision loss over decades; however, no treatments are available to halt progression or restore lost vision. If neovascularization develops (i.e., wet AMD), vision loss occurs more rapidly, over months. Dry AMD is the most common cause of vision loss in the developed world. Vitamin and mineral supplements may prevent later progression in some people, but no treatments are available. MC-1101 is a 1% vasoactive compound that purportedly increases choroidal flow to the macula, reduces inflammation, and prevents rupture of Bruch's membrane. The unnamed active ingredient is used as an oral antihypertensive. MC-1101 is applied topically, twice daily. Studies reportedly show that the active compound reaches the back of the eye through this administration route. MacuCLEAR, Inc., Plano, TX Phase II/III trial ongoing; FDA granted fast-track status; drug is a 505(b)(2) compound, which means it was approved but is modified for this indication	Vitamin and mineral supplementation	Improved choroidal flow Reduced inflammation Slowed progression of visual loss Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vatiquinone for treatment of inherited mitochondrial diseases	Patients in whom Friedreich's ataxia or Leigh syndrome has been diagnosed	Inherited mitochondrial diseases are a group of rare neurometabolic disorders caused by dysfunctional mitochondria inherited from 1 or both parents; Friedreich's ataxia and Leigh syndrome are among the more severe types. Friedreich's ataxia is an autosomal recessive disorder caused by a defect in the frataxin gene, leading to symptoms including ataxia, diabetes, sensorimotor deficiencies, muscle weakness, and heart failure. Leigh syndrome has a primarily autosomal recessive inheritance pattern, but can also display mitochondrial, or maternal, inheritance in 20% to 25% of cases; it can be caused by any of more than 30 DNA mutations and is marked by progressive loss of sensorimotor function, along with respiratory dysfunction. These diseases are increasingly debilitating, severely limiting patients' ability to function independently; disease-related symptoms, particularly cardiac and respiratory symptoms, are often fatal. FDA-approved interventions for these diseases do not exist; consequently, there is an unmet need for effective treatments. Vatiquinone (EPI-743) is a parabenzoquinone drug purported to treat symptoms of inherited mitochondrial diseases by augmenting endogenous glutathione biosynthesis, an essential biological process for controlling oxidative stress, an identified biomarker of Friedreich's ataxia and related inherited mitochondrial diseases. In ongoing clinical trials, vatiquinone is administered orally, in dosages up to 400 mg daily. Edison Pharmaceuticals, Inc., Mountain View, CA Phase IIb (Friedreich's ataxia), phase II/III (Leigh syndrome), and phase II (general inherited mitochondrial diseases) trials ongoing; Oct 2010, FDA granted orphan drug status for treating inherited mitochondrial respiratory chain diseases; Feb 2014, FDA granted orphan status for treating Friedrich's ataxia; Jun 2014, FDA granted orphan status for treating Leigh syndrome	No approved or recommended pharmacotherapies are available Palliative care (e.g., physical therapy, speech therapy, wheelchair use) Treatment of secondary symptoms (e.g., cardiovascular surgery, to treat secondary heart failure and arrhythmia, insulin and oral pharmacotherapy, to treat secondary diabetes mellitus)	Delayed disease progression Improved visual and hearing acuity Improved quality of life Reduced reliance on wheelchairs Reduced risk of diabetes and heart failure

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vepoloxamer for treatment of sickle cell disease	Patients in whom sickle cell disease (SCD) has been diagnosed	SCD is an autosomal recessive disorder that affects about 100,000 people in the U.S. and Europe and can present as sickle cell anemia and sickle beta-0 thalassemia. Increased disease prevalence is seen in people of African and Mediterranean descent; about 1 in 500 African-American children have sickle cell anemia. In SCD, sickled red blood cells are more susceptible to oxidative damage and inappropriate adhesion, which can lead to vaso-occlusive crisis (VOC). VOC causes severe pain by obstructing vasculature and requires hospitalization. Patients may progress to thromboembolic events, stroke, organ failure, or early death. VOC is typically managed with hydration and pain medication but cannot be halted. The only FDA-approved treatment for SCD, hydroxyurea, can reduce VOC incidence but is not effective in about 1/3 of adult patients. Vepoloxamer (MST-188) is a surfactant-containing, hydrophilic poloxamer that limits adhesion of sickled cells to each other and vascular endothelium, actions responsible for VOC. Vepoloxamer may shorten duration of painful VOC and may not lead to adverse effects associated with available treatments for SCD. In clinical trials, vepoloxamer is administered intravenously by continuous infusion of 100 mg/kg/hour for 1 hour followed by 30 mg/kg for up to 48 hours. Mast Therapeutics, Inc., San Diego, CA Phase III trials ongoing; FDA granted orphan drug status	Allogeneic hematopoietic stem cell transplantation Analgesics Blood transfusion Hydroxyurea Statins Supplemental oxygen	Fewer hospitalizations and rehospitalizations Reduced health disparities in African Americans Reduced occurrence of acute chest syndrome Reduced severity and duration of VOCs Improved quality of life
Vonapanitase for prevention of arteriovenous access dysfunction	Patients with chronic kidney disease who have an arteriovenous fistula (AVF) or arteriovenous graft (AVG) for hemodialysis access	Vascular access grafts for chronic hemodialysis often have high failure rates and poor outcomes. After surgery, blood flow to an access might drastically reduce or stop due to tissue growth inside the blood vessel. Further surgical intervention or alternative prolonged catheter dialysis is associated with increased morbidity and mortality. The recombinant, human, pancreatic elastase drug called vonapanitase (formerly PRT-201) might increase longevity of AVFs or AVGs by preventing tissue growth in the blood vessels to which it is applied. The drug is applied topically during AVF or AVG surgery at a dosage of 10 or 30 mcg. Proteon Therapeutics, Inc., Waltham, MA Phase III trials ongoing; FDA granted orphan drug and fast-track statuses; also under study for symptomatic peripheral artery disease	Catheter dialysis Surgery to restore blood flow to access	Decreased access failure (e.g., thrombosis, loss of unassisted patent access) Decreased morbidity and mortality Unassisted maturation of access

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Wearable artificial kidney for managing end-stage renal disease	Patients in whom end-stage renal disease has been diagnosed	Conventional dialysis requires that most patients receive dialysis 3 times a week, for several hours each session, at home or in a clinic. In peritoneal dialysis, dialysate is infused into the abdomen through a permanent indwelling catheter to remove toxins. Peritoneal lining acts as a filter, as spent dialysate solution is drained from the peritoneal cavity. With wearable artificial kidneys (WAKs), dialysate is cleaned and reinfused through external pumps and filtration components that are attached to the front of a vest or waist belt worn by the patient. WAKs are used under medical supervision in clinical trials, but patients might be trained to use them independently in any setting, because WAKs are portable and weigh about 10 lb. WAKs can potentially work at all times like a regular kidney. AWAK Technologies, Inc., Burbank, CA, with Debiotech S.A., Lausanne, Switzerland, and Neokidney Development bv, Bussum, the Netherlands Blood Purification Technologies, Inc., Beverly Hills, CA Unphased trial ongoing (Blood Purification Technologies); AWAK and partners expect to start clinical trials in 2017; FDA selected the WAK as 1 of 3 technologies for its new innovation pathway in Apr 2012	Conventional home dialysis systems Kidney transplantation	Adequate filtration of toxins from kidneys Improved mobility Reduced infection rates Improved quality of life
Wearable battery-powered exoskeleton (Indego) to enable mobility in community or home setting for patients with paraplegia	Patients with spinal cord injury resulting in paraplegia	Conventional manual and powered wheelchairs are the primary assistive devices used to restore some degree of mobility in people who have had a spinal cord injury resulting in paraplegia. However, long-term wheelchair use is associated with thinning bones, pressure sores, and problems with urinary, cardiovascular, and digestive systems. These devices also do not help users walk or climb stairs. A wearable powered exoskeleton, such as the Indego, could provide greater mobility and freedom to individuals with paraplegia from spinal cord injury. The Indego system comprises a set of computer-controlled, motorized leg braces that restore the ability to walk with crutches to patients with paraplegia who are able to use their hands and shoulders and who have good bone density and cardiovascular health. Patients control movement by leaning forward to walk and leaning backward to slow down or stop. The Indego has a battery life of up to 4 hours and is intended for use at home or in a community setting. Parker Hannifin Corp., Cleveland, OH Pivotal trial ongoing; manufacturer expects FDA clearance in 2015	ReWalk Personal exoskeleton Weight-supported standing systems Wheelchairs (powered and manual)	Decreased complications from being wheelchair bound Improved mobility Improved independence Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Wearable battery-powered exoskeleton (ReWalk Personal) to enable mobility in community or home setting for patients with paraplegia	Patients with spinal cord injury resulting in paraplegia	Conventional manual and powered wheelchairs are the primary assistive devices used to restore some degree of mobility in people who have had a spinal cord injury resulting in paraplegia. However, long-term wheelchair use is associated with thinning bones, pressure sores, and problems with urinary, cardiovascular, and digestive systems. These devices also do not help users walk or climb stairs. A wearable powered exoskeleton in development, such as the ReWalk-Personal™, could provide greater mobility and freedom to individuals with paraplegia from spinal cord injury. The ReWalk-Personal system comprises a set of computer-controlled, motorized leg braces that restore the ability to walk with crutches to patients with paraplegia who are able to use their hands and shoulders and who have good bone density and cardiovascular health. Exoskeletons generally move at a rate of 1 mph and have a battery life of about 2–4 hours. The ReWalk-Personal is intended for use at home or in a community setting. Argo Medical Technologies, Ltd., Yokneam Ilit, Israel (manufacturer of ReWalk-Personal) distributed in the U.S. by Bionics Research, Inc., Mt. Laurel, NJ FDA cleared ReWalk-Personal under de novo pathway Jun 2014; FDA required postmarket studies; available in Europe since late 2012; ReWalk-Personal study for home and community use ongoing; commercialization of a competing device, Indego, planned for 2015	Weight-supported standing systems Wheelchairs	Decreased complications from being wheelchair bound Improved independence Improved mobility Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Wearable early warning system (Brain Sentinel) for detection of generalized tonic-clonic seizures	Patients in whom generalized tonic-clonic (GTC) seizures or partial onset seizures with secondary generalization has been diagnosed	GTC seizures are the most common seizure type and affect more than 750,000 Americans. Experts also consider GTC seizures to be the most severe type; when not quickly identified and addressed, GTC seizure events are associated with trauma, fractures, status epilepticus, and sudden unexplained death in epilepsy (SUDEP). Rapid detection and intervention are key to managing patients and preventing severe symptoms. The standard for GTC seizure detection is video electroencephalography (EEG), which is collected and then independently reviewed by a trained neurologist; however, this process is primarily limited to use within a hospital epilepsy monitoring unit. An unmet need exists for interventions providing accurate, rapid GTC seizure detection for patients outside of specialized hospital environments. The Brain Sentinel Seizure Detection System is a electromyography (EMG)-based device intended to quickly detect GTC seizures and provide remote alerts, notifying caregivers of GTC seizure events and recording related seizure activity. The device is worn on the patient's bicep and measures electrical activity from arm muscles. The Brain Sentinel reportedly can detect GTC seizures as quickly as 30 seconds after onset. It can be used in home, inpatient, or skilled nursing environments. In clinical trials, patients wear the Brain Sentinel for up to 1 month, with constant monitoring. Brain Sentinel, San Antonio, TX Multiple phase III trials ongoing	Video encephalography review by trained neurologists in specialized monitoring units	Faster GTC response times Increased outpatient GTC seizure detection Decreased mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Zorblisa for treatment of epidermolysis bullosa	Patients in whom epidermolysis bullosa (EB) has been diagnosed	EB is an inherited skin condition caused by a mutation in 1 of 18 genes involved in collagen formation. It is characterized by extensive, chronic blisters, lesions, and pruritus. Patients with the most severe forms often die within the 1st year of life from infection in an open wound; others die from squamous cell carcinoma before they are 30 years old. Patients may experience blisters in mucosal membranes (e.g., mouth, esophagus, anus), scars, contractures, and fused digits. No treatments are available; symptom management (i.e., bandaging, antibiotics) is provided as wounds arise. Allantoin is a naturally occurring nitrogenous compound that is used in toothpaste, shampoo, and skin creams as a conditioning agent; however, it has a short half-life. Zorblisa is a topical cream with a stabilized form of allantoin at higher concentrations (3% to 6%) than those used in over-the-counter products. It purportedly speeds healing of wounds and reduces the total body surface area affected by blisters at a given time. It is applied once daily, over the whole body, topically, indefinitely. Scioderm, Inc., Raleigh, NC, acquired by Amicus Therapeutics, Cranbury, NJ Phase III trial ongoing; FDA granted breakthrough therapy and orphan drug statuses; intends to initiate rolling new drug application in 3rd quarter 2015	Bandaging Skin grafts	Improved healing time Reduced incidence of blisters Reduced rate of infection Reduced mortality Improved quality of life

Table 9. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 50 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Actoxumab/bezlotoxumab for treatment of *Clostridium difficile*–associated diarrhea	Patients in whom *Clostridium difficile*–associated diarrhea has been diagnosed	Recurrent *C. difficile* infection (CDI) is responsible for significant morbidity, mortality, and costs; recurrent CDI can be extremely resistant to treatment, and up to 60% of patients previously treated for recurrent CDI with antibiotics develop further recurrence after therapy is stopped. Options to relieve acute symptoms are needed. Actoxumab (MK-3415) and bezlotoxumab (MK-6072), together known as MK-3415A, are monoclonal antibodies designed to block the activity of *C. difficile* toxins A and B, respectively, which are purportedly involved in CDI pathogenesis. In a clinical trial, actoxumab/bezlotoxumab was administered as a single intravenous infusion of 10 mg/kg. Merck & Co., Inc., Whitehouse Station, NJ No phase III trials ongoing	Fecal microbiota transplant Fidaxomicin Metronidazole Vancomycin	Increased clinical cure rates Reduced CDI recurrence
Amikacin Inhale for the treatment of gram-negative pneumonia	Critically ill patients who are on ventilators in intensive care units (ICUs)	Gram-negative pneumonias often result as a complication of other patient conditions or surgeries and can account for up to 85% of hospital-acquired pneumonias. Gram-negative pneumonias are prevalent in patients in ICUs who have been put on ventilators for breathing assistance and can complicate treatment. Between 25% and 50% of these patients will die. Effective treatment options are needed. Amikacin Inhale (NKTR-061, BAY41-6551) is a drug-device combination that combines a liquid formulation of the aminoglycoside antibiotic amikacin with proprietary liquid pulmonary technology. It is intended to deliver amikacin deep into the infected lungs of patients with gram-negative pneumonia. Administered 400 mg of aerosolized amikacin every 12 hours for 10 days as an adjunctive treatment for intubated and mechanically ventilated patients. Nektar Therapeutics, San Francisco, CA Bayer AG, Leverkusen, Germany Phase III trials ongoing; Nov 2014, FDA granted qualified infectious disease product status	Intravenous antibacterial therapy	Increased cure rates Reduced treatment failures Increased survival Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bacterial spores (SER-109) for treatment of recurrent *Clostridium difficile* infection	Patients in whom recurrent *Clostridium difficile* infection (CDI) has been diagnosed	Fecal microbiota transplantation has demonstrated high efficacy against recurrent CDI, in limited studies. However, fecal transplantation requires identifying and screening appropriate donors, which can be labor intensive and limits the diffusion of the procedure to a small number of specialty facilities. SER-109 is a combination of spores from pure bacterial strains identified using the manufacturer's proprietary Microbiome Therapeutics™ platform technology. It is thought to induce environmental changes in the gut microbiota that restore a healthy state in patients with recurrent CDI. SER-109 also purportedly induces sustained changes in the gut flora that could prevent CDI recurrence. Seres Health, Inc., Cambridge, MA Phase II trials ongoing; phase III trial planned; FDA granted orphan drug and breakthrough therapy statuses	Fecal microbiota transplant Fidaxomicin Metronidazole Vancomycin	Increased clinical cure rates Reduced CDI recurrence

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Blue-violet LED light source (Indigo-Clean) for prevention of hospital-acquired infection	Patients who are at risk for hospital acquired infection (HAI)	Hospital-acquired infections (HAIs) are a major cause of morbidity and mortality in the U.S.; they collectively cause about 100,000 deaths annually. An estimated 50% or more of HAIs are preventable; HAI incidence has been shown to decline after infection-control policies are enacted in patient settings. Chemical disinfectants, ozone treatment, and ultraviolet (UV) light all have efficacy against HAI-causing microbes, but these interventions are short-lasting and may require that areas to be treated are unoccupied. Indigo-Clean™ is an LED light source that is designed to continuously emit blue-violet visible light at a 405 nm wavelength, which has demonstrated antibacterial and antifungal activity. Use of the light source is believed to pose no risk to patients and can be used in patient-occupied areas. The 405 nm light, also called High-Intensity Narrow-Spectrum Light Environmental Disinfection System (HINS-light EDS), photoexcites light-absorbing microbial porphyrins. The activated porphyrin molecules react with oxygen to produce reactive oxygen species (ROS), which then cause oxidative damage to the microbial cells that ultimately results in cell death. Indigo-Clean is effective against pathogens that cause HAIs, including gram-positive bacteria (e.g., *Staphylococcus aureus*, *Streptococcus pyogenes*, *Mycobacterium* species), gram-negative bacteria (e.g., *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*), and *Candida* species (yeast). Drug-resistant forms of these microbes, such as methicillin-resistant *Staphylococcus aureus (*MRSA), are equally susceptible to Indigo-Clean. Indigo-Clean is also effective against spore-forming bacteria such as *Clostridium difficile*, but complete disinfection of spores may require longer exposure to the blue-violet light. In clinical trials, The device has been tested in inpatient and outpatient settings and intensive care units. It may be used to disinfect solid surfaces, contaminated liquids, and biofilms. Kenall Manufacturing, Kenosha, WI Clinical trials ongoing; commercialized in the U.S. and Canada; manufacturer has established Clinical Partners Program for diffusion into patient care settings	Chemical disinfectant solutions Ozone treatment UV light exposure	Reduced incidence of HAIs Decreased mortality due to HAI complications

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Brilacidin for treatment of acute bacterial skin infection	Patients in whom acute bacterial skin and skin structure infection (ABSSSI) has been diagnosed	Drug-resistant bacteria and the shrinking clinical pipeline of new agents to treat serious skin infections continue to pose issues for effectively managing patients. Antibiotics with new mechanisms of action are needed for ABSSSI. Brilacidin (PMX-30063) is a novel, synthetic defensin-mimetic antibiotic. Defensins are proteins that are part of the human innate immune system that target and disrupt bacterial cell membranes, leading to lysis. By targeting bacterial membranes, brilacidin purportedly avoids current resistance mechanisms and may be less likely to develop future resistance. Brilacidin is composed of biomimetic compounds that mimic key biological properties of proteins but are purported to be more stable and inexpensive to produce than natural proteins. Brilacidin is thought to have broad-spectrum activity and has been shown to kill *Staphylococcus aureus* in human blood samples in vitro. Administered intravenously. Cellceutix Corp., Beverly, MA Phase II trial completed; Dec 2014, FDA granted qualified infectious disease product status; Jul 2015, manufacturer announced that phase III trials are planned	Clindamycin Linezolid Trimethoprim-sulfamethoxazole Vancomycin	Improved complete clinical response Improved complete microbiologic response Improved infection resolution/cure rate

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Brincidofovir for prevention of viral infection after hematopoietic stem cell transplant	Patients who have recently received a hematopoietic stem cell transplant (HSCT)	Viral infections, such as infections caused by cytomegalovirus (CMV) and BK virus (BKV), are recognized as a significant cause of morbidity and mortality in immunocompromised patients, such as those who have undergone HSCT. Immunocompromised pediatric HSCT patients are particularly susceptible to serious and/or fatal viral infections, for which no treatments are approved. Brincidofovir (CMX001) purportedly is a broad spectrum antiviral for treating or preventing life-threatening double-stranded DNA (dsDNA) viral diseases. It has been tested for efficacy against CMV, adenovirus, smallpox, and Ebola. Brincidofovir combines the manufacturer's PIM (phospholipid intramembrane microfluidization) conjugate technology with cidofovir, a selective inhibitor of viral DNA polymerase and an approved antiviral agent for treating CMV infection. PIM technology covalently modifies the cidofovir molecule so that it mimics a naturally occurring phospholipid metabolite that can use natural uptake pathways to achieve oral availability. Additionally, brincidofovir is purported to be significantly more potent in inhibiting viral DNA synthesis than cidofovir. Administered orally, twice weekly, for up to 3 months not to exceed 4 mg/kg in pediatric or adult patients. Chimerix, Inc., Durham, NC Phase III trial ongoing; FDA granted fast-track status; also under study for preventing CMV reactivation after kidney transplantation	Cidofovir (off label) Ganciclovir	Decreased rate of organ rejection Increased time to organ rejection Reduced viral load

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Brincidofovir for treatment of severe adenovirus infection	Patients in whom severe adenovirus infection has been diagnosed	Adenovirus infections often have signs and symptoms that resemble common colds. However, patients infected with adenovirus type 14 (Ad14) can have a hospitalization rate of up to 40% with severe symptoms of pneumonia, shortness of breath, and organ-related complications including eye, bladder, and gastrointestinal problems. Brincidofovir (CMX001) is intended to be a broad spectrum antiviral for treating or preventing life-threatening double-stranded DNA (dsDNA) viral diseases. Brincidofovir combines the manufacturer's PIM (phospholipid intramembrane microfluidization) conjugate technology with cidofovir, a selective inhibitor of viral DNA polymerase. PIM technology covalently modifies the cidofovir molecule so that it mimics a naturally occurring phospholipid metabolite that can use natural uptake pathways to achieve oral availability. Additionally, brincidofovir is purported to be significantly more potent in inhibiting viral DNA synthesis than cidofovir. Administered orally, twice weekly, for up to 3 months not to exceed 4 mg/kg in pediatric or adult patients. Chimerix, Inc., Durham, NC Phase III trial ongoing; FDA approved for treating cytomegalovirus infection	Supportive care Cidofovir (off label) Ribavirin (off label)	Reduced mortality Reduced length of stay Shorter time to symptom resolution
Clostridium difficile vaccine (ACAM-CDIFF) for prophylaxis before obtaining treatment in a health care facility	At-risk individuals, including adults facing imminent hospitalization or current or impending residence in a long-term care or rehabilitation facility	*Clostridium difficile* is a common source of hospital-acquired infection that can lead to significant morbidity, mortality, lengthened hospital stays, and increased cost. More options to prevent *C. difficile* infection are needed. *C. difficile* vaccine (ACAM-CDIFF™) consists of a toxoid from the bacterium intended to induce protective antibody responses. In clinical trials, the vaccine was administered as an intramuscular injection at weeks 0, 1, and 4. Sanofi, Paris, France Phase III trial ongoing; Nov 2010, FDA granted fast-track status	Hospital infection control programs	Reduced *C. difficile* infection rates Reduced use of antibacterial drugs Reduced hospitalization time Reduced isolation

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Daclatasvir (Daklinza) and sofosbuvir (Sovaldi) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	HCV treatment options are not effective in all patients and are associated with frequent adverse events, a long duration of therapy, and low patient adherence. Effective treatments that improve clinical outcomes and safety in a shorter time are needed. Daclatasvir (Daklinza®) is a 1st-in-class inhibitor of HCV NS5A, which is a multifunctional, nonenzymatic endoplasmic reticulum (ER) membrane–associated phosphoprotein. This protein regulates multiple steps of the HCV life cycle, including viral RNA replication and virion maturation. Although the role of the protein is poorly understood, NS5A is known to be required for viral replication. Researchers propose that daclatasvir destabilizes the association of NS5A with the ER membrane, thus inhibiting functional virions from forming. It may be used in combination with sofosbuvir or simeprevir. Administered orally, 60 mg, once daily. Bristol-Myers Squibb, New York, NY Jul 2015, FDA approved daclatasvir in combination with sofosbuvir for treating HCV genotype 3 infection; May 2015, daclatasvir/sofosbuvir received an amended breakthrough therapy status to include treatment of patients infected with HCV genotype 1 who have cirrhosis, as well as for patients infected with HCV genotype 1 who experience post-transplant HCV infection recurrence; manufacturer announced plans for supplemental FDA filings for difficult-to-treat HCV populations by the end of 2015	Direct-acting antivirals (e.g., Harvoni®, Olysio®, Sovaldi®, Viekira Pak™)	Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 12 weeks) Decreased need for liver transplant Improved quality of life
Debio 1450 for treatment of *Staphylococcus aureus* infections	Patients in whom recurrent *Staphylococcus aureus* infections have been diagnosed	*S. aureus* infections are often drug resistant and cause difficult-to-treat infections that can be life-threatening. Treatment options that can combat emerging resistant strains are needed. Debio 1450 is purported to inhibit FabI, an essential enzyme in *S. aureus* lipid and biotin biosynthesis. Debio 1450 purportedly has staphylococcal-specific activity that could preserve the patient's gut microbiota and reduce side effects and additional antibacterial resistance. In clinical trials, patients are receiving Debio 1450 at a dose of 120, 240, or 360 mg once or twice daily, orally, or 120, 240, or 360 mg once or twice daily, intravenously, for up to 10 days. Debiopharm, S.A., Lausanne, Switzerland Phase II trial ongoing; FDA granted qualified infectious disease product and fast-track statuses	Clindamycin Doxycycline Linezolid Trimethoprim-sulfamethoxazole Vancomycin	Increased clinical cure rate Reduced time required for treatment

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Delamanid (Deltyba) for treatment of tuberculosis	Patients in whom tuberculosis (TB) has been diagnosed	TB has developed resistance to existing antibiotic therapies and treatment is further complicated by a lengthy regimen. Treatments that can improve outcomes in antibiotic-resistant infections and shorten treatment duration are needed. Delamanid (Deltyba™) purportedly addresses these unmet needs. As a nitro-dihydro-imidazooxazole derivative, it purportedly inhibits the synthesis of mycolic acid, which is a component of the TB bacteria cell wall. Delamanid is administered orally, 100 mg, twice daily, for 2 months and 200 mg, once daily, for 4 months, in addition to standard TB regimens. Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan Phase III (non-U.S.) trial ongoing	Ethambutol Ethionamide Isoniazid Kanamycin Ofloxacin Pyrazinamide Rifampicin	Improved patient adherence with therapy Reduced spread of infection Reduced time to clinical response Resolution of active TB infection Improved quality of life
DNA gyrase inhibitor (AZD0914) for treatment of gonorrhea	Patients in whom gonorrhea has been diagnosed	Resistance to other antibiotics has made injectable cephalosporins in combination with azithromycin or doxycycline the recommended treatment for gonorrhea infections. Cephalosporin-resistant gonorrhea has been detected in Europe, Japan, and Australia. New treatment options are needed for emergent resistant infections. AZD0914 is a novel DNA gyrase inhibitor purported to halt bacterial DNA replication. In a clinical trial, it is administered once, intramuscularly, at a dose of 2,000 or 3,000 mg. AstraZeneca, London, UK Phase II trial ongoing; FDA granted qualified infectious disease product and fast-track statuses	Cephalosporins Fluoroquinolones	Bacterial eradication at end of therapy Reduced transmission Resolution of symptoms

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Dual-release ciprofloxacin (Pulmaquin) for treatment of *Pseudomonas aeruginosa*–related bronchiectasis	Patients in whom bronchiectasis (BE) related to *Pseudomonas aeruginosa* lung infection has been diagnosed	Bronchiectasis (BE) is characterized by dilated bronchi, airway inflammation, and bacterial colonization and affects about 110,000 people in the U.S. Chronic infection with *P. aeruginosa* is common and may contribute to increased symptoms, decreased quality of life, and worsened forced expiratory volume in 1 second (FEV_1) values. No licensed antibiotic therapies are available for patients who have *P. aeruginosa*-related BE; oral, inhaled, or intravenous antibiotics are used off label and do not always improve patient outcomes. Dual-release ciprofloxacin for inhalation (Pulmaquin®; ARD-3150;/DRCFI) is an investigational formulation of the FDA-approved broad-spectrum fluoroquinolone antibiotic ciprofloxacin, which blocks the activity of bacterial DNA topoisomerases. ARD-3150/DRCFI is intended for treating patients who have concomitant BE and *P. aeruginosa* lung infection; it is a mixture of liposomal ciprofloxacin (Lipoquin®/ARD-3100) and unencapsulated ciprofloxacin for direct delivery to the airways. Liposomal-complexed ciprofloxacin is slowly released over 24 hours; free ciprofloxacin is immediately released in the airways. Dose for 2 ongoing phase III trials is not specified, but patients will receive ARD-3150/DRCFI, inhaled, once daily, in 3 cycles of 28 days on and 28 days off, for 24 weeks. In a phase IIb trial, ARD-3150/DRCFI (150 mg liposomal ciprofloxacin with 60 mg free ciprofloxacin) was administered in combination with a PARI LC Sprint nebulizer powered by a PARI Turbo Boy-S compressor. Aradigm Corp., Hayward, CA, and Grifols, S.A., Barcelona, Spain Phase III trials ongoing; FDA granted fast-track, orphan drug, and qualified infectious disease product statuses	Antibiotics (off-label; e.g., combination cephalosporin/aminoglycoside, ciprofloxacin, low-dose gentamycin, tobramycin)	Reduced duration of therapy Simplified dosing Improved adherence Fewer adverse events Reduced overall cost of treatment

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Engineered low-dose imatinib-based protein kinase inhibitor (IkT-001Pro) for treatment of progressive multifocal leukoencephalo-pathy	Patients in whom progressive multifocal leukoencephalo-pathy (PML) has been diagnosed	PML is a rare, potentially fatal, demyelinating viral brain disease that leads to severe motor disability and cognitive decline. PML is thought to be caused by JC virus (JCV) activation when patients are immunosuppressed as a result of HIV, chemotherapy, organ transplantation, or immunosuppressive therapies. No cure is available for PML or underlying pathogenic JCV. IkT-001Pro is an engineered medication whose active ingredient, imatinib, is a host-directed protein kinase inhibitor shown to disrupt JCV replication. Although imatinib use for cancer treatment has resulted in poor tolerability, IkT-001Pro purportedly treats PML with a safer, lower dose of imatinib. Inhibikase Therapeutics, Inc., Atlanta, GA No clinical trials are registered; company estimates that clinical development will begin in the 2nd half of 2015; May 2014, FDA granted orphan drug status	Antiviral medications (experimental) Highly active antiretroviral therapy	Increased use of primary prescribed immunomodulating medication Reduced mortality Improved quality of life
Eravacycline for treatment of complicated bacterial infections	Patients in whom complicated intra-abdominal (cIAI) or urinary tract (cUTI) bacterial infections have been diagnosed	Eravacycline is fully synthetic antibiotic derived from tetracycline purported to have broad-spectrum activity against multidrug-resistant gram-positive, gram-negative, atypical, or anaerobic infections. Eravacycline is intended to treat the majority of patients as a 1st-line empiric oral monotherapy or for use as an intravenous-to-oral step-down therapy. The drug has shown potency against *Acinetobacter baumannii, Enterobacteriaceae* expressing extended spectrum beta-lactamases (ESBLs), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), *Enterococcus faecalis*, and penicillin-resistant strains of *Streptococcus pneumonia*. Eravacycline could also be used an empiric countermeasure for inhalation disease caused by *Bacillus anthracis*, *Francisella tularensis,* or *Yersinia pestis*. Eravacycline is being developed for treating 2 types of bacterial infections (cIALs and cUTIs), which are often acquired in a hospital setting (hospital-acquired infections or HAIs). In phase III trials, patients are receiving eravacycline 1 mg/kg, intravenously, twice daily, or 1.5 mg/kg, intravenously, once daily, plus 200–250 mg orally, twice daily, as monotherapy. Tetraphase Pharmaceuticals, Inc., Watertown, MA Phase III trials ongoing; FDA granted fast-track status; company anticipates submitting a new drug application by the end of 2015	Carbapenems Fluoroquinolones (e.g., Levofloxacin) Tigecycline	Improved clinical response Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Favipiravir (Avigan) for treatment of Ebola virus disease	Patients infected with Ebola virus who have a low-to-moderate viral load	Ebola virus disease (EVD) has a 50% mortality rate. It is caused by a virus of the family *Filoviridae*, genus e*bolavirus*. Of 5 identified Ebola virus species, 4 are known to cause disease in humans: Ebola virus (*Zaire ebolavirus*); Sudan virus (*Sudan ebolavirus*); Taï Forest virus (*Taï Forest ebolavirus*, formerly *Côte d'Ivoire ebolavirus*); and Bundibugyo virus (*Bundibugyo ebolavirus*). Treatment is optimal supportive care. No FDA-approved treatments exist for EVD, but several agents are being given through FDA's compassionate use program, depending on availability. Favipiravir (Avigan®) purportedly inhibits the Ebola virus RNA polymerase, inhibiting replication of the viral genome. In a clinical trial, favipiravir was administered orally, 2,400 mg, at hours 0 and 8, 1,200 mg at hour 16, then 1,200 mg, twice daily, through day 9. FujiFilm Pharmaceuticals U.S.A., Inc., Boston, MA MediVector, Inc., Boston, MA Phase II trial ongoing	Convalescent serum (plasma from patients who have recovered from EVD) Supportive care	Increased survival rate Reduced mortality Symptom resolution
Fidaxomicin (Dificid) to prevent *Clostridium difficile* infection after transplantation	Patients receiving a transplant who develop *Clostridium difficile* infection (CDI)	Patients who receive a transplant, such as bone marrow, hematopoietic stem cells, or a solid organ (e.g., heart, lung, kidney, liver, pancreas), are prescribed immunosuppressive therapy, which places them at risk for serious infections, including CDI. CDI can result in significant morbidity, mortality, and costs. Fidaxomicin (Dificid®) is a 1st-in-class macrocyclic antibiotic that inhibits bacterial RNA polymerase. It has a narrow spectrum and selectively eradicates CDI with minimal disruption to the normal intestinal flora, which could facilitate prophylactic use. In clinical trials, patients are receiving fidaxomicin 200 mg, orally, once or twice daily, for 7–10 days. Merck & Co., Inc., Whitehouse Station, NJ Phase III and IV trials ongoing; FDA approved May 2011 for treating recurrent *C. difficile*–associated diarrhea	Prophylactic antifungal and quinolone antibiotic	Reduced *C. difficile* infection rate Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fostemsavir for treatment of HIV	Patients in whom HIV infection has been diagnosed	HIV remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments. HIV drug resistance, poor tolerance to existing treatments, and high lifelong cost of therapy present opportunities for the development of novel and effective HIV therapies. Fostemsavir (BMS-663068) is an attachment inhibitor that binds directly to the HIV gp120 protein, and it is thought to prevent the initial attachment of HIV virions to host CD4+ cells. Preventing binding of HIV virions to host cells is thought to prevent all subsequent steps in HIV viral replication. Administered orally, 600 mg, twice daily. Bristol-Myers Squibb, New York, NY Phase III trial ongoing; Jul 2015, FDA granted breakthrough status	Antiretroviral therapy	Improved CD4+ T-cell counts Improved control of viral load Reduced antiviral resistance Reduced morbidity Improved quality of life
Grazoprevir/ elbasvir for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Interferon (IFN)-based treatments for HCV are not effective in all patients. Available treatments are also associated with frequent adverse events and a long duration of therapy; effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. Grazoprevir/elbasvir (MK-5172A) is a fixed-dose combination tablet containing grazoprevir, an oral NS3/4a protease inhibitor intended to block the activity of HCV protease, and elbasvir, an HCV NS5A inhibitor. NS5A is a multifunctional, nonenzymatic endoplasmic reticulum (ER) membrane–associated phosphoprotein that regulates multiple steps of the HCV life cycle, including viral RNA replication and virion maturation. Grazoprevir/elbasvir is being evaluated for treating HCV genotypes 1, 2, 3, 4, and 6 infections. In clinical trials, grazoprevir/elbasvir (100 mg/50 mg) were administered orally, once daily with or without ribavirin (RBV) for 12 weeks. Additionally, grazoprevir/elbasvir (100 mg/50 mg) is being evaluated for oral administration once daily with sofosbuvir (400 mg) for 4, 6, 8, or 12 weeks. Merck & Co., Inc., Whitehouse Station, NJ Phase III trials ongoing; FDA granted breakthrough therapy status for treating patients with chronic HCV genotype 4 infection and for treating patients with chronic HCV genotype 1 infection with end-stage renal disease on hemodialysis; May 2015, new drug application submitted for treating patients with chronic HCV genotype 1, 4, or 6 infection; Jul 2015, FDA granted priority review and set a decision date of Jan 28, 2016	Direct-acting antivirals (e.g., Harvoni®, Olysio®, Sovaldi®, Technivie™, Viekira Pak™)	Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 12 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Hemoperfusion adsorption column (Toraymyxin) for treatment of sepsis	Patients in whom severe sepsis has been diagnosed	Patients with severe sepsis have a mortality rate of 40% to 60%; novel treatments to improve outcomes are needed. Toraymyxin® is an extracorporeal direct hemoperfusion adsorption column packed with polystyrene fibers and coated with the antibiotic polymyxin B; it is purported to bind and remove endotoxin from the bloodstream of patients with sepsis. Endotoxin is responsible for triggering systemic immune responses leading to sepsis. Patients are treated with 2 columns over a 24-hour period. Spectral Diagnostics, Inc., Toronto, Ontario, Canada Phase III trial ongoing	Intravenous antibiotics Supportive therapy	Improved hemodynamics and organ function Reduced 28-day mortality
Hemopurifier blood filter for reducing patients' viral load in life-threatening infectious disease	Patients affected by pandemic disease or bioterrorism agents	Many life-threatening viral infections are resistant to treatment or no approved treatment options are available. Nonspecific treatment methods that are applicable to a wide range of serious infections and can improve viral control and treatment outcomes are needed. The Aethlon Hemopurifier is a blood filter that works with conventional dialysis systems or other blood pumping technology using a broad-spectrum approach to attract and capture infectious agents from the bloodstream during pandemics or bioterrorism events. The device reportedly has broad-spectrum capabilities against viral pathogens, including HIV, hepatitis C virus (HCV) and numerous bioterror and pandemic threats. The device purportedly can reduce average viral load of greater than 50% when used for 4 hours in HCV- or HIV-infected patients without administration of antiviral drugs. The device is under study in clinical trials on HCV viral load reduction when used in combination with HCV standard of care drug therapy. In vitro studies have shown that the Hemopurifier captures Dengue hemorrhagic virus, Ebola hemorrhagic virus, Lassa hemorrhagic virus, West Nile virus, H5N1 avian influenza virus, 2009 H1N1 influenza virus, the reconstructed Spanish flu of 1918 virus, and monkeypox virus, which serves as a model for human smallpox infection. Aethlon Medical, Inc., San Diego, CA Early phase clinical trial ongoing; available under FDA expanded access program for treating Ebola virus disease since Nov 2014	Antivirals Antibiotics Standard public health measures for containing and treating pandemic disease and/or biological weapon threats	Increased survival from life-threatening infections Reduced disease severity in infected patients Reduced load of infectious agent in patients Reduced spread of infection by infected patients

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ibalizumab for treatment of HIV infection	Patients in whom HIV has been diagnosed	HIV infection remains a chronic illness resulting in high morbidity and mortality. HIV drug resistance, poor tolerance to existing treatments, and high lifelong costs of therapy indicated a need for improved therapeutic options. Ibalizumab is purported to be a nonimmunosuppressive monoclonal antibody that binds CD4, the major HIV receptor expressed on the surface of T cells and macrophages. Ibalizumab purportedly competes with HIV for CD4-binding sites, thereby slowing the HIV infectious cycle. Administered intravenously at a dose of 800 mg every 2 weeks or 2,000 mg every 4 weeks in combination with the optimized background regimen. TaiMed Biologics, Inc., Taipei, Taiwan Phase III trials ongoing; FDA granted breakthrough therapy status Feb 2015	Antiretroviral therapy Enfuvirtide Maraviroc	Decreased viral load Decreased morbidity Increased survival Slower development of resistance
Intestinally derived microbiota suspension (RBX2660) for treatment of recurrent *Clostridium difficile* infection	Patients in whom recurrent *Clostridium difficile* infection (CDI) has been diagnosed	Fecal microbiota transplantation has demonstrated high efficacy against recurrent CDI, in limited studies. However, fecal transplantation requires identifying and screening appropriate donors, which can be labor intensive and limits the diffusion of the procedure to a small number of specialty facilities. RBX2660 is a microbiota restoration therapy being developed as an off-the-shelf, standardized preparation of intestinally derived microbes. It is intended to be more acceptable to patients and more convenient for physicians than fecal microbiota transplantation. It is administered as a rectal enema. Rebiotix, Inc., Roseville, MN Phase II trial ongoing; FDA granted fast-track status	Fecal microbiota transplant Fidaxomicin Metronidazole Vancomycin	Increased clinical cure rates Reduced CDI recurrence

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ledipasvir and sofosbuvir (Harvoni) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Interferon (IFN)-based treatments for HCV are not effective in all patients. Available treatments are also associated with frequent adverse events and a long duration of therapy; effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. NS5A is a multifunctional, nonenzymatic endoplasmic reticulum (ER) membrane–associated phosphoprotein, which regulates multiple steps of the HCV life cycle, including viral RNA replication and virion maturation. Although the role of the protein is poorly understood, NS5A is required for viral replication. Ledipasvir is an oral NS5A inhibitor purported to block the ability of the viral NS5A protein to attach to the ER of infected hepatocytes, which is thought to be required for functional virions to form. Ledipasvir was approved as a fixed-dose combination tablet with sofosbuvir (Harvoni®). Administered as a single tablet (90 mg ledipasvir and 400 mg sofosbuvir) taken orally, once daily, with or without food. Gilead Sciences, Inc., Foster City, CA FDA approved Oct 2014 for treating chronic HCV genotype 1 infection	Direct-acting antivirals (e.g., Olysio®, Sovaldi®, Viekira Pak™)	Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 12 weeks) Decreased need for liver transplant Improved quality of life
Letermovir for prevention of human cytomegalovirus reactivation after organ transplantation	Patients undergoing organ transplantation who could be at risk of reactivation of human cytomegalovirus (HCMV)	HCMV is the primary cause of morbidity and mortality during the 1st 6 months after a patient receives an organ transplant. Ganciclovir is considered expensive and not appropriate or effective in preventing HCMV reactivation in many patients. Letermovir (AIC246) is a quinazoline that purportedly targets the HCMV terminase enzyme. The terminase enzyme is crucial for concatemeric HCMV DNA cleavage during the replication process and its subsequent packaging into the HCMV virions. This is purported to be a novel mechanism of action that should remain effective against strains resistant to current therapy targeting the HCMV DNA polymerase. In a clinical trial, letermovir was administered orally, 120 or 240 mg, once daily. AiCuris GmbH & Co. KG, Wuppertal, Germany Merck & Co., Inc., Whitehouse Station, NJ Phase III trial ongoing; FDA granted orphan drug and fast-track statuses	Cidofovir (off label) Ganciclovir	Decreased rate of organ rejection Increased time to organ rejection Reduced HCMV load

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lonafarnib for treatment of hepatitis D virus infection	Patients in whom hepatitis D virus infection has been diagnosed	Hepatitis D virus (HDV) occurs only as a co-infection in individuals with hepatitis B virus (HBV) infection. HDV infection leads to more severe liver disease than HBV alone and is associated with accelerated fibrosis, cancer, and liver failure. No treatments exist for HDV infection. Lonafarnib purportedly inhibits farnesyl transferase, a host-cell enzyme involved in a process called prenylation, which is essential to HDV replication. Because prenylation is a host-cell process, lonafarnib is thought to have a higher barrier to resistance than direct-acting antiviral agents. Lonafarnib is administered orally, 100–200 mg, daily, for other indications. Eiger BioPharmaceuticals, Inc., San Carlos, CA Phase II trials ongoing; FDA granted orphan drug and fast-track statuses	HBV treatment Supportive care	Reduced HDV RNA levels Improved liver function
Nitazoxanide for treatment of influenza	Patients in whom viral influenza has been diagnosed	Influenza continues to cause significant morbidity and mortality in susceptible patients. Resistance to existing antiviral agents and the need for broad coverage against different strains of influenza present a significant unmet medical need. Nitazoxanide (NT-300) is a thiazolide with a broad spectrum of anti-infective activity. It may interfere with protease activity and the maturation and intracellular transport of the viral hemagglutinin protein (other drugs inhibit neuraminidase), leading to a reduction in viral replication. In trials, the drug is being administered orally, 600 mg, twice a day, for 5 days as monotherapy or in combination with oseltamivir. Romark Laboratories, L.C., Tampa, FL Phase III trial completed	Oseltamivir Zanamivir	Reduced complications of influenza infection Shorter duration of symptoms

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ombitasvir/ paritaprevir/ ritonavir and dasabuvir (Viekira Pak) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Interferon (IFN)-based treatments for HCV are not effective in all patients. Available treatments are also associated with frequent adverse events and a long duration of therapy; effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. Viekira Pak™ is an IFN-free option intended to improve treatment success and tolerability in patients chronically infected with HCV. The regimen consists of paritaprevir, an NS3/4A HCV protease inhibitor, co-administered with ritonavir; dasabuvir, a nonnucleoside NS5B polymerase inhibitor intended to bind HCV RNA-dependent RNA polymerase and inhibit replication of the viral genome; and ombitasvir, an NS5A inhibitor purported to block viral NS5A protein attachment to the endoplasmic reticulum of infected hepatocytes, which is thought to be required for functional virions to form. 2 ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg) tablets are taken once daily (in the morning) and 1 dasabuvir (250 mg) tablet is taken twice daily (morning and evening) for 12 weeks with ribavirin (RBV). Patients with HCV genotype 1a infection with cirrhosis require 24 weeks of therapy. Patients with HCV genotype 1b infection without cirrhosis do not require RBV. Viekira Pak can also be used off-label for treating chronic HCV genotype 4 infections. AbbVie, North Chicago, IL Enanta Pharmaceuticals, Inc., Watertown, MA FDA approved Dec 2014 for treating patients with chronic HCV genotype 1 infection; Apr 2015, FDA accepted new drug application and granted priority review for treating patients with chronic HCV genotype 4 infection	Direct-acting antivirals (e.g., Harvoni®, Olysio®, Sovaldi®)	Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 12 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ozone and hydrogen peroxide-based sterilization system (AsepticSure) to reduce health care–acquired infections	Patients at risk for health care–acquired infections (HAIs)	HAIs are the 4th leading cause of death in the U.S. About 1 in 20 hospitalized U.S. patients acquires an HAI, resulting in 100,000 deaths each year. Bacteria on surfaces in intensive care units are said to be responsible for 35% to 80% of HAIs. AsepticSure is a small, portable device purported to sterilize hard and fabric surfaces in a health care or hospital room or surgical suite in 80–90 minutes. The device is placed in the center of the room, then the room is evacuated and sealed off with tape. With a remote control, the device is activated to release ozone and hydrogen peroxide (1%) at a specific humidity into the room for sterilization. After the cycle is run, the device purportedly returns the air to U.S. Environmental Protection Agency (EPA) standards and the room (air, surfaces, and textiles) is sterilized and ready for use. Medizone International, Inc., Sausalito, CA Beta testing in U.S. hospitals planned; Jun 2015, manufacturer filed final product submission with EPA	Antimicrobial copper touch surfaces Terminal cleaning procedures using bleach and cleaning of visibly soiled surfaces as necessary Peracetic acid Xenon/UV light	Reduced bacteria isolated from surfaces Reduced infection rates Reduced morbidity and mortality
Polyclonal immune globulin (Civacir) for prevention of hepatitis C virus infection recurrence after liver transplantation	Patients with hepatitis C virus (HCV) infection who are undergoing liver transplantation	Approximately 25% to 30% of patients in the U.S. who have HCV and receive a liver transplant will develop cirrhosis within 5 years, due to HCV infection of the transplanted organ. Immunosuppressive drugs used to prevent organ rejection may promote HCV infection. No approved therapies exist for preventing HCV recurrence after liver transplant. In recent years, the direct-acting antiviral (DAA) sofosbuvir in combination with ribavirin (RBV) has been used off label to prevent HCV recurrence after liver transplantation, but this treatment is not effective in 30% to 50% of patients. Civacir® is an investigational polyclonal immune globulin (IgG) solution from pooled human plasma that purportedly contains neutralizing antibodies against HCV (HCIG). Civacir is being tested in patients who are infected with HCV genotypes 1–6 and are receiving a liver transplant. In a phase III trial, patients are receiving a 10% solution of Civacir, intravenously, at a dose of 200 or 300 mg/kg. Patients receive a single infusion before transplantation and 15 infusions after, over 10 weeks. BioTest AG, Dreieich, Germany Phase III trial ongoing; FDA granted orphan drug and fast-track statuses	Interferon/RBV Sofosbuvir/RBV	Prevented HCV recurrence Prevented cirrhosis Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pretomanid for treatment of pulmonary tuberculosis	Patients in whom multidrug-resistant/drug-susceptible tuberculosis (TB) has been diagnosed	TB has developed resistance to existing antibiotic therapies and treatment is further complicated by a lengthy regimen. Treatments that can improve outcomes in antibiotic-resistant infections and shorten treatment duration are needed. Pretomanid (PA-824) is a nitroimidazole, a class of antibacterial agents that has activity in vitro against all tested drug-resistant clinical isolates. It is intended to shorten treatment time and simplify treatment. In clinical trials, pretomanid is given at a dose of 200 mg, orally, once daily as part of an anti-tuberculosis drug regimen. Novartis International AG, Basel, Switzerland Bayer AG, Leverkusen, Germany Phase III trial ongoing; FDA granted orphan drug and fast-track statuses	Ethambutol Ethionamide Isoniazid Kanamycin Ofloxacin Pyrazinamide Rifampicin	Reduced duration of therapy Simplified dosing Improved adherence Reduced adverse events Reduced overall cost of treatment
Prime-boost vaccine regimen (MVA-BN-filo and Ad26.ZEBOV) for prevention of Ebola virus infection	Patients at risk of contracting Ebola virus infection	Ebola virus disease (EVD) has a 50% mortality rate. It is caused by a virus of the family *Filoviridae*, genus e*bolavirus*. Of 5 identified Ebola virus species, 4 are known to cause disease in humans: Ebola virus (*Zaire ebolavirus*); Sudan virus (*Sudan ebolavirus*); Taï Forest virus (*Taï Forest ebolavirus*, formerly *Côte d'Ivoire ebolavirus*); and Bundibugyo virus (*Bundibugyo ebolavirus*). Treatment is optimal supportive care. No FDA-approved treatments exist for EVD, but several agents are being given through FDA's compassionate use program, depending on availability. This intervention uses a prime-boost regimen to induce protective immunity against infection with the Ebola virus Zaire strain. The vaccine is delivered by administering the MVA-BN®-filo vaccinia vector used to deliver Ebola antigens as a priming vaccine, followed by a booster immunization with Ad26.ZEBOV, a recombinant adenovirus vector that is also used to deliver Ebola antigens. Combined use of the vaccines was initially intended for protection against Ebola Zaire, Ebola Sudan, and Marburg viruses. However, the manufacturers decided to focus on the Ebola Zaire strain to expedite clinical development. Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ (Ad26.ZEBOV) Bavarian Nordic A/S, Kvistgaard, Denmark (MVA-BN-filo) Phase II and III trials ongoing	Convalescent serum (plasma from patients who have recovered from EVD) Supportive care	Increased symptom resolution Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
PRO 140 monoclonal antibody for treatment of HIV infection	Patients chronically infected with HIV	HIV remains a chronic illness resulting in high morbidity and mortality; HIV drug resistance, poor tolerance to existing treatments, and high lifelong cost of therapy present opportunities for the development of novel and effective HIV therapies. Viral entry inhibitors are a class of HIV antiretrovirals that block fusion of viral and cellular membranes, thus preventing infection of susceptible cells. Maraviroc (Selzentry®) is an approved viral entry inhibitor that directly binds to the active site of the CCR5 chemokine receptor that serves as the coreceptor for HIV infection. However, its use is associated with toxicity and adverse effects, possibly due to interference with normal CCR5 cellular activity. Additionally, viral resistance to maraviroc may develop. PRO 140 is a humanized monoclonal antibody that binds to the hydrophilic extracellular domain of CCR5 and does not affect normal CCR5 function. PRO 140 purportedly increases the efficacy of current antiretrovirals, is expected to have better tolerability (it is not metabolized in the liver), and has demonstrated in vitro efficacy against maraviroc-resistant viruses. In a phase III trial, patients are receiving 1 dose of PRO 140, 350 mg, subcutaneously, in combination with existing antiretroviral therapy during the 1st week of treatment. Patients will then receive PRO 140, 350 mg, subcutaneously, once weekly, for an additional 24 weeks, in combination with optimized background therapy. CytoDyn, Inc., Vancouver, WA Phase II/III trial ongoing; FDA granted fast-track status Feb 2006; manufacturer plans to also develop PRO 140 for preventing graft-versus-host disease (GVHD)	Antiretroviral therapy (e.g., maraviroc) Therapeutic vaccination (investigational)	Decreased viral load Decreased morbidity Increased survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Recombinant chimpanzee adenovirus type 3–based vaccine (ChAd3-EBO Z) for prevention of Ebola virus disease	Patients at risk for Ebola virus disease (EVD)	EVD has a 50% mortality rate. It is caused by a virus of the family *Filoviridae*, genus e*bolavirus*. Of 5 identified Ebola virus species, 4 are known to cause disease in humans: Ebola virus (*Zaire ebolavirus*); Sudan virus (*Sudan ebolavirus*); Taï Forest virus (*Taï Forest ebolavirus*, formerly *Côte d'Ivoire ebolavirus*); and Bundibugyo virus (*Bundibugyo ebolavirus*). Treatment is optimal supportive care. No FDA-approved treatments exist for EVD, but several agents are being given through FDA's compassionate use program, depending on availability. Recombinant chimpanzee adenovirus type 3 (ChAd3) is used to deliver glycoprotein antigens from the Ebola Zaire and Sudan strains; the vaccine is called ChAd3-EBO Z or GSK3390107A. The vaccine vector purportedly delivers the Ebola genetic material into human cells to induce protective immune responses without the ability to replicate or produce infectious virus. In clinical trials, it is being evaluated alone and in combination with Emergent BioSolutions' MVA-EBO Z vaccine candidate as well as Janssen/Crucell's Ad26.ZEBOV candidate. The vaccine will be administered as a single intramuscular injection containing $2x10^{10}$ or $2x10^{11}$ particle units in 1 mL. GlaxoSmithKline, Middlesex, UK The National Institute of Allergy and Infectious Diseases, Bethesda, MD Phase I and II trials ongoing	Convalescent serum (plasma from patients who have recovered from EVD Supportive care	Increased symptom resolution Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
RHB-104 for treatment of Crohn's disease due to *Mycobacterium avium* paratuberculosis infection	Patients with Crohn's disease that shows evidence of *Mycobacterium avium* paratuberculosis	Crohn's disease has no cure currently. Existing treatments suppress inflammation and provide symptomatic relief for a limited period. To reduce the need for surgery and reduce morbidity, better treatments are needed. RHB-104 is an antibiotic thought to have activity against *M. avium* paratuberculosis, which is thought by some investigators to play a role in the development of Crohn's disease. The manufacturer claims the bacterium can be found in 40% to 50% of these patients. In a clinical trial 5 capsules were administered twice daily, orally, containing clarithromycin (95 mg), rifabutin (45 mg), and clofazimine (10 mg). Licensed to RedHill Biopharma, Ltd., Tel Aviv, Israel, by UCF Research Foundation, Orlando, FL Phase III trial ongoing; companion diagnostic test trial planned; the company and Quest Diagnostics had a pre-submission meeting with FDA regarding development of a commercial companion diagnostic test for detecting *M. avium* paratuberculosis in Crohn's disease patients; in the 2nd or 3rd quarter of 2015, RedHill intends to initiate a study to assess the clinical utility of a companion diagnostic test	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (e.g., prednisone) Helminthic therapy Immunomodulators (e.g., azathioprine) Low-dose naltrexone Monoclonal antibodies (e.g., natalizumab, infliximab)	Avoided surgery Complete microbiologic response Resolved symptoms
rVSV-ZEBOV vaccine for prevention of Ebola virus disease	Patients at risk for Ebola virus disease (EVD)	EVD has a 50% mortality rate. It is caused by a virus of the family *Filoviridae*, genus e*bolavirus*. Of 5 identified Ebola virus species, 4 are known to cause disease in humans: Ebola Zaire virus (*Zaire ebolavirus* or ZEBOV); Ebola Sudan virus (*Sudan ebolavirus*); Ebola Taï Forest virus (*Taï Forest ebolavirus*, formerly *Côte d'Ivoire ebolavirus*); and Ebola Bundibugyo virus (*Bundibugyo ebolavirus*). Treatment is optimal supportive care. No FDA-approved treatments exist for EVD, but several agents are being given through FDA's compassionate use program, depending on availability. rVSV-ZEBOV comprises an attenuated strain of vesicular stomatitis virus (VSV) modified to express the Ebola Zaire virus glycoprotein, which purportedly induces neutralizing antibodies against Ebola that are capable of preventing infection. Merck & Co., Inc., Whitehouse Station, NJ, NewLink Genetics Corp., Ames, IA Phase I and III trials ongoing (PREVAIL [Liberia], STRIVE [Sierra Leone], Ebola ça suffit [Guinea])	Convalescent serum (plasma from patients who have recovered from EVD) Supportive care	Increased symptom resolution Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Sofosbuvir (Sovaldi) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Interferon (IFN)-based treatments for HCV are not effective in all patients. Available treatments are also associated with frequent adverse events and a long duration of therapy; effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. Sofosbuvir (Sovaldi™) is a uridine nucleotide analogue intended to inhibit HCV NS5B polymerase activity, which may limit viral replication by inhibiting viral genome replication. Sofosbuvir is administered in conjunction with ribavirin (RBV) or simeprevir, or it is given in a fixed-dose combination with ledipasvir. Administered orally, 400 mg, once daily. Gilead Sciences, Inc., Foster City, CA Phase III trials ongoing; FDA approved Dec 2013 for treating HCV genotype 1, 2, 3, or 4 infection, including patients co-infected with HIV or with hepatocellular carcinoma awaiting liver transplantation	Direct-acting antivirals (e.g., Harvoni®, Olysio®, Viekira Pak™) IFN/RBV	Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 12 weeks) Decreased need for liver transplant Improved quality of life
Solithromycin (CEM-101) for treatment of gonorrhea	Patients in whom gonorrhea has been diagnosed	Resistance to other antibiotics has made injectable cephalosporins in combination with azithromycin or doxycycline the recommended treatment for gonorrhea infections, but cephalosporin-resistant gonorrhea has been detected in Europe, Japan, and Australia. New treatment options are needed for emergent resistant infections. Solithromycin (CEM-101) is a novel fluoroketolide (macrolide) antibiotic that exerts its antibacterial activity by reversibly binding to the 50S subunit of the bacterial ribosome, blocking protein synthesis. It is administered orally, 1,000 mg, once daily. Cempra, Inc., Chapel Hill, NC Phase III trial ongoing; FDA granted qualified infectious disease product status and fast-track status	Cephalosporins Fluoroquinolones	Bacterial eradication at end of therapy Reduced transmission Resolution of symptoms

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Surotomycin (MK-4261) for treatment of recurrent *Clostridium difficile* infection	Patients in whom recurrent *Clostridium difficile* infection (CDI) has been diagnosed	Recurrent CDI is responsible for significant morbidity, mortality, and costs; recurrent CDI can be extremely resistant to treatment. Up to 60% of patients treated for recurrent CDI with antibiotics develop further recurrence after therapy is stopped, which suggests that other therapeutic options are needed. Surotomycin is a novel cyclic lipopeptide, which purportedly disrupts bacterial membrane potential, inhibiting bacterial metabolism. Administered orally, 250 mg, twice daily, for 10 days. Merck & Co., Inc., Whitehouse Station, NJ Phase III trial ongoing; FDA granted qualified infectious disease product and fast-track statuses	Fidaxomicin Metronidazole Vancomycin	Reduced CDI recurrence rate Shorter hospital stays Improved time to resolution of diarrhea
SynCon DNA vaccine (INO-4212) for treatment or prevention of Ebola virus disease	Patients at risk of contracting Ebola virus disease (EVD) or who are infected with the virus	EVD has a 50% mortality rate. It is caused by a virus of the family *Filoviridae*, genus e*bolavirus*. Of 5 identified Ebola virus species, 4 are known to cause disease in humans: Ebola virus (*Zaire ebolavirus*); Sudan virus (*Sudan ebolavirus*); Taï Forest virus (*Taï Forest ebolavirus*, formerly *Côte d'Ivoire ebolavirus*); and Bundibugyo virus (*Bundibugyo ebolavirus*). Treatment is optimal supportive care. No FDA-approved treatments exist for EVD, but several agents are being given through FDA's compassionate use program, depending on availability. SynCon®/INO-4212 immunotherapy is a DNA vaccine or comprised of multiple immunogenic sequences derived from antigens from multiple strains of Ebola virus (INO-4201 and INO-4202). SynCon/INO-4212 is being tested in combination with an electroporation (EP) device (Cellectra®) to deliver the vaccine—which purportedly facilitates vaccine uptake by local antigen-presenting cells—and to induce protective antibody and T-cell responses against Ebola antigens. The vaccine could be used for prophylaxis or as immunotherapy in infected individuals. In a phase I trial, INO-4212 and its individual components are being tested alone and in combination with INO-9012, a proprietary interleukin-12 immune activator, administered intradermally (ID) or intramuscularly (IM), followed by electroporation using Cellectra. Dosage is not specified. Inovio Pharmaceuticals, Inc., Plymouth Meeting, PA Phase I trial ongoing	Convalescent serum (plasma from patients who have recovered from EVD) Supportive care	Increased symptom resolution Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
T2Candida Panel for diagnosis of fungal bloodstream infection	Patients in whom a fungal bloodstream infection (BSI) is suspected	Approximately 1.6 million BSIs are diagnosed in the U.S. each year, with 500,000 deaths. These infections are caused by a number of bacteria and fungi; *Candida* (yeast) is the 4th most common cause of BSIs. Rapid and accurate diagnosis of BSIs is essential to initiate appropriate treatment, limit development of sepsis, and prevent mortality. Initiation of treatment within 12 hours of symptom onset can reduce mortality by up to 75%. Blood cultures typically take 2–6 days to identify a pathogen, and sensitivity rates are 50% to 60%. T2Candida Panel is a rapid diagnostic test developed to detect 5 fungal *Candida* strains (*C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, *C. krusei*) from a single blood sample. The panel is used in conjunction with the T2Dx instrument, using the proprietary T2 Magnetic Resonance (T2MR) platform. T2Candida Panel/T2Dx delivers diagnostic test results in 3–5 hours, with a sensitivity of 91.1% and a specificity of 99.4%, and a lower limit of detection of 1 CFU/mL. T2 Biosystems, Lexington, MA Phase III trial ongoing; Sept 2014, FDA cleared via 513(f)(2) *de novo* pathway	Diagnostic blood culture	Earlier treatment and improved outcomes
Tafenoquine for treatment of *Plasmodium vivax* infection	Patients in whom *Plasmodium vivax* infection has been diagnosed	Malaria caused by *P. vivax* is the 2nd leading cause of malaria deaths and is difficult to treat because of the presence of a dormant, liver stage of the parasite (hypnozoites) causing relapses that can occur any time between 3 weeks and several years after initial infection. Better treatment options are needed. Tafenoquine is an 8-aminoquinoline for treating *P. vivax* (relapsing) malaria. Current standard of care for treating hypnozoites is primaquine, also an 8-aminoquinoline; it requires 14-day treatment and is associated with hemolytic anemia in some patients. Tafenoquine can be administered in a single dose, and is purported to be effective against hypnozoites. GlaxoSmithKline, Middlesex, UK Phase III trial ongoing; FDA granted breakthrough therapy status	Chloroquine phosphate Mosquito nets Primaquine	Reduced incidence of malaria infection Relapse efficacy Increased overall survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tetravalent vaccine (ChimeriVax) for prevention of dengue virus infection	People who are at risk of contracting dengue virus infection	Dengue virus is a mosquito-borne agent that causes severe fever as well as head and body aches in more than half of people infected. No effective treatments or vaccines are available. ChimeriVax™ (CYD-TDV) is a tetravalent dengue virus vaccine is comprised of the backbone of the yellow fever virus vaccine with genes from the 4 dengue serotypes inserted to provide broad protection against all dengue virus serotypes. CYD-TDV is administered as a subcutaneous injection at 0, 6, and 12 months. Sanofi, Paris, France Phase III trials ongoing	Platelet transfusion (if needed) Supportive therapy to prevent circulatory shock	Reduced dengue virus infection rate Reduced hospitalizations Reduced morbidity Reduced mortality
Therapeutic vaccine (Remune) for HIV-1 infection	Patients in whom HIV-1 infection has been diagnosed	HIV remains a chronic illness with high morbidity and mortality in the absence of effective treatments. HIV drug resistance, poor tolerance to existing treatments, and high lifelong cost of therapy present opportunities for the development of novel and effective HIV therapies. Remune® is a therapeutic vaccine that purportedly elicits improved immune responses against HIV antigens in patients infected with HIV-1, which could improve viral control and reduce the need for antiretroviral therapy, as well as reduce drug resistance. Remune consists of a suspension of killed HIV-1 virus particles (Zairian HIV-1 strain HZ-321) containing gp 120–depleted HIV-1 and p24 emulsified with incomplete Freund's adjuvant). Remune is intended to be used in combination with antiretroviral drugs to reduce viral load and increase CD4+ T-cell counts in patients. The vaccine is administered as an intramuscular injection. Immune Response BioPharma, Inc., Atlantic City, NJ Phase II (pediatric) and phase III (adult) trials planned; FDA granted orphan drug status for treating pediatric patients through 16 years of age with HIV/AIDS; Jan 2015, biologics license application received by FDA; decision date set for Nov 26, 2015	Antiretroviral therapy Off-the-shelf therapeutic vaccines (in development)	Reduced morbidity Reduced time to viral load reduction Reduced use of antiretroviral therapy (ART) Sustained control of viral load after cessation of therapy Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
TransVax for prevention of cytomegalovirus reactivation in hematopoietic cell transplant recipients	Patients who have received a stem cell transplant	Human cytomegalovirus (HCMV) infection can lead to organ transplant rejection and is the primary cause of morbidity and mortality during the 1st 6 months after a patient receives an organ transplant. Ganciclovir is considered expensive and not appropriate or effective in preventing HCMV reactivation in many patients. TransVax™ (ASP0113) is a DNA vaccine designed to induce adaptive immune responses capable of preventing reactivation of latent cytomegalovirus or introduction of the virus through donor cells or tissues in transplant recipients. Administered as an intramuscular injection. Vical, Inc., San Diego, CA Astellas Pharma, Inc., Tokyo, Japan Phase III trial ongoing	Cidofovir (off label) Ganciclovir	Decreased rate of organ rejection Increased time to organ rejection Reduced HCMV load
Vaccine (PF-06425090) for prevention of *Clostridium difficile* infection	At-risk individuals, including adults facing imminent hospitalization or current or impending residence in a long-term care or rehabilitation facility	*Clostridium difficile* is a common source of hospital-acquired infection that can lead to significant morbidity and mortality, lengthened hospital stays, and increased cost. More options to prevent *C. difficile* infection are needed. *C. difficile* vaccine (PF-06425090) consists of modified protein subunits of the *C. difficile* toxins A and B, which are intended to induce protective antibody responses to ameliorate symptoms. In clinical trials, the vaccine was administered as an intramuscular injection at weeks 0, 1, and 4. Pfizer, Inc., New York, NY Phase II trial ongoing; FDA granted fast-track status	Hospital infection-control programs	Reduced *C. difficile* infection rates Reduced use of antibacterial drugs Shorter hospitalizations Reduced isolation protocols
Vaginal ring (dapivirine) for prevention of HIV infection	Women at high risk of contracting HIV infection	Although behavior-change programs have resulted in dramatic reductions in HIV transmission in the U.S., there remains no truly effective means to prevent HIV infection among populations at high risk of such an infection. A latex ring that can be placed in the vagina, slowly releasing an antiretroviral drug—similar to birth-control rings—could help reduce the rate of HIV transmission. The vaginal ring contains the nonnucleoside reverse transcriptase inhibitor dapivirine. Dapivirine is not used to treat HIV, so developers expect the prevalence of HIV strains resistant to the drug to be low. The ring contains dapivirine 25 mg, inserted intravaginally, once monthly. International Partnership for Microbicides, Silver Spring, MD Phase III trials ongoing	Condoms Harm reduction campaigns Preexposure prophylaxis (tenofovir/ emtricitabine)	Reduced transmission and incidence of HIV

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Viral RNA polymerase inhibitor (BCX4430) for treatment of Ebola virus infection	Patients infected with Ebola virus	Ebola virus disease (EVD) has a 50% mortality rate. It is caused by a virus of the family *Filoviridae*, genus *ebolavirus*. Of 5 identified Ebola virus species, 4 are known to cause disease in humans: Ebola virus (*Zaire ebolavirus*); Sudan virus (*Sudan ebolavirus*); Taï Forest virus (*Taï Forest ebolavirus*, formerly *Côte d'Ivoire ebolavirus*); and Bundibugyo virus (*Bundibugyo ebolavirus*). Treatment is optimal supportive care. No FDA-approved treatments exist for EVD, but several agents are being given through FDA's compassionate use program, depending on availability. BCX4430 is a nucleotide analogue that purportedly inhibits the active site of the viral RNA-dependent RNA polymerase required for Ebola virus replication. In a phase I trial, patients are receiving BCX4430 as an intramuscular injection, but it may also be suitable for intravenous or oral administration. BCX4430 is also purported to have antiviral activity against Marburg virus. BioCryst Pharmaceuticals, Inc., Durham, NC Phase I trial ongoing; Mar 2015, BioCryst awarded an advanced development contract by Biomedical Advanced Research and Development Authority (BARDA)	Convalescent serum (plasma from patients who have recovered from EVD) Supportive care	Increased survival rate Reduced mortality Symptom resolution
Viral RNA polymerase inhibitor (favipiravir) for treatment of influenza	Patients in whom influenza has been diagnosed or is suspected	Influenza continues to cause significant morbidity and mortality in susceptible patients; better treatments are needed because of the development of resistance to existing agents. Favipiravir purportedly inhibits the influenza virus RNA polymerase, inhibiting viral replication. The drug is purported to be effective against highly pathogenic or drug-resistant influenza strains. Administered orally, 1,800 mg, twice daily, for 1 day, and 800 mg, twice daily, on days 2–5. FujiFilm Pharmaceuticals U.S.A., Inc., Boston, MA MediVector, Inc., Boston, MA No phase III trials ongoing	Oseltamivir Zanamivir	Shorter hospitalization time Reduced virus titers Relieved symptoms

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Zmapp for treatment of Ebola virus infection	Patients in whom Ebola virus disease (EVD) has been diagnosed	EVD has a 50% mortality rate. It is caused by a virus of the family *Filoviridae*, genus e*bolavirus*. Of 5 identified Ebola virus species, 4 are known to cause disease in humans: Ebola virus (*Zaire ebolavirus*); Sudan virus (*Sudan ebolavirus*); Taï Forest virus (*Taï Forest ebolavirus*, formerly *Côte d'Ivoire ebolavirus*); and Bundibugyo virus (*Bundibugyo ebolavirus*). Treatment is optimal supportive care. No FDA-approved treatments exist for EVD, but several agents are being given through FDA's compassionate use program, depending on availability. Zmapp is a passive immunotherapy that is a combination of 3 humanized monoclonal antibodies against the Ebola virus Zaire strain produced in a tobacco leaf–based expression system. The antibodies are intended to help the patient's immune system resolve the infection. Administered intravenously. Mapp Biopharmaceutical, Inc., San Diego, CA Phase I/II trials ongoing; FDA authorized use for treating EVD under expanded access protocols; FDA granted fast-track status	Convalescent serum (plasma from patients who have recovered from EVD Supportive care	Increased survival Increased symptom resolution Reduced mortality

Table 10. AHRQ Priority Condition: 10 Obesity: 7 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bariatric embolization of abdominal arteries for treatment of severe obesity	Adults with body mass index (BMI) of more than 40 kg/m^2	In the U.S., 34.9% of adults are obese. Available pharmacologic and surgical options can have serious side effects or adverse events, warranting the need for novel approaches for treating severe obesity. Bariatric embolization of arteries is a minimally invasive technique that uses a catheter to deliver tiny polymer beads that restrict blood flow in specific blood vessels of the stomach to suppress some of the body's signals for feeling hungry, leading to weight loss. This action is thought to decrease ghrelin, a hormone associated with appetite, which in turn induces weight loss. This intervention is reportedly the 1st catheter-based procedure intended to directly address morbid obesity. In clinical trials, various embolic beads are being used, including BeadBlock® 300-500 Micron and Embosphere Microspheres. Clinical trial participants must have BMI of 40 kg/m^2 or higher. Dayton Interventional Radiology, Dayton, OH The Ohio State University Wexner Medical Center, Columbus, OH Johns Hopkins Hospital, Baltimore, MD 2 trials ongoing (GET LEAN and BEAT Obesity); FDA granted investigational device exemption status for GET LEAN trial	Adjustable gastric banding Bariatric surgery (e.g., gastric bypass, sleeve gastrectomy) Liraglutide (Saxenda®) Lorcaserin (Belviq®) Naltrexone/bupropion (Contrave®) Orbera™ intragastric balloon Orlistat (Xenical®) Phentermine/ topiramate (Qsymia®) ReShape™ Integrated Dual Balloon System VBLOC Maestro® vagus nerve blocking	Decreased comorbidities Total weight loss Improved quality of life
Deep brain stimulation for treatment-refractory morbid obesity	Patients classified as overweight or obese on the basis of body mass index	In the U.S., 34.9% of adults are obese. Among children and adolescents aged 2–19 years, 32.9 million are overweight or obese and 12.7 million are obese. Available pharmacologic and surgical options can have serious side effects or adverse events, warranting the need for more novel approaches for treating obesity. Deep brain stimulation (DBS) involves implanting a battery-operated medical device (neurostimulator) in the brain to deliver electrical stimulation to targeted areas that control the brain's reward system (i.e., frontal cortex, nucleus accumbens, ventral tegmental area). The type of DBS device being used was not disclosed. Allegheny Singer Research Institute, Pittsburgh, PA Ohio State University, Columbus University of Southern California, Los Angeles Unphased trials ongoing	Adjustable gastric banding Bariatric surgery (e.g., gastric bypass, sleeve gastrectomy) Liraglutide (Saxenda®) Lorcaserin (Belviq®) Naltrexone/bupropion (Contrave®) Orbera™ intragastric balloon Orlistat (Xenical®) Phentermine/ topiramate (Qsymia®) ReShape™ Integrated Dual Balloon System VBLOC Maestro® vagus nerve blocking	Decreased food cravings Decreased obesity-associated comorbidities (e.g., prediabetes, high blood pressure) Increased weight loss Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Endoluminal sleeve (EndoBarrier) for preoperative weight loss or treatment of obesity	Patients with body mass index (BMI) of more than 35 kg/m^2 who need to lose weight before bariatric surgery	Available pharmacologic and surgical options for obesity can have serious side effects or adverse events, warranting the need for more novel approaches for treating both obesity and type 2 diabetes mellitus. EndoBarrier® is a nonsurgical, endoluminal sleeve that is endoscopically inserted into the stomach using a guidewire. The device is a duodenal-jejunal bypass liner designed to mimic Roux-en-Y gastric bypass. Surgeons deploy the sleeve in the duodenal bulb, where it can stay in place for up to 12 months. The liner of the device consists of a 60 cm impermeable sleeve intended to move partially digested food through the gastrointestinal tract without allowing nutrients to be absorbed, to achieve weight loss. Surgeons can remove the device with an endoscopic retrieval system. GI Dynamics, Inc., Lexington, MA Mar 5, 2015, FDA placed enrollment hold on pivotal trial (ENDO) after 4 cases of hepatic abscess; Jul 30, 2015, manufacturer terminates ENDO pivotal trial after 7 cases of hepatic abscess (3.5% of subjects); company to evaluate options after analyzing available trial data; Aug 21, 2015, company plans to restructure and lay off 46% of staff by end of 2015	Adjustable gastric banding Bariatric surgery (e.g., gastric bypass, sleeve gastrectomy) Liraglutide (Saxenda®) Lorcaserin (Belviq®) Naltrexone/bupropion (Contrave®) Orbera™ intragastric balloon Orlistat (Xenical®) Phentermine/ topiramate (Qsymia®) ReShape™ Integrated Dual Balloon System VBLOC Maestro® vagus nerve blocking	Preoperative weight loss Improved patient safety Reduced side effects Reduced morbidity
Fecal microbiota transplantation for metabolic syndrome in obese patients	Obese patients in whom metabolic syndrome has been diagnosed	The prevalence of metabolic syndrome is increasing in the U.S., warranting the need for effective therapies aimed at reducing coronary artery disease, stroke, and diabetes mellitus. Obese patients are thought to have an imbalance in the flora of their lower intestinal tract that could be contributing to insulin resistance. A transplant of healthy flora from another person's fecal matter has been suggested as a way to treat metabolic syndrome. In an effort to treat insulin resistance and obesity, fecal matter is harvested from healthy, lean donors, processed, and transferred via enema into obese patients who have metabolic syndrome. Catholic University of the Sacred Heart, Milan, Italy Academic Medical Centre at the University of Amsterdam, the Netherlands Phase III trials ongoing; fecal microbiota therapy has also been used to treat other conditions, such as recurrent *Clostridium difficile* infection	Antiobesity pharmacotherapy Diet and behavior changes Surgical intervention (e.g., bariatric surgery)	Improved fecal flora composition Resolution of metabolic syndrome Weight loss

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Food-based polymer (Gelesis100) for treatment of obesity	Overweight adults with body mass index (BMI) >30 kg/m^2	In the U.S., 34.9% of adults are obese. Among children and adolescents aged 2–19 years, 32.9 million are overweight or obese and 12.7 million are obese. Pharmacologic options have expanded with new drug approvals since 2012; however, the competing drugs have significant potential side effects and work in only a proportion of patients taking them. Additional pharmacologic options are needed. Gelesis100 is a polymer that may promote weight loss without central nervous system effects. Gelesis100 is a highly absorbent hydrogel containing polymer particles of food materials that expand when in contact with liquid in the stomach. The polymer expands into numerous hydrogel beads in the stomach, giving a "full" feeling to suppress hunger. The hydrogel keeps food in the stomach longer, giving stomach acid more time to break down both the food and the hydrogel, which begins to release its water; everything then moves to the small intestine where the gel can re-expand to some extent, slowing the absorption of fatty materials and sugars. Gelesis100 capsules may be taken orally, after meals. Gelesis, Inc., Boston, MA Pilot study completed; pivotal study projected to be completed in the 4th quarter of 2016; FDA submission projected by mid-2017	Liraglutide (Saxenda®) Lorcaserin (Belviq®) Naltrexone/bupropion (Contrave®) Orbera™ intragastric balloon Orlistat (Xenical®) Phentermine/ topiramate (Qsymia®) ReShape™ Integrated Dual Balloon System VBLOC Maestro® vagus nerve blocking	Decreased comorbidities Total weight loss Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Liraglutide (Saxenda) for treatment of obesity	Patients at risk of developing diabetes with a body mass index (BMI) greater than 30 kg/m^2 or between 27 and 30 kg/m^2 with an associated comorbidity	In the U.S., 34.9% of adults are obese. Among children and adolescents aged 2–19 years, 32.9 million are overweight or obese and 12.7 million are obese. Pharmacologic options have expanded with new drug approvals since 2012; however, the competing drugs have significant potential side effects and work in only a proportion of patients taking them. Additional pharmacologic options are needed. Liraglutide (Saxenda®) is approved for treating type 2 diabetes mellitus and acts as a glucagon-like peptide 1 analogue; the drug reduces blood glucose levels by increasing insulin secretion, which delays gastric emptying and suppresses glucagon secretion, potentially leading to weight loss. This treatment showed potential in preclinical studies and studies in overweight patients without diabetes to reduce food intake and induce weight loss. In a clinical trial, liraglutide was administered as a once-daily, subcutaneous injection of 3 mg. Novo Nordisk a/s, Bagsværd, Denmark FDA approved Dec 2014 as “an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with obesity (BMI ≥30 kg/m^2) or who are overweight (BMI ≥27 kg/m^2) in the presence of at least one weight-related comorbid condition”	Adjustable gastric banding Bariatric surgery (e.g., gastric bypass, sleeve gastrectomy) Lorcaserin (Belviq®) Naltrexone/bupropion (Contrave®) Orbera™ intragastric balloon Orlistat (Xenical®) Phentermine/ topiramate (Qsymia®) ReShape™ Integrated Dual Balloon System VBLOC Maestro® vagus nerve blocking	Decreased comorbidities Total weight loss Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
ReShape Integrated Dual Balloon System for treatment of obesity	Patients in whom obesity has been diagnosed, with a body mass index (BMI) between 30 and 40 kg/m^2 who have been unable to lose weight through a supervised diet and behavior modification program	Modifications to diet and exercise are frequently inadequate for reducing weight in patients who are severely overweight or obese. Intermediate interventions between invasive surgery and lifestyle changes and drugs could fill a therapeutic gap. The ReShape™ Integrated Dual Balloon System is an intragastric, dual balloon designed to reduce stomach capacity, thereby increasing satiety with less food, for up to 6 months. After the clinician endoscopically places the balloons with the guidewire through the mouth, they are inflated with a total of 900 cc of saline. The dual-balloon design purportedly reduces device displacement. Endoscopic placement takes 15–30 minutes. The device can stay in the stomach for up to 6 months, and then it must be removed endoscopically using a snare to deflate and remove the balloon through the patient's mouth. ReShape Medical, Inc., San Clemente, CA Jul 2015, FDA approved without requiring an FDA advisory panel meeting; the approved indication is "for weight reduction when used in conjunction with diet and exercise, in obese patients with a Body Mass Index (BMI) of 30 – 40 kg/m^2 and one or more obesity-related comorbid conditions. It is indicated for use in adult patients who have failed weight reduction with diet and exercise alone;" maximum balloon placement period is 6 months; CE marked in 2007	Adjustable gastric banding Bariatric surgery (e.g., gastric bypass, sleeve gastrectomy) Liraglutide (Saxenda®) Lorcaserin (Belviq®) Naltrexone/bupropion (Contrave®) Orbera™ intragastric balloon Orlistat (Xenical®) Phentermine/ topiramate (Qsymia®) VBLOC Maestro® vagus nerve blocking	Decreased comorbidities (e.g., prediabetes, high blood pressure) Increased weight loss Improved quality of life

Table 11. AHRQ Priority Condition: 11 Peptic Ulcer Disease and Dyspepsia: 9 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Alicaforsen for treatment of ulcerative colitis	Patients in whom ulcerative colitis (UC) has been diagnosed	Patients with UC have abnormally and chronically activated immune systems in the absence of any known invader, leading to periodic bouts of abdominal pain, diarrhea, and rectal bleeding. Available therapies for UC may become less effective over time, have long-term side effects, and fail to adequately control symptoms in many patients, contributing to poor quality of life. UC is typically treated with anti-inflammatory drugs with varied success, and investigators have not found a long-term cure or strategy besides surgery to prevent periodic disease flares. Alicaforsen is an antisense ICAM-1 (intercellular adhesion molecule) inhibitor intended to treat UC. The drug purportedly targets the overexpressed intracellular adhesion protein associated with inflammation. In clinical trials, alicaforsen has been administered by enema. Atlantic Healthcare plc, Essex, UK, in collaboration with Isis Pharmaceuticals, Carlsbad, CA Phase III trial ongoing; FDA granted orphan drug status for pouchitis	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (e.g., prednisone) Immunomodulators (e.g., azathioprine) Monoclonal antibodies (e.g., natalizumab, infliximab)	Improved clinical response Improved quality of life Reduced systemic absorption

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fecal microbiota transplantation for treatment of ulcerative colitis	Patients in whom ulcerative colitis (UC) has been diagnosed	Patients with UC have abnormally and chronically activated immune systems in the absence of any known invader, leading to periodic bouts of abdominal pain, diarrhea, and rectal bleeding. Available therapies for UC may become less effective over time, have long-term side effects, and fail to adequately control symptoms in many patients, contributing to poor quality of life. UC is typically treated with anti-inflammatory drugs with varied success, and investigators have not found a long-term cure or a strategy besides surgery to prevent periodic disease flares. Fecal microbiota transplantation is a procedure designed to restore balance to the microbiota of the bowel after it has been disturbed by antibiotics or other environmental changes in the colon, changes that lead to the dominance of toxin-producing strains that can cause disease. Fecal matter from a healthy donor is collected and mixed with a solution and transplanted into the recipient via colonoscopy. Multiple institutions worldwide, including Montefiore Medical Center, Bronx, NY, and the Medical Center for Digestive Diseases at The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China Phase II and II/III trials in adults and phase I trials in children ongoing; procedure might be adopted by gastroenterologists who are using the procedure for treating recurrent *Clostridium difficile* infection	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (e.g., prednisone) Immunomodulators (e.g., azathioprine) Monoclonal antibodies (e.g., natalizumab, infliximab)	Reduced relapse frequency Reduced use of medications Improved symptoms Reduced or postponed need for surgery Improved quality of life
Ibodutant for treatment of diarrhea-predominant irritable bowel syndrome	Patients in whom diarrhea-predominant irritable bowel syndrome (IBS-D) has been diagnosed	IBS is a functional gastrointestinal disorder of unclear etiology with no known cure. About 30% of diagnosed IBS cases can be attributed to IBS-D. Available treatments are purportedly ineffective in many patients, and no new treatment options have been available for decades. The only approved treatment in the U.S. for IBS-D is alosetron, and this intervention is associated with safety issues. Ibodutant is a tachykinin NK2 receptor antagonist that may reduce bowel muscle contraction frequently associated with hypersensitivity to stimuli. Clinical data suggest that NK2 receptor blockage affects intestinal motility and pain sensation without affecting normal gut motor function. In clinical trials, ibodutant has been administered as an oral tablet, 10 mg, once daily. The Menarini Group, Florence, Italy Phase III trials ongoing	Antispasmodic drugs Bile acid sequestrants Tricyclic antidepressants	Reduced abdominal pain and bloating symptoms Long-term relief

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Kappaproct for treatment of resistant ulcerative colitis	Patients with treatment-refractory ulcerative colitis (UC) who may be candidates for colectomy	Patients with UC have abnormally and chronically activated immune systems in the absence of any known invader, leading to periodic bouts of abdominal pain, diarrhea, and rectal bleeding. Available therapies for UC may become less effective over time, have long-term side effects, and fail to adequately control symptoms in many patients, contributing to poor quality of life. UC is typically treated with anti-inflammatory drugs with varied success, and investigators have not found a long-term cure or strategy besides surgery to prevent periodic disease flares. Kappaproct® (DIMS0150) is a DNA-based immunomodulatory sequence (DIMS) that binds to the Toll-like receptor 9 (TLR9) inside immune cells and on epithelial cell surfaces, triggering production of anti-inflammatory cytokines. The treatment goal is to reduce inflammation and promote healing of mucosal wounds. A secondary goal is to resensitize cells to steroid effects in patients for whom steroids have become ineffective. The manufacturer claims the drug has virtually no absorption beyond the colon, limiting systemic side effects. In 250 trial patients, investigators identified no confirmed drug-related serious adverse effects, such as such as osteoporosis, diabetes, serious infections, or malignancies, that may be associated with competing treatments. The drug is administered as an enema solution in 1 or 2 doses; a clinical trial is testing 2 doses of 30 mg each, 4 weeks apart. InDex Pharmaceuticals AB, Stockholm, Sweden Phase III trials ongoing	Aminosalicylates Antibiotics (for infected abscess) Colectomy Corticosteroids (e.g., budesonide, prednisolone, prednisone) Immunomodulators (e.g., azathioprine, cyclosporine, methotrexate) Monoclonal antibodies (e.g., adalimumab, infliximab, natalizumab)	Increased remission rates Improved mucosal healing Reduced need for colectomy

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ozanimod for treatment of ulcerative colitis	Patients in whom ulcerative colitis (UC) has been diagnosed	Patients with UC have abnormally and chronically activated immune systems in the absence of any known invader, leading to periodic bouts of abdominal pain, diarrhea, and rectal bleeding. Available therapies for UC may become less effective over time, have long-term side effects, and fail to adequately control symptoms in many patients, contributing to poor quality of life. UC is typically treated with anti-inflammatory drugs with varied success, and investigators have not found a long-term cure or strategy besides surgery to prevent periodic disease flares. An oral drug that is more effective than current treatment options for UC could increase remission, reduce need for surgery in severe cases, and reduce or eliminate the need for office- or clinic-based infusion therapy (e.g., vedolizumab [Entyvio®], natalizumab [Tysabri®]). Ozanimod (RPC1063) is a selective modulator of the sphingosine-1-phosphate (S1P) receptor subtypes 1 and 5, in development for autoimmune indications. S1P is believed to be a major regulator of vascular and immune systems. The goal of this increased selectivity is to improve upon efficacy and safety profiles of available treatments. A late-phase trial is evaluating ozanimod at a 1 mg, daily, oral dosage. Receptos, Inc., San Diego, CA Phase III trial ongoing	Azathioprine Cyclosporine Integrin receptor antagonists (e.g., vedolizumab) Mercaptopurine Topical 5-aminosalicylic acid (5-ASA) preparations Tumor necrosis factor (TNF)-alpha inhibitors	Improved remission rates Reduced need for surgical treatment Improved quality of life
Remestemcel-L (Prochymal) for treatment of Crohn's disease	Patients in whom Crohn's disease has been diagnosed	Investigators have not found a cure for Crohn's disease, which causes inflammation of the gastrointestinal tract, most often at the end of the small intestine, leading to pain and diarrhea. Treatments are aimed at symptomatic relief. Patients with Crohn's disease frequently experience damage to their bowels and require surgery; no regenerative therapies are approved. Remestemcel-L (Prochymal®) consists of allogeneic, bone marrow–derived human mesenchymal stem cells (MSCs), which purportedly reduce inflammation and promote crypt regeneration in damaged intestine. The manufacturer has developed a specific "expansion" process for these cells, which are intended to be used off the shelf and delivered as an intravenous infusion. In clinical trials, administered 3 times, 200 million cells per infusion, 42 days apart. Mesoblast, Ltd., Melbourne, Australia Phase III trials ongoing; FDA granted orphan and fast-track statuses	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (e.g., prednisone) Immunomodulators (e.g., azathioprine) Monoclonal antibodies (e.g., natalizumab, infliximab)	Increased disease remission Improved disease symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Rifaximin (Xifaxan) for treatment of nonconstipating irritable bowel syndrome	Patients in whom nonconstipating irritable bowel syndrome (IBS) has been diagnosed	IBS is a functional gastrointestinal disorder of unclear cause with no known cure. Rifaximin (Xifaxan®) is a nonabsorbable antibiotic approved for treating traveler's diarrhea and under study for IBS with diarrhea. Rifaximin is purported to reduce abdominal bloating by treating bacterial overgrowth in the small intestine. In an ongoing clinical trial, investigators are studying repeat treatment of patients who had an initial response after 14 days of rifaximin. The medication is being given at 550 mg, orally, 3 times a day. Valeant Pharmaceuticals International, Inc., Montreal, Quebec, Canada May 2015, FDA approved as Xifaxan 550 mg for treating irritable bowel syndrome with diarrhea in adults	Antispasmodic drugs Opioids Serotonin agonists Tricyclic antidepressants	Reduced abdominal pain and bloating symptoms Long-term relief
Tofacitinib (Xeljanz) for treatment of ulcerative colitis	Patients in whom ulcerative colitis (UC) has been diagnosed	Patients with UC have abnormally and chronically activated immune systems in the absence of any known invader, leading to periodic bouts of abdominal pain, diarrhea, and rectal bleeding. Available therapies for UC may become less effective over time, have long-term side effects, and fail to adequately control symptoms in many patients, contributing to poor quality of life. UC is typically treated with anti-inflammatory drugs with varied success, and investigators have not found a long-term cure or strategy besides surgery to prevent periodic disease flares. Tofacitinib (Xeljanz®) is a tyrosine kinase inhibitor specifically targeting the Janus kinase-3 (JAK 3) signaling pathway believed to mediate several processes involved in chronic inflammatory diseases, such as antibody production by B cells, production of rheumatic factor, and activation of T cells. By inhibiting the JAK 3 pathway, tofacitinib might suppress the inflammatory reactions that are the basis of UC. In clinical trials, tofacitinib has been administered twice daily, orally, in 0.5, 1, 3, 5, 10, or 15 mg doses. Pfizer, Inc., New York, NY Phase III trials ongoing	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (e.g., prednisone) Immunomodulators (e.g., azathioprine) Monoclonal antibodies (e.g., natalizumab, infliximab)	Improved clinical response Reduced flare symptoms Reduced or postponed need for surgery Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ustekinumab for treatment of moderate to severe ulcerative colitis	Patients in whom moderate to severe active ulcerative colitis (UC) has been diagnosed	Patients with UC have abnormally and chronically activated immune systems in the absence of any known invader, leading to periodic bouts of abdominal pain, diarrhea, and rectal bleeding. Available therapies for UC may become less effective over time, have long-term side effects, and fail to adequately control symptoms in many patients, contributing to poor quality of life. UC is typically treated with anti-inflammatory drugs with varied success, and investigators have not found a long-term cure or strategy besides surgery to prevent periodic disease flares. Ustekinumab is a human interleukin-12 and interleukin-23 inhibitor under evaluation for intravenous induction therapy and subcutaneous injection maintenance therapy of moderate to severe ulcerative colitis. In a clinical trial, ustekinumab is administered as an intravenous infusion (130 mg or 6 mg/kg) for initial induction therapy and subsequently for maintenance therapy, 90 mg, by subcutaneous injection, every 8 or 12 weeks. Janssen Research & Development unit of Johnson & Johnson, New Brunswick, NJ Phase III trial ongoing; FDA approved for psoriasis and psoriatic arthritis	Azathioprine Cyclosporine Integrin receptor antagonists (e.g., (vedolizumab) Mercaptopurine Tumor necrosis factor (TNF)-alpha inhibitors	Increased remission rates Reduced relapse rates

Table 12. AHRQ Priority Condition: 12 Pregnancy, Including Preterm Birth: 7 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bi-directional communication (SmartMoms) for management of weight in pregnant women	Pregnant women who have a body mass index of 25 kg/m^2 or more	Pregnant women in the U.S. are at increased risk of exceeding pregnancy weight goals at term as recommended by Institute of Medicine guidelines, leaving mother and child susceptible to poor postpartum health outcomes. SmartMoms is a pregnancy weight–management program consisting of screening visits, weight-management advice, 2nd and 3rd trimester health testing, and postnatal followup. The most recent SmartMoms intervention involves weekly delivery of weight-management strategies from a counselor via a smartphone. Patients will also be asked to submit weight data (using a provided scale) and nutritional information via smartphones. Pennington Biomedical Research Center, Baton Rouge, LA, in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases and Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada Phase III trial ongoing	Other perinatal weight-management strategies	Improved maternal and fetal health outcomes Improved perinatal weight management Reduced morbidity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Family Nurture Intervention for treatment of depression and anxiety in mothers of preterm infants	Mothers of infants delivered in hospital environments between 26 and 34 weeks' postmenstrual age	Depression and anxiety are pronounced in mothers who have delivered a premature infant. Postpartum depression in these women has an estimated prevalence as high as 70%. Additionally, the immediate separation of mothers and premature infants who cannot be discharged home, along with infants' prolonged hospitalization in neonatal intensive care units (NICUs), can exacerbate these disorders. Early postnatal interventions are needed for these women. Recent research suggests that early maternal mental health intervention can positively affect mental health outcomes for children, preventing or minimizing depressive disorder symptoms in adolescence and adulthood. The Family Nurture Intervention (FNI) is a multifaceted behavioral program that attempts to address mental health disorders in mothers of preterm infants while mother and infant are still inpatients. FNI emphasizes extended treatment in conjunction with the Calming Cycle hypothesis, a theory that repeated mutual resolution of mother and infant stress and discomfort resolves stress more rapidly and lowers overall discomfort. The program incorporates elements of traditional nurturing and kangaroo care (focusing on skin-to-skin contact), along with techniques including odor-cloth exchange, and vocal soothing; FNI also involves outreach to other family members, providing them with tools to support the mother and newborn after inpatient release. In clinical trials, FNI is facilitated by specially trained nurture specialists, often former NICU nurses, and is offered to mother-infant pairs when the infant is born in the hospital as a singleton or twin at 26 to 34 weeks' gestation. Intervention efficacy is measured by psychological and neurobehavioral assessments, along with electroencephalogram and echocardiogram recordings. Colombia University College of Physicians and Surgeons, New York, NY Unphased trials ongoing	Kangaroo care Standard NICU care	Decreased adolescent and adult depression symptoms Improved overall family bonding, interaction, and support Reduced postpartum anxiety Reduced postpartum depression Shortened NICU stays Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gonadotropin-releasing hormone antagonist (Elagolix) for treatment of endometriosis	Patients in whom endometriosis has been diagnosed	Endometriosis is a painful disorder in which endometrium grows outside the uterus, commonly in the ovaries, bowel, or tissue lining the pelvis. Injectable gonadotropin-releasing hormone (GnRH) agonists can take up to several weeks to suppress symptoms for patients with endometriosis. Elagolix is a nonpeptide GnRH antagonist that has a rapid onset in suppressing hormones (stops ovulation and endometriosis symptoms) without a hormonal flare or injection-site reactions. Elagolix suppresses GnRH secretion from the pituitary gland, which lessens hormone-dependent symptoms. Titration might make it possible to maintain appropriate levels of estrogen, thus preventing menopausal-like hormonal levels and bone loss. In clinical trials, the drug is taken at 150 mg, once daily, or 200 mg, twice daily, orally. AbbVie, North Chicago, IL, in collaboration with Neurocrine Biosciences, Inc., San Diego, CA Phase III trials ongoing; also under study for uterine fibroids	Excision of endometrial growth and scar tissue Hormonal contraceptives (e.g., depot medroxyprogesterone acetate) Hysterectomy Peptide GnRH agonists and antagonists Steroids	Improved composite pelvic signs and symptoms score (measures dysmenorrhea, nonmenstrual pelvic pain, dyspareunia, pelvic tenderness, and induration) Improved patient global impression of change Less pain (visual analog scale) Maintained bone mineral density Improved quality of life
Off-label cytomegalovirus hyperimmune globulin (Cytogam) for prevention of congenital cytomegalovirus infection in pregnant women	Pregnant women in whom primary cytomegalovirus (CMV) infection has been diagnosed	Pregnant women who become newly infected with CMV during pregnancy risk passing the infection to the fetus, which may cause pregnancy loss or disabilities (e.g., deafness, psychomotor disability) after birth. No standard treatment is available for pregnant women with a primary CMV infection. CMV hyperimmune globulin (Cytogam®) is an immune globulin G (IgG) containing a standardized amount of CMV antibody pooled from donated human plasma. It may reduce the risk of fetal infection when given to the pregnant woman. It is administered intravenously, 100 mg/kg. Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD Phase III trial ongoing	Antiviral (e.g., ganciclovir) administered to infant after birth	Improved cognitive and motor skills for infant Improved survival for fetus and neonate Reduced incidence of sensorineural hearing loss in infant Reduced neonatal infectious morbidity (e.g., sepsis, pneumonia) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Recombinant antithrombin (ATryn) for treatment of preterm preeclampsia	Pregnant women with early onset preterm preeclampsia (between 23 and 30 weeks' gestation)	Preeclampsia is a condition that occurs only during pregnancy and affects the placenta. It is characterized by abnormal development of blood vessels from the uterus to the placenta and can cause prematurity, fetal abnormality, and fetal death. Women with preeclampsia experience systemic inflammation and high blood pressure, which can potentially lead to stroke, seizure, organ failure, or death. Preeclampsia that does not result in death resolves after birth. If labor has to be induced early because of preeclampsia, preterm fetuses (before 37 weeks' gestation) are underdeveloped and at risk of complications. Conversely, pregnant women with preeclampsia have better outcomes with earlier delivery. Antihypertensive drugs may lower maternal blood pressure. ATryn is a recombinant antithrombin with anticoagulant effects. It is approved for preventing thromboembolic events in perioperative and peripartum patients with hereditary antithrombin deficiency. The manufacturer is seeking to expand ATryn's approved indication for treating preeclampsia. ATryn is administered by continuous infusion. Initial loading dose is 250 mg over 15 minutes followed by 2,000 mg over 24 hours for 7–14 days. rEVO Biologics, Inc., a subsidiary of LFB S.A., Les Ulis, France Phase III trial ongoing; FDA accepted investigational new drug application Mar 2014	Antihypertensive medication Induced labor Magnesium sulfate to temporarily stop seizures	Increased gestational age at delivery Reduced fetal morbidity Reduced fetal mortality Reduced maternal morbidity Reduced maternal mortality
Recombinant human Clara Cell 10kDa protein (CG100) for prevention of bronchopulmonary dysplasia	Preterm neonates in whom respiratory distress syndrome has been diagnosed	Preterm neonates may develop respiratory distress syndrome if their lungs have not fully developed before birth. To address this, preterm infants may receive corticosteroids to speed lung development and surfactants to supplement a deficiency. However, they may still require oxygen therapy and positive-pressure ventilation, which may injure the lungs by causing an inflammatory response. Infant patients who are still receiving oxygen by their original due date receive a diagnosis of bronchopulmonary dysplasia and may experience chronic respiratory morbidity (e.g., asthma, infections, rehospitalization). Recombinant human Clara cell 10kDa protein (CG100) is intended to supplement the most abundant protein in mucosal fluids, which is deficient in premature infants. It is administered as a single intratracheal dose to preterm infants. Therabron Therapeutics, Inc., Rockville, MD Phase II trial ongoing; FDA granted orphan drug status	Corticosteroids Surfactants	Reduced incidence of bronchopulmonary dysplasia Reduced morbidity (e.g., infection, asthma, hospitalization) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Retosiban for prevention or delay of preterm birth	Pregnant women who are experiencing preterm labor between 24 and 34 weeks' gestation	Preterm birth occurring before 37 weeks' gestation is a leading cause of infant morbidity and mortality. Available tocolytic agents to try to halt or delay preterm labor are not effective in many women and reportedly may delay birth by as little as 48 hours. For women who can safely delay labor and birth (i.e., those who do not have preeclampsia or uterine infections), treatment is needed to halt preterm labor and delay preterm birth. Retosiban is an oxytocin receptor antagonist that may be able to halt or delay preterm labor and birth by blocking oxytocin receptors in the placenta and inhibiting intracellular signaling pathways that lead to uterine contraction. It is administered by intravenous infusion at a dosage of 6 mg over 5 minutes followed by 6–12 mg/hour, depending on patient response, for 48 hours. GlaxoSmithKline, Middlesex, UK Phase III trial ongoing	Bed rest Hydration Tocolytic agents (e.g., beta-receptor agonist, calcium-channel blockers, COX-2 inhibitors, magnesium sulfate, nitric oxide donors)	Improved neonatal outcomes Prolonged time to delivery Reduced neonatal hospital stays Reduced neonatal intensive care unit use

Table 13. AHRQ Priority Condition: 13 Pulmonary Disease, Asthma: 23 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Adipose-derived mesenchymal stem cells for treatment of chronic obstructive pulmonary disease	Patients in whom chronic obstructive pulmonary disease (COPD) has been diagnosed	Patients with COPD develop progressive deterioration of lung function that often results in respiratory failure and death. Available treatment options only reduce the frequency and severity of exacerbations and slow the rate of deterioration. Treatments to improve the respiratory status of patients with COPD are needed. Autologous, adipose-derived mesenchymal stem cells purportedly adhere to damaged and inflamed areas in the lung. The cells purportedly secrete proangiogenic and antiapoptotic growth factors, such as vascular endothelial growth factor and hepatocyte growth factor, which could promote anti-inflammatory processes and vascular and tissue regeneration and could improve symptoms. Administered as an intravenous injection. StemGenex, La Jolla, CA Unphased trial starting	Glucocorticoids Long-acting anticholinergic agents Long-acting beta-2 agonists Prophylactic azithromycin Roflumilast	Improved lung function Reduced cost from exacerbations Reduced incidence of exacerbations Increased survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ataluren (Translarna) for treatment of nonsense mutation cystic fibrosis	Patients in whom cystic fibrosis (CF) due to a nonsense mutation (nmCF) has been diagnosed	No curative treatments exist for CF. Molecular treatments are being developed to reduce the mucus buildup and exacerbations that are hallmarks of the disease. Patients are also treated with antibiotics to manage infections. Treatments providing improved CF symptom management are needed. Ataluren (Translarna™) is a protein-restoration therapy designed to form full-length, functional cystic fibrosis transmembrane regulator (CFTR) protein in patients with nmCF. Nonsense mutations are the cause of CF in an estimated 10% of cases in the U.S. and Europe and more than 50% of CF cases in Israel. The drug is intended to improve lung function and in clinical trials is given orally, 10 mg/kg, 3 times daily. PTC Therapeutics, Inc., South Plainfield, NJ Phase III trials ongoing; FDA granted orphan drug status	Antibiotics Bilevel positive airway pressure ventilators Chest physiotherapy Gene therapies (viral vector or liposome delivery of normal CFTR) Lung transplant	Improved lung function Reduced need for additional therapies Increased survival Improved quality of life
Benralizumab for treatment of asthma	Patients in whom moderate persistent or severe uncontrolled asthma has been diagnosed	About 10% of patients with asthma do not respond to high doses of inhaled corticosteroids and long-acting beta-2 antagonists. Uncontrolled asthma can lead to hospitalization or death. Patients with severe asthma must take systemic corticosteroids that can lead to adverse events. Benralizumab is a monoclonal antibody that purportedly binds to the interleukin-5 receptor alpha (IL-5Rα), which is expressed on the surface of eosinophils, a type of leukocyte thought to play a key role in asthma and possibly other inflammatory respiratory diseases. Benralizumab bound to the surface of eosinophils is thought to subsequently deplete eosinophils by inducing antibody-dependent cellular cytotoxicity, leading to symptom improvement. It could be used in combination with corticosteroids and bronchodilator therapy. Administered as a subcutaneous injection of 100 mg, every 4 weeks for the 1st 3 cycles and every 8 weeks thereafter. Medimmune subsidiary of AstraZeneca, London, UK Phase III trials ongoing	Bronchial thermoplasty Inhaled corticosteroids Ipratropium Leukotriene modifiers Long- or short-acting beta agonists Omalizumab Theophylline	Improved asthma control Improved asthma exacerbation rate Fewer emergency room visits Reduced hospitalization Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Benralizumab for treatment of chronic obstructive pulmonary disease	Patients in whom chronic obstructive pulmonary disease (COPD) has been diagnosed	Patients with COPD develop progressive deterioration of lung function that often results in respiratory failure and death. Available treatment options only reduce the frequency and severity of exacerbations and slow the rate of deterioration. Treatments to improve the respiratory status of patients with COPD are needed. Benralizumab is a monoclonal antibody that purportedly binds to the interleukin-5 receptor alpha (IL-5Rα), which is expressed on the surface of eosinophils, a type of leukocyte thought to play a key role in COPD exacerbations and possibly other inflammatory respiratory diseases. Benralizumab bound to the surface of eosinophils is thought to subsequently deplete eosinophils by inducing antibody-dependent cellular cytotoxicity, leading to symptom improvement. Administered as a subcutaneous injection, 100 mg, every 4 weeks for the 1st 3 cycles and every 8 weeks thereafter. Medimmune subsidiary of AstraZeneca, London, UK Phase III trials ongoing	Azithromycin (off label) Glucocorticoids Long-acting anticholinergic agents Long-acting beta-2 agonists Roflumilast	Reduced cost due to exacerbations Reduced incidence or duration of exacerbations Increased survival Improved quality of life
Cysteamine (Lynovex) for adjunctive treatment of cystic fibrosis	Patients in whom cystic fibrosis (CF) has been diagnosed	No curative treatments exist for CF. Molecular treatments are being developed to reduce the mucus buildup and exacerbations that are hallmarks of the disease. Patients are also treated with antibiotics to manage infections. Treatments providing improved CF symptom management are needed. Cysteamine (Lynovex®) is a novel molecule purported to have mucolytic activity. It also purportedly improves lung function with broad-spectrum antibacterial activity that can penetrate biofilms to treat drug-resistant bacteria. In clinical trials, cysteamine was orally administered in gel capsule form; an inhalable dry powder is also being developed for chronic use. NovaBiotics, Ltd., Aberdeen, UK Phase I/II trial ongoing; Sept 2014, FDA granted orphan drug status	Antibiotics Mucolytics	Improved lung function Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Dupilumab for treatment of asthma	Patients in whom moderate persistent or severe uncontrolled asthma has been diagnosed	In the U.S., 25 million people have asthma; 10% to 20% of patients who have persistent or severe asthma do not respond to conventional beta-2-agonist/corticosteroid treatment. These treatments are not curative. Additionally, long-term use of these drugs may exacerbate bronchial inflammation and sensitivity and may increase risk of death. Asthma is a chronic inflammatory condition largely mediated by activation of Th2 cells, which secrete the cytokines interleukin (IL)-4, IL-5, IL-9, and IL-13 and promote immunoglobulin E (IgE) secretion from B cells, activation of mast cells, and airway inflammation. Dupilumab is a fully human monoclonal antibody that binds to IL-4R alpha and blocks the action of IL-4 and IL-13 cytokines. In a phase III trial, patients are receiving dupilumab, subcutaneously, every 2 weeks (loading plus double dose) for 52 weeks, in addition to current asthma controller medications. The exact dose was not specified; 2 doses (dose 1 and dose 2) are being tested. Regeneron Pharmaceuticals, Inc., Tarrytown, NY, and Sanofi, Paris, France Phase III trials ongoing; dupilumab is also being developed for treating atopic dermatitis, chronic sinusitis, and eosinophilic esophagitis	Leukotriene modifiers Long-acting beta-2-agonists (LABAs) with corticosteroids Mast cell stabilizers Oral corticosteroids Short-acting beta-2-agonists Theophylline	Improved asthma control Fewer emergency room visits Fewer hospitalizations Decreased mortality Improved quality of life
Endobronchial valve system (Zephyr) for treatment of heterogeneous emphysema	Patients in whom heterogeneous emphysema has been diagnosed	Treatment for advanced emphysema involves lung volume-reduction surgery, which has risk of serious complications; less invasive treatment options are needed. This implanted endobronchial valve system (Zephyr®) is intended as a minimally invasive treatment of hyperinflation in the lungs, using devices that purportedly reduce a patient's diseased lung volume without surgery. According to the company, the procedure involves placing "small, 1-way valves in targeted airways to direct the flow of air out of diseased portions of the lung." Clinicians typically place 3–4 valves per lobe during a procedure, and the total procedural time purportedly takes 15–30 minutes, depending on the number of valves placed. The valves are coated with medical-grade silicone to prevent tissue growth through the nitinol retainer. Pulmonx, Inc. (formerly Emphasys), Redwood City, CA Multicenter pivotal investigational device exemption clinical trial ongoing	Antibiotics Bronchodilators Corticosteroids Oxygen Pulmonary rehabilitation program Surgery (lung-reduction volume surgery, bullectomy, lung transplantation)	Improved lung function Improved activities of daily living Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Inhaled amikacin (Arikayce) for treatment of nontuberculous *Mycobacteria* infection	Patients in whom pulmonary nontuberculous mycobacterial (NTM) lung infection has been diagnosed	Most NTM infections are resistant to many common antibiotics, and NTM infection requires treatment with lengthy multidrug regimens; few effective treatments exist. Amikacin (Arikayce®), an approved antibiotic against a variety of NTM, is a semisynthetic aminoglycoside derived from kanamycin. It is being developed as a sustained-release formulation of amikacin encapsulated inside small fat particles using an optimized, investigational eFlow® Nebulizer System. Amikacin is intended to deliver higher levels of drug to the lungs than previously possible through existing formulations of amikacin while minimizing systemic exposure to the drug. Administration is via inhalation, 560 mg over 13 minutes, once daily. Insmed, Inc., Monmouth Junction, NJ Phase III trial ongoing; FDA granted qualified infectious disease product, orphan drug, fast-track, and breakthrough therapy statuses. Arikayce is approved for other indications and sometimes used off label for treating NTM, but existing formulation is not intended for that use.	Amikacin (injectable) Amoxicillin/clavulanate Capreomycin Clarithromycin Clofazimine Ethionamide Fluoroquinolones Imipenem/cilastatin Isoniazid Kanamycin Linezolid Pyrazinamide Streptomycin Terizidone Thioacetazone	Resolved abnormalities as seen on computed tomographic scan Improved rate of culture conversion to negative Improved 6-minute walk distance and oxygen saturation Extended time before need for rescue antimycobacterial drugs
Injectable proenzyme of urokinase (LTI-01) for treating empyema	Patients in whom empyema has been diagnosed	Empyema is a collection of pus in the space between the lung and the inner surface of the chest wall. It is usually caused by bacterial pneumonia, surgery, or complications from trauma. Empyema complicates pneumonia and increases the risk of permanent lung damage or death. Patients require long-term antibiotic treatment and drainage; better treatment options are needed. LTI-01 is a proenzyme of urokinase that purportedly has fibrinolytic activity capable of degrading scar tissue in lungs of patients with empyema. It is thought to promote fluid drainage while minimizing bleeding risk and other complications. The drug is intended to replace surgery and ineffective use of off-label treatments. In a clinical trial, LTI-01 was administered with instillation of a chest tube. Lung Therapeutics, Inc., Austin, TX Phase I trial planned; FDA granted orphan drug status Dec 2014	Antibiotics Chest tube Surgery (decortication)	Reduced duration of drainage Reduced duration of oxygen therapy Reduced duration of intravenous antibiotic therapy Reduced duration of fever Shorter hospital stay

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lebrikizumab for treatment of moderate to severe uncontrolled asthma	Patients in whom moderate to severe uncontrolled asthma has been diagnosed	Despite use of available therapies, some patients with asthma experience uncontrolled symptoms. Lebrikizumab is a humanized monoclonal antibody designed to block the activity of interleukin-13 (IL-13), a contributor to asthma that is produced by T-helper type 2 cells; lebrikizumab may be more effective in patients with elevated serum periostin levels (a surrogate marker for elevated IL-13). In phase III trials, patients are receiving lebrikizumab subcutaneously. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials ongoing	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long-acting beta agonists Omalizumab (Xolair) Short-acting beta agonists Theophylline	Improved asthma control Improved asthma exacerbation rate Reduced emergency room visits Reduced hospitalization Improved quality of life
Lumacaftor/ivacaft or (Orkambi) for treatment of cystic fibrosis	Patients with cystic fibrosis (CF) who have the delta *F508-CFTR* gene mutation	No curative treatments exist for CF. Molecular treatments are being developed to reduce the mucus buildup and exacerbations that are hallmarks of the disease. Patients are also treated with antibiotics to manage infections. Treatments providing improved CF symptom management are needed. Lumacaftor (VX-809) is considered a corrector of the cystic fibrosis transmembrane regulator (*CFTR*) gene mutation; it is intended to increase CFTR protein regulator function by increasing its movement to the cell surface. It is given in combination with ivacaftor (Vertex's other CF drug). Administered orally, lumacaftor (400–600 mg), once or twice daily, with ivacaftor (250 mg), twice daily, in clinical trials. An oral fixed-dose regimen of 400 mg lumacaftor/250 mg ivacaftor, taken twice daily, is also being tested. Vertex Pharmaceuticals, Inc., Cambridge, MA FDA approved Jul 2015	Antibiotics Bilevel positive airway pressure ventilators Chest physiotherapy Gene therapies (viral vector or liposome delivery of normal CFTR) Lung transplant	Improved lung function Increased survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lung volume-reduction coil (RePneu) for treatment of emphysema	Patients with upper and/or lower lobe heterogeneous emphysema and/or multiple emphysematous lobes with focal tissue defects	Treatment for advanced emphysema involves lung volume-reduction surgery, which has risk of serious complications; less invasive treatment options are needed. RePneu™ is a minimally invasive procedure intended to reduce lung volume by implanting devices that compress the volume of diseased hyperinflated lung tissue to make room for healthier lung tissue to function. RePneu is a wirelike device described as a lung-volume nitinol preformed coil; it is intended to compress the volume of lung tissue where deployed and is delivered to the lung uncoiled (in a straight line) using a bronchoscope and fluoroscopic visualization (with patient under conscious sedation or general anesthesia). About 10 coils are delivered during a procedure; once deployed in the desired locations of the diseased alveolar tissue, the catheter is retracted and the coils regain their original curved shape, pulling and compressing diseased hyperinflated tissue to reduce the lung volume and enable healthy lung tissue to expand and contract, improving breathing. PneumRx, Inc., Mountain View, CA Phase III trial ongoing	Antibiotics Bronchodilators Corticosteroids Oxygen Pulmonary rehabilitation program Surgery (lung volume reduction surgery, bullectomy, lung transplantation)	Improved lung function, physical endurance, and activities of daily living Improved scores in St. George's Respiratory Questionnaire (which measures impaired health and perceived well-being in airways diseases)
Lysophosphatidic acid receptor antagonist (BMS-986020) for treatment of idiopathic pulmonary fibrosis	Patients in whom idiopathic pulmonary fibrosis (IPF) has been diagnosed	IPF is a progressive, debilitating disease characterized by inflammation and scarring (fibrosis) in the lungs, with a median survival time from diagnosis of 2–5 years; 5-year survival rate is about 20%. 2 approved treatments are available to slow disease progression, however they do not cure IPF. BMS-986020 is a small-molecule antagonist to the lysophosphatidic acid receptor (LPA1), a G-protein–coupled receptor involved in lipid-mediated mitogenic signaling. The LPA1 signaling pathway is thought to play a pivotal role in mediating fibroblast migration and vascular leakage leading to abnormal healing and fibrosis associated with IPF pathogenesis. Inhibiting LPA1-mediated signaling could slow the progression of IPF. In a phase II trial, patients are receiving BMS-986020 600 mg, orally, once or twice daily. Bristol-Myers Squibb, New York, NY Phase II trial ongoing; FDA granted orphan drug status	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Methotrexate Nintedanib Penicillamine Pirfenidone Pulmonary rehabilitation Supplemental oxygen	Improved lung function measured by forced vital capacity Improved ability to perform activities of daily living Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Masitinib for treatment of severe asthma	Patients in whom severe, persistent asthma has been diagnosed	About 10% of patients with asthma do not respond to high doses of inhaled corticosteroids and long-acting beta-2 antagonists. Uncontrolled asthma can lead to hospitalization or death. Patients with severe asthma must take systemic corticosteroids that can lead to adverse events. Masitinib is an orally administered tyrosine kinase inhibitor that purportedly targets the activity of mast cells, which are involved in triggering asthma attacks. The drug purportedly targets mast cells through selectively inhibiting KIT, platelet-derived growth factor receptor, Lyn, and, to a lesser extent, fibroblast growth factor receptor 3. Masitinib is administered orally, 6 mg/kg, daily, in clinical trials. AB Science S.A., Paris, France Phase III trial ongoing; also under investigation for treating a wide variety of cancers and other indications, including amyotrophic lateral sclerosis, Alzheimer's disease, and rheumatoid arthritis	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long- or short-acting beta agonists Omalizumab (Xolair®) Theophylline	Improved asthma control Improved asthma exacerbation rate Fewer emergency room visits Reduced hospitalization Improved quality of life
Mepolizumab (Nucala) for treatment of chronic obstructive pulmonary disease	Patients in whom chronic obstructive pulmonary disease (COPD) has been diagnosed	Patients with COPD develop progressive deterioration of lung function that often results in respiratory failure and death. Available treatment options only reduce the frequency and severity of exacerbations and slow the rate of deterioration. Treatments to improve the respiratory status of patients with COPD are needed. Mepolizumab (Nucala®) is a humanized monoclonal antibody designed to bind and inhibit the activity of interleukin-5 (IL-5). IL-5 purportedly plays a crucial role in the maturation, growth, and chemotaxis (movement) of eosinophils, inflammatory white blood cells implicated in COPD exacerbations. In clinical trials, it is administered subcutaneously, 100 mg or 300 mg, once every 4 weeks. GlaxoSmithKline, Middlesex, UK Phase III trials ongoing	Azithromycin (off label) Glucocorticoids Long-acting anticholinergic agents Long-acting beta-2 agonists Roflumilast	Reduced cost due to exacerbations Reduced incidence or duration of exacerbations Increased survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mepolizumab (Nucala) for treatment of eosinophilic asthma	Patients in whom eosinophilic asthma has been diagnosed	Eosinophilic asthma occurs in about 30% of patients with severe uncontrolled asthma. Uncontrolled asthma can lead to hospitalization or death. Patients with severe asthma must take systemic corticosteroids that can lead to adverse events. Mepolizumab (Nucala®) is a humanized monoclonal antibody designed to bind and inhibit the activity of interleukin-5 (IL-5). IL-5 purportedly plays a crucial role in the maturation, growth, and chemotaxis (movement) of eosinophils, inflammatory white blood cells implicated in asthma and not found in the lungs under normal circumstances. Administered intravenously, 75 mg, or subcutaneously, 100 mg, every 4 weeks. GlaxoSmithKline, Middlesex, UK Phase III trials ongoing; Jun 2015, an FDA advisory committee unanimously recommended mepolizumab for add-on maintenance in patients 18 years or older with severe eosinophilic asthma; FDA decision date is Nov 4, 2015; also under investigation for treating chronic obstructive pulmonary disease (COPD)	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long-acting beta agonists Omalizumab (Xolair®) Short-acting beta agonists Theophylline	Improved asthma control Improved asthma exacerbation rate Fewer emergency room visits Reduced hospitalizations Improved quality of life
Nintedanib (Ofev) for treatment of idiopathic pulmonary fibrosis	Patients in whom idiopathic pulmonary fibrosis (IPF) has been diagnosed	IPF is a progressive, debilitating disease characterized by inflammation and scarring (fibrosis) in the lungs, with a median survival time from diagnosis of 2–5 years; 5-year survival rate is about 20%. Few approved treatments are available. Nintedanib is a tyrosine kinase inhibitor that has activity against vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor tyrosine kinases, which are thought to play a role in IPF pathogenesis. Nintedanib is intended for treating IPF and slowing of disease progression and symptoms. Administered orally, 150 mg, twice daily. Boehringer Ingelheim GmbH, Ingelheim, Germany FDA approved Oct 2014 for treating IPF	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Methotrexate Penicillamine Pirfenidone Pulmonary rehabilitation Supplemental oxygen	Improved lung function measured by forced vital capacity Improved ability to perform activities of daily living Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pirfenidone (Esbriet) for treatment of idiopathic pulmonary fibrosis	Patients in whom idiopathic pulmonary fibrosis (IPF) has been diagnosed	IPF is a progressive, debilitating disease characterized by inflammation and scarring (fibrosis) in the lungs, with a median survival time from diagnosis of 2–5 years; 5-year survival rate is about 20%. Few approved treatments are available. Pirfenidone (Esbriet®) is a small molecule that inhibits the synthesis of transforming growth factor–beta, which purportedly is involved in fibrosis, and tumor necrosis factor–alpha, which is involved in mediating inflammation. The drug is administered orally, 801 mg, 3 times daily. Genentech, Inc., San Francisco, CA, subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland FDA approved Oct 2014 for treating IPF	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Methotrexate Nintedanib Penicillamine Pulmonary rehabilitation Supplemental oxygen	Improved lung function measured by forced vital capacity Improved ability to perform activities of daily living Slowed disease progression Improved quality of life
Portable warm blood perfusion system (Organ Care System; OCS) for normothermic lung transplantation	Patients who require a lung transplant	About 1,750 lung transplantations were performed in the U.S. in 2012, with about 1,600 patients remaining on the national waiting list for lung transplants. Current methods of organ preservation during transplantation leave the organ susceptible to significant damage. Only 10% to 30% of available donor lungs are being used for transplant, and in 10% to 20% of patients who have undergone lung transplantation, the lungs are so severely damaged, the patient requires additional support therapies (i.e., ventilation, pharmacologic interventions). The development of new strategies to better preserve or improve the quality of donor lungs could affect the number of lungs available for transplantation. The Organ Care System (OCS) is designed to maintain the organ in a warm, functioning state outside of the body to optimize organ health and allow for continuous clinical evaluation. Through an internal gas supply, internal monitor, and pulsatile pumping system, OCS purportedly provides blood oxygenation and flow, warms the lung as necessary, maintains humidity, and protects the lung from contamination from the time of removal from the donor to implantation in the recipient. TransMedics, Inc., Andover, MA Phase III trials ongoing	Cold-storage preservation Xvivo Lung Perfusion System	Increased graft survival Decreased graft dysfunction Increased use of available organs Reduced total cost of care Improved patient outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Portable warm blood perfusion system (Xvivo Perfusion System; XPS) for normothermic lung transplantation	Patients awaiting lung transplant	About 1,750 lung transplantations were performed in the U.S. in 2012, with about 1,600 patients remaining on the national waiting list for lung transplants. Current methods of organ preservation during transportation from donor to recipient leave the organ susceptible to significant damage. Only 10% to 30% of available donor lungs are being used for transplantation, and in 10% to 20% of patients who have undergone lung transplantation, the lungs are so severely damaged, the patient requires additional support therapies (i.e., ventilation, pharmacologic interventions). The development of new strategies to better preserve or improve the quality of donor lungs could increase the number of lungs available for transplantation. Donor lungs that might otherwise not be usable are housed in the Xvivo (XPS™) perfusion system, which is a sterile, normothermic, perfusion system that uses mechanical ventilation with controlled perfusion flows and pressures in the pulmonary vasculature, with the restorative Steen Solution™. The XPS is purported to recondition donor lungs and increase the pool of lungs suitable for transplantation. XVIVO Perfusion AB, Göteborg, Sweden FDA approved Aug 2014	Cold-storage preservation Organ Care System	Increased graft survival Decreased graft dysfunction Increased use of available organs Reduced total cost of care Improved patient outcomes
Reslizumab (Cinquil) for treatment of eosinophilic asthma	Patients in whom eosinophilic asthma has been diagnosed	Eosinophilic asthma occurs in about 30% of patients with severe uncontrolled asthma. Uncontrolled asthma can lead to hospitalization or death. Patients with severe asthma must take systemic corticosteroids that can lead to adverse events. Reslizumab (Cinquil™) is a humanized monoclonal antibody designed to bind and inhibit the activity of interleukin-5 (IL-5). IL-5 purportedly plays a crucial role in the maturation, growth, and chemotaxis (movement) of eosinophils, inflammatory white blood cells implicated in asthma and not found in the lungs under normal circumstances. Administered intravenously, 0.3 mg/kg or 3 mg/kg, once every 4 weeks, for a total of 4 doses. Teva Pharmaceutical Industries, Ltd., Petah-Tikva, Israel Phase III trial ongoing; Jun 2015, FDA accepted biologics license application; FDA decision date set for Mar 2016	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long-acting beta agonists Omalizumab Short-acting beta agonists Theophylline	Improved asthma control Improved asthma exacerbation rate Fewer emergency room visits Reduced hospitalizations Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Simtuzumab for treatment of idiopathic pulmonary fibrosis	Patients in whom idiopathic pulmonary fibrosis (IPF) has been diagnosed	IPF is a progressive, debilitating disease characterized by inflammation and scarring (fibrosis) in the lungs, with a median survival time from diagnosis of 2–5 years; 5-year survival rate is about 20%. 2 approved treatments are available to slow disease progression; however, they do not cure IPF. Simtuzumab (GS-6624) is a monoclonal antibody that blocks the activity of the enzyme lysyl oxidase-like 2 (LOXL2). LOXL2 is involved in the biogenesis of connective tissue and promotes collagen fiber crosslinking. Inhibiting LOXL2 could slow the progression of IPF. In phase II trials, patients are receiving simtuzumab subcutaneously, 125 mg, weekly, for up to 254 weeks. Gilead Sciences, Inc., Foster City, CA Phase II trials ongoing; FDA granted orphan drug status Apr 2011; simtuzumab is also being developed for treating colorectal and pancreatic cancers, liver fibrosis, and myelofibrosis	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Methotrexate Nintedanib Penicillamine Pirfenidone Pulmonary rehabilitation Supplemental oxygen	Improved lung function measured by forced vital capacity Improved ability to perform activities of daily living Slowed disease progression Improved quality of life
Tralokinumab for treatment of asthma	Patients in whom moderate persistent or severe uncontrolled asthma has been diagnosed	About 10% of patients with asthma do not respond to high doses of inhaled corticosteroids and long-acting beta-2 antagonists. Uncontrolled asthma can lead to hospitalization or death. Patients with severe asthma must take systemic corticosteroids that can lead to adverse events. Tralokinumab is a human monoclonal antibody that purportedly binds and neutralizes interleukin-13 (IL-13), a key cytokine thought to be central to asthma pathogenesis. In clinical trials, tralokinumab was administered subcutaneously, 300 mg, every 2 weeks. Medimmune subsidiary of AstraZeneca, London, UK Phase III trials ongoing	Bronchial thermoplasty Inhaled corticosteroids Ipratropium Leukotriene modifiers Long- or short-acting beta agonists Omalizumab Theophylline	Improved asthma control Improved asthma exacerbation rate Fewer emergency room visits Reduced hospitalization Improved quality of life

Table 14. AHRQ Priority Condition: 14 Substance Abuse: 15 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Buprenorphine implants (Probuphine) for treatment of opioid dependence	Patients in whom opioid dependence has been diagnosed	Many patients with opioid dependence attempt abstinence, but relapse rates remain high. This intervention uses subdermal buprenorphine implants, administered either alone or after sublingual buprenorphine-naloxone tablet induction. Buprenorphine is a partial agonist of opioid receptors; it binds more strongly to receptors in the brain than other opioids and may reduce reaction of opioids when in system. In clinical trials, patients received four 80 mg buprenorphine implants simultaneously, intended to remain implanted for 6 months. Braeburn Pharmaceuticals subsidiary of Apple Tree Partners, Princeton, NJ (licensee) Titan Pharmaceuticals, Inc., South San Francisco, CA (manufacturer) Phase III trials completed; Apr 2013, FDA issued complete response letter requesting more efficacy data; manufacturer plans to resubmit new drug application with additional data in late 2015	Opioid maintenance/ replacement therapy (e.g., buprenorphine, methadone, naltrexone) Psychotherapy (e.g., cognitive behavior therapy)	Resolution of problems with adherence, diversion Reduced illicit use of opioids Improved health outcomes associated with abstinence Improved quality of life
Evzio for emergency treatment of opioid overdose by nonclinicians	Patients in whom an opioid overdose is known or suspected	According to recent data from the U.S. Centers for Disease Control and Prevention, more than 16,000 deaths a year are attributable to opioid analgesics; this total is estimated to represent almost 75% of all pharmaceutical-overdose deaths. Most fatal opioid overdose events occur outside of controlled health care environments, in the presence of lay persons who may not be equipped with or trained to use emergency intervention tools and medications commonly used by professionals. An unmet need exists for simple, safe, and effective interventions for use in treating opioid overdoses in these situations. Evzio™ is a naloxone auto-injector device approved for emergency use in suspected cases of opioid overdose. Each device is equipped with a battery-powered electronic voice instruction system to direct laypersons in its use. Each Evzio device contains a single dose of 0.4 mg naloxone, delivered as a 0.4 mg / 0.4 mL naloxone hydrochloride injection; in the event of electronic voice instruction system failure, the injection can still be delivered. The device is also available in “trainer” version, identical to the full model, but without an injection needle component or naloxone dose. Retail packages include 2 single-dose devices and 1 trainer device. kaléo, Richmond, VA Apr 2014, FDA approved Evzio for emergency treatment of known or suspected opioid overdose	Immediate professional medical care Intranasally delivered naloxone for nonclinician use (investigational) Naloxone emergency kits	Reduced opioid overdose mortality rate

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Handheld, portable fingerprinting device (Intelligent Fingerprinting Technology) to detect substance abuse	Individuals suspected of illicit drug use	Detection of drugs and their metabolites in body fluids (e.g., blood, urine, saliva) is limited by invasiveness, biohazard risks, cross reactivity with other substances in the samples, a requirement for cold or frozen sample transport and storage, susceptibility to contamination leading to false positives, and the potential for a person to undermine the test. To address these limitations, a manufacturer has developed Intelligent Fingerprinting Technology, a handheld fingerprint drug testing device that analyzes the minute traces of sweat deposited in subjects' fingerprints. According to the manufacturer, the technology detects drug metabolites, not the drug itself. Additionally, the company purports that samples are quick and easy to collect, are impossible to cheat, are stable at room temperature, and do not require additional sample preparation. The company is positioning this product for use by law enforcement, and in workplaces and institutions (e.g., prisons, the military). Intelligent Fingerprinting, Norwich, UK (developer) SmartStart, Inc., Grapevine, TX (U.S. development partner) Addoz Oy, Forssa, Finland (clinical trial partner) University of Eastern Finland, Joensuu (clinical trial partner) Unregistered clinical trial (announced by Intelligent Fingerprinting) initiated in 2014	Other body fluid testing (urine, saliva, blood) Field sobriety tests	Improved detection of illicit substances Reduced invasiveness of drug testing Reduced turnaround time for drug testing Reduced biohazard risk Reduced risk of cross reactivity Improved health outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interactive text messaging program for prevention of hazardous alcohol use	Adolescents and young adults at risk for hazardous alcohol consumption or in whom high-risk alcohol consumption behaviors have been diagnosed	According to the U.S. Centers for Disease Control and Prevention and the National Institute on Alcohol Abuse and Alcoholism, hazardous alcohol use accounts for nearly 80,000 deaths and an economic cost of over $220 billion. The most common form of hazardous alcohol use, binge drinking, was the direct cause of more than half of those deaths and is also a risk factor for many other adverse health outcomes, including motor-vehicle crashes, suicides, and fetal alcohol syndrome. Binge drinking also encompasses half of the total alcohol consumption in the U.S., and 90% of alcohol consumed by underage youths and young adults. An unmet need exists for effective interventions and delivery methods, addressing these populations that effectively prevent hazardous drinking behaviors and promote responsible attitudes towards alcohol consumption. This intervention, a targeted program based around 3 established health behavior models, uses an interactive text message system cued to high-risk binge drinking periods and includes followup messages to promote positive alcohol use behavior (e.g., motivational messages, abstinence support, and passive positive reinforcement) and redirect negative alcohol use behavior (e.g., goal support, goal setting, and resistance support). In an ongoing clinical trial, high-risk young adults admitted to emergency departments received regular messages and real-time response-based feedback on Thursdays, to promote positive behaviors over weekends, with followup messages and queries on Sundays. Multiple investigators and developers Brown University, Providence, RI HealthStratica, LLC, Pittsburgh, PA (commercial licensee and developer) University of Nebraska-Lincoln University of Pittsburgh School of Medicine, PA (primary clinical trial site) Phase III trial ongoing	In-person behavioral therapy In-person educational and informational sessions	Increased responsible alcohol consumption attitudes Reduced alcohol consumption-related hospitalizations Reduced alcohol consumption-related adverse patient outcomes Reduced hazardous alcohol consumption Improved patient quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Intranasal naloxone spray for emergency treatment of opioid overdose by nonclinicians	Patients in whom an opioid overdose is known or suspected	According to recent data from the U.S. Centers for Disease Control and Prevention, more than 16,000 deaths a year are attributable to opioid analgesics; this total is estimated to represent almost 75% of all pharmaceutical-overdose deaths. Most fatal opioid overdoses occur outside of controlled health care environments, in the presence of laypeople who may not be equipped with or trained to use emergency medications commonly used by professionals. An unmet need exists for simple, safe, and effective interventions for treating opioid overdoses in these situations. Naloxone nasal spray is a single-use intervention intended for emergency use in suspected opioid overdoses. The device purportedly provides a unit dose (0.4 mg) of naloxone, via a safe, disposable, intranasal delivery system. AntiOp, Inc., Lexington, KY (original developer) Indivior, Inc., Richmond, VA (licensee and manufacturer) AntiOp completed a rolling new drug application (NDA) in early 2015, and subsequently sold all technology rights to Indivior; Aug 2015, FDA accepted NDA submission with priority review status; Jul 2014, FDA granted fast-track status	Evzio® Immediate professional medical care Naloxone emergency kits	Reduced mortality
Noninvasive trimethylamine test (TMA SIFT-MS breath analysis) for diagnosis of acute alcoholic hepatitis	Patients suspected of having acute alcoholic hepatitis or chronic or nonchronic liver disease	Acute alcoholic hepatitis is an inflammatory liver disease caused by excessive alcohol consumption. Symptoms of acute alcoholic hepatitis include general discomfort, liver enlargement, and elevated liver enzyme levels; these symptoms are also present in other liver diseases, complicating diagnosis. Concentrations of various volatile organic compounds (VOCs) also are elevated in the breath of patients with acute alcoholic hepatitis and other liver diseases. The only methods of differentiating acute alcoholic hepatitis from other diseases involve invasive blood assays and liver biopsies. Trimethylamine (TMA) has been identified as a VOC whose distinctly elevated concentration in patients with acute alcoholic hepatitis may make it a diagnostic marker. In a prospective clinical trial, noninvasive breath analyses of TMA concentrations via selected-ion flow-tube mass spectrometry (SIFT-MS) were successfully used to distinguish patients with acute alcoholic hepatitis from healthy patients and patients with other liver diseases, and a combined TMA plus pentane (TAP) score accurately predicted a diagnosis of alcoholic hepatitis. Cleveland Clinic, Cleveland, OH (investigators) Clinical trial completed	Blood assay Liver biopsy (to conduct liver enzyme function tests)	Faster diagnosis of disease Reduced cost of care Improved quality of life (by advancing appropriate treatment)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label baclofen for treatment of alcohol use disorder	Patients in whom alcohol use disorder has been diagnosed	Only 36% of patients with alcohol use disorder experience full remission using available therapy options. Improved treatment options are needed. Baclofen is a derivative of gamma-aminobutyric acid (GABA) that acts as an agonist at GABA-B receptors. In alcohol-dependent individuals, data suggest that baclofen may decrease alcohol intake, enhance abstinence time, reduce alcohol craving, and minimize the signs of alcohol withdrawal syndrome. It also may not be habit forming. Some studies also suggest that this agent may be effective in patients with liver disease. In clinical trials, oral baclofen has been tested at oral doses of 5–200 mg, daily. Numerous investigators, including the National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, and Ethypharm, Saint-Cloud, France Multiple phase II, III, and IV trials ongoing; Oct 2003, FDA approved oral baclofen (as Kemstro) for treating signs and symptoms of muscle spasticity resulting from multiple sclerosis	Acamprosate Benzodiazepines Cognitive behavior therapy Disulfiram Gabapentin Naltrexone Psychotherapy	Reduced alcohol consumption Increased abstinence rates Decreased alcohol craving Decreased alcohol withdrawal symptoms
Off-label baclofen for treatment of cocaine dependence	Patients in whom a cocaine dependence has been diagnosed	The National Survey on Drug Use and Health estimated that in 2008, 1.9 million people had used cocaine within the past month. Similar surveys have estimated that up to 34 million Americans have tried cocaine at least once. Regular cocaine use can lead to dependence, which has been demonstrated to lead multiple adverse effects, including stroke, heart attack, rhabdomyolysis, sexual dysfunction, and fatal overdose. Investigators have not found a universally effective medication for treating cocaine dependence. Baclofen is a gamma-aminobutyric acid (GABA) derivative that acts as an agonist at GABA-B receptors. In cocaine-dependent patients, baclofen may decrease cocaine consumption, increase duration of abstinence, and reduce cravings for cocaine. In clinical trials, patients are administered baclofen orally at dosages up to 60 mg, daily, for up to 7 weeks. National Institute on Drug Abuse, Bethesda, MD University of Pennsylvania, Philadelphia Phase II trial ongoing; Oct 2003, FDA approved oral baclofen (as Kemstro) for treating signs and symptoms of muscle spasticity resulting from multiple sclerosis	Cognitive behavior therapy Modafinil Off-label pharmacotherapy (e.g., disulfiram) Psychotherapy Other GABAergic medications (i.e., tiagabine)	Reduced reward associated with cocaine use Reduced cocaine consumption Reduced relapse Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label intranasal oxytocin for treatment of alcohol use disorder	Patients in whom alcohol use disorder has been diagnosed	Only 36% of patients with alcohol use disorder experience full remission using available therapies. Additionally, these patients often have comorbid social deficits and mental health disorders. An unmet need exists for effective interventions that address primary symptoms of alcohol use disorder, including cravings and overconsumption, as well as secondary and comorbid symptoms. Preliminary studies have found that oxytocin administration correlates with reduced alcohol consumption and withdrawal symptoms among patients with alcohol use disorders. Release of oxytocin, a hormone, is also associated with improved social cognition and may alleviate social deficits in impaired patients. Researchers purport that intranasally administered oxytocin may be a safe, effective single or chronic treatment for alcohol use disorder. Separate studies are investigating intranasal oxytocin's efficacy for reducing alcohol cravings, alcohol consumption, and alcohol use withdrawal symptoms. In clinical trials, intranasal oxytocin is administered at dosages up to 40 IU; dosage protocols range between 1 and 6 daily administrations, for up to 12 weeks. Medical University of South Carolina, Charleston National Institutes of Health, Bethesda, MD San Francisco Veterans Affairs Medical Center, San Francisco, CA University of North Carolina, Chapel Hill University of California, San Francisco Phase I, II, and IV trials ongoing; FDA approved oxytocin for inducing labor, producing uterine contractions during the 3rd stage of labor, and controlling postpartum bleeding or hemorrhage	Acamprosate Benzodiazepines Disulfiram Gabapentin Naltrexone Psychotherapy	Reduced alcohol consumption Reduced alcohol cravings Reduced alcohol withdrawal symptoms Reduced comorbid social cognition deficits Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label mifepristone (Mifeprex) for treatment of alcohol use disorder	Patients in whom alcohol use disorder has been diagnosed	Only 36% of patients with alcohol use disorder experience full remission using available therapy options. Improved treatment options are needed. Research has suggested that pharmacotherapy efficacy is linked to the protracted abstinence phase, a phase in which impaired glucocorticoid receptor feedback and other central nervous system dysregulation can influence alcohol relapse. Mifepristone is a glucocorticoid receptor antagonist and steroidal antiprogestogen. Because alcohol dependence has been associated with glucocorticoid hormone hyperactivity and because glucocorticoid receptors have been found to mediate adaptation to environmental challenges and stress, mifepristone may have a use in reducing alcohol dependence. In ongoing clinical trials for treating alcohol use disorders, mifepristone is administered orally, 600 mg/day, for 1 week. The Scripps Research Institute, La Jolla, CA Phase II trial ongoing; Sep 2000, FDA approved mifepristone (as Mifeprex®) for the medical termination of intrauterine pregnancy through 49 days' pregnancy; Feb 2012, FDA also approved mifepristone (as Korlym®) for treating hypoglycemia in patients who have Cushing's syndrome	Acamprosate Benzodiazepines Cognitive behavior therapy Disulfiram Gabapentin Naltrexone Psychotherapy	Reduced alcohol consumption Reduced relapse Improved health outcomes associated with abstinence Improved quality of life
Off-label mifepristone (Mifeprex) for treatment of cocaine dependence	Patients in whom cocaine dependence has been diagnosed	The National Survey on Drug Use and Health estimated that in 2008 there were 1.9 million current (past-month) cocaine users; similar surveys have estimated that up to 34 million Americans have tried cocaine at least once. Regular cocaine use can lead to dependence, which has been demonstrated to lead multiple adverse effects, including stroke, heart attack, rhabdomyolysis, sexual dysfunction, and fatal overdose. Investigators have not found a universally effective medication for treating cocaine dependence. Mifepristone (Mifeprex®) is a glucocorticoid receptor antagonist. Because cocaine dependence has been associated with glucocorticoid hormone hyperactivity and because the glucocorticoid receptor has been found to mediate adaptation to environmental challenges and stress, mifepristone may have utility in reducing cocaine dependence. In clinical trials, mifepristone is administered orally, at a dosage of 600 mg, 3 times weekly for 4 weeks. New York State Psychiatric Institute, New York The Scripps Research Institute, La Jolla, CA Phase II/III trial ongoing; mifepristone is FDA approved to end early pregnancy	Cognitive behavior therapy GABAergic medications (e.g., baclofen, tiagabine) Modafinil Off-label pharmacotherapy (e.g., disulfiram) Psychotherapy	Reduced reward associated with cocaine use Reduced cocaine consumption Reduced relapse Improved health outcomes associated with abstinence Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label ondansetron for treatment of alcohol use disorder	Patients in whom alcohol use disorder has been diagnosed	Only 36% of patients with alcohol use disorder experience full remission using available therapy options. Serotonin 5-HT_3 receptors are a novel therapeutic target for this population. Ondansetron is a serotonin 5-HT_3 receptor antagonist and is intended to exert its effects on alcohol dependency through cortico-mesolimbic dopamine system modulation. The 5-HT system has been found to be a major regulator of alcohol-consumption severity, which underpins the hypothesis that medications that affect the function of the 5-HT transporter may be viable treatments for this population. Research groups are independently studying ondansetron's efficacy for treating patients with alcohol use disorders of varying severity and with alcohol use disorder and comorbid mental health disorders. In clinical trials, ondansetron is administered to patients in oral tablets at various dosages, up to 16 mcg/kg, twice daily. Johns Hopkins University, Baltimore, MD National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD Stanley Medical Research Institute, Chevy Chase, MD University of Maryland, College Park University of Pennsylvania, Philadelphia University of Texas Southwestern Medical Center, Dallas University of Virginia, Charlottesville Phase III trials completed; phase II, III, and IV trials ongoing; Apr 1998, FDA approved ondansetron (as Zofran®) for treating chemotherapy-induced nausea and vomiting	Acamprosate Benzodiazepines Cognitive behavior therapy Disulfiram Gabapentin Naltrexone Psychotherapy	Improved health outcomes associated with abstinence Reduced alcohol consumption Reduced alcohol cravings Reduced relapse Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label topiramate (Topamax) for treatment of alcohol use disorder	Patients in whom alcohol use disorder has been diagnosed	Only 36% of patients with alcohol use disorder experience full remission using available therapy options. Additionally, these patients often have comorbid substance abuse and mental health disorders. GABA receptors offer a novel therapeutic target for these patients. Topiramate (Topamax®) is a GABAergic anticonvulsant and mood stabilizer that purportedly is an effective treatment for reducing alcohol consumption in patients with heavy drinking behaviors or alcohol use disorder, including those with comorbid bipolar disorder, post-traumatic stress disorder, and traumatic brain injury. Topiramate is also hypothesized to have increased efficacy in reducing alcohol consumption in patients with heavy drinking behaviors who have certain genetic markers. In completed and ongoing clinical trials, topiramate is administered orally, at dosages up to 250 mg, daily, either alone, in combination with other drugs, or in combination with behavior therapy. Investigators include U.S. Department of Veterans Affairs, Washington, DC; National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD; University of California, San Diego; University of California, San Francisco; University of Cincinnati, Cincinnati, OH; University of Connecticut, Storrs; University of Pennsylvania, Philadelphia; and University of Virginia, Charlottesville Phase II, II/III, III, and IV trials ongoing; in 2014, a published meta-analysis determined that topiramate was superior to 2 standard alcohol use disorder medications for reducing alcohol consumption and cravings; Jan 1997, FDA approved topiramate (as Topamax) as adjunctive therapy for partial onset seizures	Pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone) Psychotherapy (e.g., cognitive behavior therapy)	Improved health outcomes associated with abstinence Reduced alcohol consumption Reduced alcohol cravings Reduced relapse Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label topiramate (Topamax) for treatment of cocaine dependence	Patients in whom cocaine dependence has been diagnosed	The National Survey on Drug Use and Health estimated that in 2008, there were 1.9 million current (past-month) cocaine users; similar surveys have estimated that up to 34 million Americans have tried cocaine at least once. Regular cocaine use can lead to dependence, which can lead to adverse effects including stroke, heart attack, rhabdomyolysis, sexual dysfunction, and fatal overdose. Investigators have not found a universally effective medication for treating cocaine dependence. Topiramate (Topamax®) is a GABAergic anticonvulsant and mood stabilizer that purportedly is an effective treatment for reducing cocaine use in patients with cocaine dependence. In clinical trials, patients received topiramate, administered in tablet form, at fixed or escalating dosages of 50, 100, 200, or 300 mg daily, alone or with an amphetamine psychostimulant (phentermine or dextroamphetamine). National Institute on Drug Abuse, Bethesda, MD New York State Psychiatric Institute, New York University of Kentucky, Lexington Phase II/III trial ongoing; Jan 1997, FDA approved topiramate (as Topamax) as adjunctive therapy for partial onset seizures; Jul 2012, FDA also approved combination topiramate-phentermine (as Qsymia®) as adjunctive therapy for chronic weight management in obese patients with 1 or more weight-related comorbidities	Modafinil Other GABAergic medications (e.g., baclofen, tiagabine) Talk therapy	Reduction in cocaine abuse relapse rates, as measured by patients' number of cocaine non-use days and cocaine-free weeks Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label zonisamide for treatment of alcohol use disorder	Patients in whom alcohol use disorder has been diagnosed	Only 36% of patients with alcohol use disorder experience full remission using available therapy options. Additionally, these patients often have comorbid substance abuse and mental health disorders. Multifaceted neuromodulators offer a novel therapeutic option for these patients. Zonisamide is a sulfonamide anticonvulsant demonstrated to also modulate GABAergic and glutamatergic neurotransmission. Purportedly, zonisamide reduces alcohol consumption in patients with heavy drinking behaviors or alcohol use disorder and can also ameliorate the symptoms of alcohol withdrawal syndrome. In completed and ongoing clinical trials, zonisamide is administered orally, at dosages up to 500 mg daily. Multiple investigators including Boston Medical Center, Boston, MA; U.S. Department of Defense, Arlington, VA; University of Connecticut Health Center, Farmington; National Institute on Alcohol Abuse and Alcoholism (NIAAA), Bethesda, MD; and Yale University, New Haven, CT Phase II and III trials ongoing; Mar 2000, FDA approved zonisamide (as Zonegran) for adjunctive treatment of partial seizures in adults with epilepsy	Pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone) Psychotherapy (e.g., cognitive behavior therapy)	Improved health outcomes associated with abstinence Reduced alcohol consumption Reduced alcohol cravings Reduced alcohol withdrawal symptoms Reduced relapse Improved quality of life

Table 15. AHRQ Priority Condition: 15 Cross-Cutting: 9 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Digital medicines (Proteus Digital Health Feedback System) for chronic conditions requiring long-term drug therapy	Patients in whom long-term drug therapy is needed for chronic conditions	According to the World Health Organization, the average medication adherence rate among patients with chronic diseases in developed nations is only 50%. The Proteus Digital Health System™ (formerly the Raisin System), a form of smart-pill technology now called "digital medicine," is being used in an attempt to improve medication adherence by patients requiring ongoing medication for chronic diseases, such as tuberculosis, diabetes, heart failure, HIV, hepatitis C virus infection, and mental health disorders. This is an edible microchip affixed to oral tablets to monitor patient adherence; a wearable data recorder in the form of a skin patch captures drug consumption and vital statistics, reminds patients of missed doses, and transmits patient data to clinicians through a mobile device. Patients ingest the sensor with medication in a separate tablet or with sensor and medication co-encapsulated. Medication with embedded sensors must obtain individual FDA regulatory approval. Sensors are being ingested separately from oral medications in ongoing trials using the device to track medication adherence. Proteus Digital Health, Inc., Redwood City, CA Phase IV trial ongoing; FDA cleared the monitoring device Mar 2010; Jul 2012, the company also received FDA clearance for the ingestible sensor; unclear when product may be on market	Conventional oral drug therapy Patient medication reminders via telephone, text message, and/or email	Improved patient outcomes and disease management by maintaining adherence and consistent oral drug dosing

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
High-throughput DNA sequencers for genetic testing	Patients in need of genetic testing for diagnosis, pharmacogenetics, or treatment selection	Using genetic information in making diagnoses and treatment decisions has become increasingly common; however, the work-intensive and costly nature of traditional nucleic acid sequencing methods have limited the widespread implementation of methods that need large amounts of sequence data. Recent years have seen substantial improvements in the technologies used to sequence nucleic acids, potentially allowing more widespread use of approaches such as whole-genome sequencing. According to the National Human Genome Research Institute, the cost of generating a full human genomic sequence dropped from about $1 million in 2008 to about $6,000 in 2013. Illumina, Inc., San Diego, CA Nov 2013, the Illumina MiSeqDx DNA sequencer and Universal Kit reagents became the 1st high-throughput sequencing system cleared by FDA; the system was cleared through the agency's de novo classification process (a regulatory pathway for some novel low- to moderate-risk medical devices not substantially equivalent to an already marketed device)	1st-generation sequencing methods Single-gene assays	Improved diagnosis Improved treatment planning Improved pharmacogenetics
Induced hypothermia (emergency preservation and resuscitation) for cardiac arrest after trauma-induced blood loss	Patients who have been in cardiac arrest for less than 5 minutes due to blood loss from penetrating trauma (e.g., gunshot wound, knife wound, explosion injury)	Patients who are in cardiac arrest due to blood loss from trauma survive only about 10% of the time. Clinicians often have insufficient time to repair an injury and stop the bleeding before the patient has gone too long without oxygen. Induced hypothermia is a well-established tool to preserve function during procedures in which a patient's oxygen supply is interrupted. A new procedure under study, called emergency preservation and resuscitation (EPR), uses this concept for trauma victims. The patient's body is flushed with ice-cold 0.9% sodium chloride through an arterial catheter in the descending thoracic aorta and cooled to about 50 ºF (10 ºC). This must be done within 20–30 minutes of injury. The patient can be maintained in this state for about 1 hour while surgeons repair the injury. Using a cardiopulmonary bypass machine with a heat exchanger, blood is reintroduced to the patient gradually to prevent ischemia-reperfusion injuries. University of Pittsburg Medical Center, PA, in collaboration with University of Maryland, College Park; University of Pennsylvania, Philadelphia; Massachusetts General Hospital, Boston; University of Arizona, Tucson; and Oregon Health and Science University, Portland Phase II trial ongoing	Cardiopulmonary resuscitation Emergency thoracotomy	Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mobile platform (Triton Fluid Management System) to monitor blood loss during surgery	Patients undergoing surgery	Methods for monitoring a patient's blood loss during surgery include visual estimation, which can be inaccurate, and catheter-based monitoring, which is invasive and also can be inaccurate. Inaccurate estimations of blood loss during surgery can lead to patient complications, morbidity, mortality, and increased costs. Also, blood used for transfusions (as a result of inaccurately estimating a large amount of blood lost during surgery) is scarce and expensive. To address this limitation, a developer has created a mobile medical platform, Triton Fluid Management System (previously called Pixel 3 System), that is intended to be used with the iPad during surgery. Using the program and iPad camera, an OR team member scans surgical surfaces (e.g., surgical sponges) that are covered in blood, then sends the image to the "cloud" (remote server storage). Once the image is on the cloud server, the application's algorithms (similar to those used in facial recognition software) determine and estimate the amount of blood present in that sample, thereby potentially offering clinicians a more accurate assessment of the amount of blood the patient has lost. The device estimates total blood and hemoglobin losses and counts sponges. Gauss Surgical, Inc., Palo Alto, CA FDA cleared through the 510(k) de novo pathway May 2014	Catheter-based measuring Visual estimation Weight-based sponge measuring (i.e., gravimetric method)	Improved accuracy of estimated blood loss More appropriate transfusion decisionmaking Reduced costs by avoiding inappropriate transfusion Reduced morbidity and mortality
Noninvasive acoustic device (HS-1000) for monitoring intracranial pressure	Patients who may be experiencing increased intracranial pressure (ICP) due to brain surgery, infection, stroke, or trauma	Increased ICP may cause swelling, stroke, brain damage, or death. Methods for monitoring ICP are invasive—a surgeon must drill a hole in the patient's skull and insert an epidural sensor, intraventricular catheter, or subdural screw. These methods are used only when necessary because patients may develop secondary infections or bleeding. A noninvasive, acoustic monitor is under development. It is composed of disposable earbuds connected to an Android-based tablet for display. 1 earbud emits a tone at a specified frequency; the other detects the sound waves after they travel through the cranium. Proprietary software calculates the intracranial pressure in mm Hg based on the received transmission. The HS-1000 can be used continuously and can take up to 4 measurements per minute. Head Sense Medical, Ltd., Netanya, Israel Unphased trial ongoing; pilot trial completed	Epidural sensor Intraventricular catheter Subdural screw	Reduced ICP Reduced morbidity and mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Patient training and risk assessment program (MSHOP) for major abdominal surgery preparation	Patients who will undergo major abdominal surgery	Patients who will undergo surgery may wait weeks before the scheduled procedure takes place. During this time, some may prepare for the surgery and the care they will need after it; others spend this time worrying. Surgical outcomes and the length of the hospital stay could be affected by patient behavior in the weeks leading up to surgery. While many clinicians give ad-hoc advice about how to prepare and what to expect, standardized programs are often not in place. The Michigan Surgical and Health Optimization Program (MSHOP) is intended to improve patient outcomes after major abdominal surgery, especially for elderly and frail patients. It is a training program that focuses on 4 areas: exercise, improved lung health (including smoking cessation), good nutrition, and stress reduction. To help achieve these goals, patients are provided with a pedometer, spirometer, online exercise and smoking cessation log, and links to community resources and information. Clinicians use a smart phone-based app to assess surgical risks and potential complications with patients while deciding on a plan of action. The app incorporates patient x-rays and computed tomography scans, using analytic morphomics to predict risks. Collaboration between Michigan Surgical Quality Collaborative, Ann Arbor; Blue Cross and Blue Shield of Michigan, Lansing; and University of Michigan, Ann Arbor Pilot studies completed; expanding to 40 Michigan hospitals; received U.S. Centers for Medicare & Medicaid Services CMS Innovation award	Ad-hoc clinician advice Prehabilitation (i.e., physical therapy before surgery)	Fewer complications Improved surgical outcomes Reduced costs Shorter hospital stays after surgery

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Patient-based 3-D printed biomodels to aid surgical planning	Patients undergoing surgery with complex anatomical and functional considerations	Surgery performed on or near vital organs can increase the complexity of the procedure and the risk of negative outcomes. Examples of these procedures include tumor resection, neurosurgery, and cardiac surgery. Although some imaging techniques allow surgeons to visualize a patient's anatomy before and during surgery, benefits are sometimes limited by 2-dimensional (2-D) displays. Printed models are 3-dimensional (3-D) objects that can be manipulated and viewed from all angles. They can give surgeons the opportunity to practice the technique on each patient's specific anatomy before performing the real surgery. The individualized models might allow surgeons to foresee difficulties in the operation, perform the real operation more quickly, or train for a procedure in which they are less experienced. Each model is based on 3-D ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), or 3-D transesophageal echocardiography. Models can be printed with multiple materials and colors to distinguish anatomical features. Brigham and Women's Hospital, Boston, MA Children's Hospital of Illinois, Peoria Emory University Hospital, Atlanta, GA, with Materialise, Leuven, Belgium Shriners Hospitals Children, Chicago, IL, with Medical Modeling, Inc., Golden, CO SimPeds3D at Boston Children's Hospital, MA Tulane University, New Orleans, LA, with Medical Modeling Brigham and Women's Hospital requires 3-D printed models for planning facial transplants; SimPeds3D program is used in 12 pediatric hospitals worldwide; programs diffusing at multiple hospitals; model manufacturers can also print cranio-maxillofacial, orthopedic, cardiovascular, and pulmonary models	Standardized surgical models Virtual simulations	Decreased damage to nearby organs and tissues Improved surgical outcomes Reduced surgical time

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Radially branched deployment system (BranchPoint) for direct delivery of therapeutics to the brain	Patients with brain cancer or neurodegenerative disease who require direct therapy delivery	Patients with diseases of the brain (e.g., glioblastoma multiforme, Parkinson's disease) may have limited drug treatment options because many drugs cannot pass the blood-brain barrier. Multiple intracranial delivery systems such as straight-line catheter delivery or implanted reservoirs cannot deliver a drug to a large or specific area of the brain without using highly invasive techniques. The BranchPoint system purportedly can deliver a drug to multiple targets within the brain through 1 point of entry, reducing the risk of bleeding and stroke and increasing accuracy. The system uses a cannula with 1 port that can be radially rotated to reorient the port. A thin, bendable catheter is guided through the cannula and out of the port to targets of variable distance and coordinates within the brain. The design may reduce drug reflux associated with other catheter-based delivery methods. The BranchPoint is compatible with intraoperative MRI to guide the catheter and target drug delivery. Accurexa, Inc., Newark, DE Jun 2015, submitted application to FDA for 510(k) clearance	Implantable reservoirs containing the drug Straight-line catheter or cannula with multiple entry points	Improved accuracy of drug delivery targeting Reduced drug reflux through catheter/cannula insertion pathway Reduced incidence of stroke and bleeding Improved quality of life
T3 Monitor for early-warning detection in critically ill patients	Patients who require hospitalization in an intensive care unit (ICU)	Patients in an ICU may be connected to 10 or more monitoring systems at any given time, which medical professionals rely on to assess the progress and status of each patient. However, the multitude of monitoring platforms may lead to information overload. The T3 Monitor, which stands for "Tracking, Trajectory, Trigger," links and synthesizes data from these systems and presents the information on a single screen. The system also stores the information indefinitely, allowing clinicians to compare present data to historical data. This information can be readily accessed remotely via a portable, Internet-enabled device. The T3 Monitor purportedly allows for better decisionmaking, care-plan adjustment, and real-time, regular analysis. Etiometry, Inc., Boston, MA FDA granted 510(k) clearance Mar 2015; installed in multiple academic hospitals; novel risk-analysis algorithms under development by Etiometry	Multiple monitoring platforms	Improved care-plan adjustment Improved decisionmaking Improved patient outcomes

Section 2. Interventions Added Since Last Update: 91 Interventions

Table 16. AHRQ Priority Condition: 01 Arthritis and Nontraumatic Joint Disease: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ustekinumab (Stelara) for treatment of spondyloarthritis	Patients in whom spondyloarthritis (SpA) has been diagnosed	SpA is a group of chronic inflammatory autoimmune diseases. SpA may be axial (affecting the sacroiliac joints and spine) or peripheral (affecting joints of the lower extremities). Prevalence of SpA in the U.S. may be as high as 1% (more than 3 million people). Patients with untreated axial SpA may progress to ankylosing spondylitis (AS), which is diagnosed by the presence of radiographic sacroiliitis (inflammation of the sacroiliac joints). 1st-line treatment for SpA and AS is nonsteroidal anti-inflammatory drugs (NSAIDs), but they may be ineffective in some patients and are associated with gastrointestinal toxicity. Ustekinumab (Stelara®) is a monoclonal antibody that FDA has approved for treating psoriasis and psoriatic arthritis. Ustekinumab blocks the activity of the proinflammatory cytokines interleukin (IL)-12 and IL-23, which may be elevated in patients who have SpA or AS. In phase III trials, patients with SpA or AS will receive 45 or 90 mg ustekinumab, subcutaneously, at weeks 0 and 4, and every 12 weeks thereafter through 52 weeks. Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ Phase III trials ongoing	NSAIDs	Reduced disease progression Improved rate of Assessment of SpondyloArthritis International Society (ASAS) 40 response Improved quality of life

Table 17. AHRQ Priority Condition: 02 Cancer: 25 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Active cellular immunotherapy (DCVAC/OvCa) for prevention of recurrent ovarian cancer	Patients with stage III epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer who have undergone debulking surgery, are chemotherapy naïve and can be either platinum sensitive or platinum resistant	No maintenance therapies are approved to preserve remission in ovarian cancer treatment. The active cellular immunotherapy DCVAC/OvCa (DCVAC) is an autologous dendritic cell–based vaccine primed with tumor cells that were killed by cell-mediated immune response via high hydrostatic pressure. The vaccine is intended to induce an immune response to ovarian cancer cells, preventing or slowing recurrence. In clinical trials, DCVAC is administered via intradermal injection alone or in parallel with chemotherapy. Sotio a.s., Prague, Czech Republic, owned by investment firm PPF Group, N.V., Amsterdam, the Netherlands Phase II trials (SOV01, SOV02, and SOV03) ongoing; FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if BRCA1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Decreased recurrence rates Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
ADXS-HPV for treatment of human papillomavirus–induced anal cancer	Patients with invasive primary squamous, basaloid, or cloacogenic carcinoma of the anal canal	The incidence of anal cancer in the U.S. is rising and human papillomavirus (HPV) infection is associated with 90% of cases. Although localized anal cancer has a 5-year survival rate of 64% to 71% due to multiagent chemotherapy, the 5-year survival rate for patients with advanced disease falls to 21% to 43% because current treatment strategies have limited efficacy. An unmet need exists for innovative therapies for patients with anal cancer. ADXS-cHER2 biotechnology consists of an attenuated strain of *Listeria monocytogenes* (Lm), which is transfected with a high-copy plasmid expressing a chimeric protein made up of the HPV 16 E7 protein and listeriolysin O (LLO) fragments; the latter will enable Lm to secrete the fused antigen. The bioengineered Lm infects antigen-presenting cells (i.e., dendritic cells) in the patient and begins secreting the E7 antigen to stimulate a T-cell response against cells overexpressing E7, which will purportedly override Treg responses and kill tumor cells. In clinical trials, ADXS11-001 is administered intravenously, $1x10^9$ cfu, once every 28 days for 4 cycles. Advaxis, Inc., Princeton, NJ Phase II trials (BrUOG and ADXS001-06) ongoing; Aug 2013, FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Alkylating agent (e.g., mitomycin C) Antimetabolites (e.g., 5-fluorouracil) Platinum-based drugs (e.g., cisplatin)	Increased overall survival Increased progression-free survival Improved quality of life
Alisertib for treatment of small cell lung cancer	Patients with small cell lung cancer (SCLC) that has progressed after platinum-based chemotherapy	SCLC is an aggressive lung cancer that spreads rapidly to adjacent lymph nodes and distal organs. Each year, about 34,000 cases are reported in the U.S., and it has a very poor prognosis compared with other types of lung cancer. The 5-year survival rate is less than 5%. No therapeutic advances have been achieved against SCLC in 25 years, with topotecan being the only treatment option in the 2nd-line setting. Aurora kinase A is a serine/threonine kinase essential for the normal progression of the cell cycle. Although Aurora kinase A absence or loss of function causes cell-cycle arrest and apoptosis, its overexpression can result in uncontrolled cell proliferation. Alisertib is a small-molecule inhibitor that targets Aurora kinase A, causing cells to arrest in the G2/M phase and undergo apoptosis. In a phase II trial, patients are treated with alisertib in combination with paclitaxel. Alisertib is administered orally, 40 mg, twice daily, in a 3 days on/4 days off regimen for 3 weeks of a 28-day cycle. Millennium Pharmaceuticals subsidiary of Takeda Pharmaceutical Co., Ltd., Osaka, Japan Phase II trial (C14018) ongoing; Jul 2013, FDA granted orphan drug status	Chemoradiation therapy Platinum-based agents (e.g., carboplatin, cisplatin) Topoisomerase inhibitors (e.g., etoposide, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Atezolizumab for treatment of renal cell carcinoma	Patients with inoperable, locally advanced or metastatic renal cell carcinoma (RCC) who have not received systemic therapy	Patients with advanced RCC have limited 1st-line treatment options, and even after patients receive tyrosine kinase inhibitors, the disease will progress and is associated with a poor prognosis. A hallmark of cancer is its ability to evade an immune response. Atezolizumab (MPDL3280A) is a novel therapeutic that is intended to prevent immune tolerance of tumor cells. The drug's target is the programmed death-1 receptor ligand (PD-L1), which is frequently expressed in tumor microenvironments and purportedly leads to downregulation of T-cell activity via activation of the programmed death-1 immune checkpoint. Atezolizumab is a monoclonal antibody specific for PD-L1 and is intended to prevent an interaction between the ligand and its receptor, potentially limiting activation of the immune checkpoint. In trials, atezolizumab is tested in combination with bevacizumab. It is administered intravenously, 1,200 mg, on days 1 and 22 of a 48-day cycle. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trial (WO29637) ongoing	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab [ramucirumab; in development]) Antimetabolites (e.g., pemetrexed, gemcitabine) Immunotherapy (e.g., interferon-alpha , interleukin-2) mTOR inhibitors (e.g., everolimus, temsirolimus) Multikinase inhibitors (e.g., axitinib, pazopanib, sorafenib, sunitinib)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Atezolizumab for treatment of triple-negative breast cancer	Patients with unresectable, locally advanced or metastatic, triple-negative breast cancer who have not received 1st-line treatment	Triple-negative breast cancer (i.e., low expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2) is not amenable to endocrine therapy or treatment with any of the targeted agents developed for breast cancer. Thus, treatment presents a significant clinical challenge, and affected patients have a median survival of about 1 year. A hallmark of cancer is its ability to evade an immune response. Atezolizumab (MPDL3280A) is a novel therapeutic that is intended to prevent immune tolerance of tumor cells. The drug's target is the programmed death-1 receptor ligand (PD-L1), which is frequently expressed in tumor microenvironments and purportedly leads to downregulation of T-cell activity via activation of the programmed death-1 immune checkpoint. Atezolizumab is a monoclonal antibody specific for PD-L1 and is intended to prevent an interaction between the ligand and its receptor, potentially limiting activation of the immune checkpoint. In a phase III trial, atezolizumab is being tested in combination with nab-paclitaxel, and it is administered intravenously at an unspecified dose. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trial (WO29522) ongoing	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine, pemetrexed) PARP inhibitors (e.g., BMN 673, niraparib, olaparib [in development]) PD-1 antibodies (e.g., pembrolizumab [in development]) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloid (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous tumor cell vaccine (FANG) for treatment of melanoma	Patients with stage IIIc–IV melanoma in whom 2nd-line treatment is not recommended	Patients with advanced melanoma have a poor prognosis and few treatment options, suggesting a need for novel treatment options. The autologous tumor cell FANG™ vaccine is manufactured from a fragment of a patient's melanoma tumor obtained during debulking surgery. The cells are electroporated to introduce a plasmid expressing rhGMCSF and the bifunctional RNA interference (RNAi) effector, short hairpin (shRNA), to target furin convertase to downregulate endogenous TGF-beta 1 and 2. The GMCSF protein is a potent stimulator of the immune system, recruiting and activating antigen-presenting cells at the site of intradermal injection, thereby promoting antigen presentation. The furin bifunctional shRNA blocks furin protein production via mRNA degradation and translational inhibition. Furin is a protease responsible for cleaving the TGF-beta precursor into the active TGF-beta 1 and 2 isoforms, which inhibit GMCSF-mediated immune activation. Inoculation of patients with FANG purportedly enhances an immune response against ovarian cancer cells and prevents cancer recurrence. In clinical trials, patients receive at least 4 and up to 12 monthly intradermal injections of the FANG vaccine ($1x10^7$ cells). Gradalis, Inc., Dallas, TX Phase II trial (FANG) ongoing; Feb 2012, FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, temozolomide) B-RAF inhibitors (e.g., dabrafenib, vemurafenib) Immunotherapy (e.g., ipilimumab, nivolumab, pembrolizumab) MEK inhibitors (e.g., trametinib [cobimetinib; in development]) Platinum-based agents (e.g., carboplatin) Taxane agents (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Avelumab for treatment of nonsmall cell lung cancer	Patients with programed death-ligand-1 (PD-L1)–positive nonsmall cell lung cancer (NSCLC) whose disease has progressed after platinum-based doublet	The 5-year survival rate for patients with advanced NSCLC is less than 15%, and patients with advanced NSCLC whose disease has progressed after 1st-line platinum-based chemotherapy have few treatment options and a poor prognosis. A hallmark of cancer is its ability to evade an immune response. Avelumab (MSB0010718C) is a novel therapeutic that is intended to prevent immune tolerance of tumor cells. The drug's target is the programmed death-1 receptor ligand (PD-L1), which is frequently expressed in tumor microenvironments and purportedly leads to downregulation of T-cell activity via activation of the programmed death-1 immune checkpoint. Avelumab is a monoclonal antibody specific for PD-L1 and is intended to prevent an interaction between the ligand and its receptor, potentially limiting activation of the immune checkpoint. In clinical trials, avelumab is administered intravenously, 10 mg/kg, once every 2 weeks, until disease progression or unacceptable toxicity. Merck KGaA, Darmstadt, Germany, in collaboration with Pfizer, Inc., New York, NY Phase III trial (JAVELIN Lung 200) ongoing	Chemotherapy with 1 or more of the following: ALK inhibitors if ALK-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) *EGFR* inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Catumaxomab (Removab) for treatment of gastric cancer	Patients with surgically resectable gastric adenocarcinoma or adenocarcinoma of the gastroesophageal junction who have received neoadjuvant chemotherapy (epirubicin, cisplatin, and capecitabine or 5-fluorouracil)	Patients with gastric cancer or gastroesophageal junction cancer have a poor prognosis with available treatments. Gastric cancer is the 4th most common diagnosed cancer worldwide, and surgery—usually combined with perioperative chemotherapy—is the most important treatment. However the 5-year survival is about 38%. Peritoneal carcinomatosis occurs after dissemination and is considered a lethal disease because of its limited treatment options. Catumaxomab (Removab®) is a chimeric monoclonal antibody that consists of a mouse-derived anti-EpCAM Fab and a rat-derived anti-CD3 Fab that is capable of binding to 3 different types of cells, including cancer cells overexpressing EpCAM, T-cells expressing CD3, and accessory cells expressing the Fcγ receptor (e.g., dendritic cells, macrophages, NK cells). Catumaxomab has been demonstrated to have antitumor activity by decreasing the growth of EpCAM-positive cells and the release of pro-inflammatory cytokines. In clinical trials, patients receive 5 intraperitoneal infusions of catumaxomab (starting at 10 mcg) on days 1, 3, 7, 10, and 17. Neovii Biotech, GmbH, Munich, Germany Phase II trials (CatuNeo and IIPOP) ongoing; Jul 2009, FDA granted orphan drug status; FDA approved for treating malignant ascites in the peritoneal cavity	Chemotherapy with 1 or more of the following: Anthracyclines (e.g., doxorubicin, epirubicin, irinotecan) Antimetabolites (e.g., 5-fluorouracil, capecitabine, gemcitabine) DCF (docetaxel, cisplatin, 5-fluorouracil) ECF (epirubicin, cisplatin, 5-fluorouracil) HER2 antibodies if HER2-positive (e.g., trastuzumab) PD-1 antibodies (e.g., pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin, oxaliplatin) Taxanes (e.g., docetaxel, paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life
CellDetect for bladder cancer screening	Patients with previously diagnosed bladder cancer	As with most types of cancer, bladder cancer diagnosed in earlier stages is associated with a higher survival rate because the disease will respond better to treatment. Unfortunately, 80% of bladder cancers recur and require constant monitoring. The 5-year survival rate of patients with stage IV bladder cancer is about 14%. A need exists for noninvasive diagnostic tools with high sensitivity and specificity for bladder cancer. CellDetect is a histochemical assay that allows clinicians to differentiate cancer cells from normal cells based on tinctoral information alongside morphological examination. The CellDetect kit combines plant-based extracts with generic dyes to stain cells collected from a urine sample. Normal cells appear green; cancer cells are stained reddish purple. In a clinical trial, urine samples from patients with bladder cancer will be tested to determine CellDetect's performance. Zetiq Technologies, Ltd., subsidiary of Micromedic Technologies, Ltd., Tel Aviv, Israel Unphased trial (ZT-CL-04B) ongoing; received CE mark Jun 2015	Biopsies (e.g., bladder biopsies, cancer-spread biopsies) Cytoscopy (e.g., fluorescent, white light) Imaging tests (e.g., bone scan, CT scan, MRI scan, pyelogram, ultrasound, x-ray) Laboratory tests (e.g., urine culture, urine cytology, urine tumor marker test)	Improved sensitivity and specificity for screening Improved predictive values Avoided unnecessary biopsies Better treatment planning Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Crizotinib (Xalkori) for treatment of ROS1-positive nonsmall cell lung cancer	Patients with nonsmall cell lung cancer (NSCLC) that harbors genetic rearrangement that leads to constitutive activation of the proto-oncogene receptor tyrosine kinase *ROS1*	The 5-year survival rate for patients with advanced NSCLC is less than 15% with current treatments. Over the past 10 years, discovery of oncogenes, such as the epidermal growth factor receptor (*EGFR*), Kirsten rat sarcoma viral oncogene (*KRAS*), V-raf murine sarcoma viral oncogene homolog B1 (*BRAF*), and anaplastic lymphoma kinase (ALK), have led to development of targeted therapies against these mutations. Crizotinib (Xalkori®) inhibits ALK (and MET kinase) activity of tumors driven by constitutive ALK activity. Similarly, chromosomal rearrangements of the proto-oncogene receptor tyrosine kinase *ROS1* are responsible for about 1% of NSCLC. Crizotinib purportedly can also be used to treat ROS1-positive NSCLC because the ATP-binding sites within the kinase domain of ROS1 and ALK share a 77% amino-acid identity. In clinical trials, crizotinib is administered orally, 250 mg, twice daily. Pfizer, Inc., New York, NY Phase II trials (EUCROSS and OO 12-01) ongoing; Apr 2015, FDA granted breakthrough therapy status; FDA approved Aug 2011 for treating locally advanced or metastatic ALK-positive NSCLC	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life
Diphenylcyclopro-penone (Samcyprone) for treatment of cutaneous metastases of malignant melanoma	Patients in whom stage IIb–IV melanoma has been diagnosed	Patients with metastatic melanoma have a poor prognosis, with current treatments yielding a 5-year survival rate of 15% to 20%. Diphenylcyclopropenone (DPCP; Samcyprone™) is a novel immunomodulator purported to target cutaneous metastases of malignant melanoma. DPCP purportedly initiates a T-cell response by altering the expression of genes and miRNAs involved in the immune response. In clinical trials, 0.4% or 0.04% gel formulations of DPCP are applied topically at the site of the lesion for 14 weeks. RXi Pharmaceuticals Corp., Marlborough, MA Phase II trial ongoing; Apr 2014, FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, temozolomide) B-RAF inhibitors (e.g., dabrafenib, vemurafenib) Immunotherapy (e.g., ipilimumab, nivolumab, pembrolizumab) MEK inhibitors (e.g., trametinib [cobimetinib; in development]) Platinum-based agents (e.g., carboplatin) Taxane agents (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
FLT3/AXL inhibitor (ASP2215) for treatment of acute myeloid leukemia bearing *FLT3* mutations	Patients with treatment-refractory acute myeloid leukemia (AML) bearing an internal tandem duplication in the *FLT3* gene (ITD-FLT3)	No *FLT3* inhibitors are available for treating AML, and patients with recurrent or treatment-refractory AML have no effective treatment options. About 30% of AML cases bear an activating mutation in the gene encoding the receptor tyrosine kinase *FLT3*, a mutation that constitutively activates various cell proliferative and anti-apoptotic pathways. Patients whose disease harbors an activating *FLT3* mutation have a worse prognosis than patients whose disease does not. ASP2215 is a kinase inhibitor with activity against multiple tyrosine kinases, including FLT3, LTK, ALK, and AXL. ASP2215 is orally administered, once daily, at an unspecified dose. Astellas Pharma, Inc., Tokyo, Japan Phase III trial ongoing	Cladribine, cytarabine, and granulocyte colony-stimulating factor (G-CSF) plus or minus mitoxantrone or idarubicin High-dose cytarabine and anthracycline Fludarabine, cytarabine, and G-CSF plus or minus idarubicin Mitoxantrone, etoposide, and cytarabine	Increased overall survival Increased progression-free survival Improved quality of life
Inecalcitol for treatment of chronic myeloid leukemia	Patients in whom chronic myeloid leukemia (CML) has been diagnosed	For the majority of patients with CML, disease is controlled using inhibitors of the *BCR-ABL* oncogene (e.g., imatinib, dasatinib, nilotinib). However, these drugs must be taken on an ongoing basis and resistance occurs in some patients. Inecalcitol is a vitamin D receptor agonist. Like calcitriol (the active form of vitamin D), inecalcitol binds to the vitamin D receptor and directs the transcriptional activation or repression of genes involved in fundamental cell processes; however, the pattern of gene expression caused by inecalcitol differs from that induced by calcitriol. In particular, research has demonstrated that inecalcitol leads to increased expression of negative regulators of the cell cycle (e.g., p21, p27) and decreased expression of positive regulators of the cell cycle (e.g., cyclin C, cyclin D1). Additionally, preclinical research has demonstrated synergistic effects of inecalcitol and BCR-ABL inhibitors on CML stem-like cells. In clinical trials, inecalcitol is orally administered, 2 mg, daily, in combination with standard imatinib treatment. Hybrigenics, S.A., Paris, France Phase II trial ongoing; FDA granted orphan drug status	Bosutinib Dasatinib Imatinib Nilotinib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Inhaled lipid-complexed cisplatin for the treatment of osteosarcoma	Patients with osteosarcoma that has metastasized to the lungs, in whom primary or secondary pulmonary recurrence has been surgically removed	Osteosarcoma is caused by abnormal growth of osteoblasts that make bone matrix, but this matrix is not as strong as the one made by normal osteoblasts. Osteosarcoma usually develops in areas of rapid bone growth (ends of bones). For patients with local tumors that are treated, the 5-year survival rate is between 60% and 80%, but it drops to 40% if osteosarcoma is metastatic and has spread only to the lungs. Although tumors can be surgically removed from the lungs, 35% of patients will experience recurrence, usually to the lungs, and have a 5-year survival rate of 25%. Inhaled lipid-complexed cisplatin (ILC) is a novel formulation of the platinum-based chemotherapy that is administered via inhalation and offers a sustained release on a nanogram scale. In clinical trials, patients are treated with 36 mg/m^2, administered via a nebulizer, once every 2 weeks, for up to 1 year. Eleison Pharmaceuticals, LLC, St. Petersburg, FL Phase II trial (EP-ILC-201) ongoing; Mar 2007, FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide, dacarbazine, ifosfamide) Anthracyclines (e.g., doxorubicin, epirubicin) Antimetabolites (e.g., gemcitabine, methotrexate) Platinum-based drugs (e.g., carboplatin, cisplatin) Topoisomerase inhibitors (e.g., etoposide, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life
Isocitrate dehydrogenase-1 inhibitor (AG-120) for treatment of acute myeloid leukemia	Patients with acute myeloid leukemia (AML) harboring a mutation in the isocitrate dehydrogenase-1 (*IDH-1*) gene	Only about 25% of patients in whom AML is diagnosed will survive for 5 years after diagnosis. Somatic mutations in the *IDH1* gene have been observed in AML cases and are thought to contribute to the pathogenesis of the disease. IDH1 is an enzyme that regulates fundamental aspects of cell metabolism. Mutant forms of IDH1 observed in AMLs lead to both a decrease in the levels of alpha-ketoglutarate (the normal IDH1 metabolite) and an increase in the levels of another metabolite, D-2-hydroxyglutarate. These shifts purportedly have several potentially tumorigenic effects (e.g., histone modification and DNA methylation) that retain cells in a dedifferentiated state. AG-120 inhibits the mutant form of IDH1. It is orally administered at an undisclosed dosage. Agios Pharmaceuticals, Inc., Cambridge, MA Phase I trial ongoing; FDA granted fast-track and orphan drug statuses	Cladribine, cytarabine, and granulocyte colony-stimulating factor (G-CSF) plus or minus mitoxantrone or idarubicin Fludarabine, cytarabine, and G-CSF plus or minus idarubicin High-dose cytarabine and anthracycline Mitoxantrone, etoposide, and cytarabine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lurbinectedin for treatment of platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer	Patients with unresectable epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease is resistant to platinum-based chemotherapy and who have received no more than 3 systemic treatments	About 80% of patients with advanced ovarian, fallopian tube, or primary peritoneal cancer will have recurrent disease after 1st-line platinum-based chemotherapy, and recurrence is associated with a poor prognosis. Lurbinectedin (PM01183) is a novel, synthetic, marine-derived compound that could address an unmet need for patients with ovarian cancer. Lurbinectedin covalently binds to the minor groove of DNA. This interaction causes double-strand breaks in the DNA, which can perturb the cell cycle and induce cell death. In a phase I clinical trial, lurbinectedin is administered intravenously, at an escalating dose of 1–4 mg, once every 3 weeks. PharmaMar subsidiary of Groupo Zeltia, Madrid Spain Phase III trial (CORAIL) ongoing; Aug 2012, FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) PARP inhibitors if BRCA1/2-mutant (e.g., olaparib) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Topoisomerase inhibitors (e.g., etoposide, doxorubicin HCl liposome injection, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Margetuximab for treatment of metastatic, HER2-positive breast cancer	Patients with locally advanced or metastatic, HER2-positive breast cancer that is refractory and has recurred after treatment with ado-trastuzumab emtansine, pertuzumab, or trastuzumab in the neoadjuvant, adjuvant, or metastatic setting	Although HER2-targeted therapies such as trastuzumab and lapatinib have improved outcomes for patients with HER2-positive advanced breast cancer, not all patients have disease that responds to these therapies. A need exists for novel treatments with higher response rates than standard HER2-targeted therapies. Margetuximab (MGAH22) is a monoclonal antibody that binds to HER2 to inhibit tumor cell growth. In contrast to other HER2-specific antibodies (e.g., pertuzumab, trastuzumab), margetuximab` has an optimized Fc region with higher affinity for the Fc-gamma receptor on macrophages; this increases their recruitment and enhances antibody-dependent cellular cytotoxicity of the tumor. Additionally, macrophages that have phagocytosed and processed a tumor cell will present tumor antigens to prime T cells, which then elicit antigen-specific immune responses against the tumor. In a phase III clinical trial, margetuximab will be administered intravenously once every 3 weeks, 15 mg/kg, in combination with capecitabine, eribulin, gemcitabine, and vinorelbine. MacroGenics, Inc., Rockville, MD Phase III trial (SOPHIA) ongoing	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine, pemetrexed) HER2-targeted antibodies (e.g., ado-trastuzumab emtansine, pertuzumab, trastuzumab) HER2-targeted kinase tyrosine inhibitors (e.g., afatinib, lapatinib) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloid (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life
Nanoparticle-camptothecin conjugate (CRLX101) for treatment of metastatic renal cell carcinoma	Patients with metastatic renal cell carcinoma (mRCC) that is not amenable to surgery whose disease has progressed after 2 or 3 standard chemotherapies	Patients with mRCC have limited 1st-line options, and even after tyrosine kinase–inhibitor treatment, the disease will progress and is associated with a poor prognosis. Nanoparticle-camptothecin conjugate (CRLX101) is a novel nanoparticle-drug conjugate (NDC) designed to target and concentrate in tumors and slowly release its anticancer agent, camptothecin, inside tumor cells. CRLX101 inhibits topoisomerase 1, which relieves DNA supercoiling during cellular replication, and hypoxia-inducible factor-1alpha (HIF-1alpha), which promotes cancer-cell survival through an unknown mechanism that promotes drug and radiation resistance. In clinical trials, patients are treated intravenously with 15 mg/m^2 of CRLX101 in combination with bevacizumab on days 1 and 15 of a 28-day cycle Cerulean Pharma, Inc., Cambridge, MA Phase II trial (CRLX101-208) ongoing; Apr 2015, FDA granted fast-track status	Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab [in development]) Cytokines (e.g., interferon, interleukin-2) mTOR inhibitors (e.g., temsirolimus) PD-1 inhibitors (e.g., nivolumab [in development]) Tyrosine kinase inhibitors (e.g., everolimus, pazopanib, sorafenib, sunitinib)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nivolumab (Opdivo) for treatment of small cell lung cancer	Patients with small cell lung cancer (SCLC) that has progressed after 1st-line treatment with platinum-based doublet chemotherapy or chemoradiation	SCLC is an aggressive lung cancer that spreads rapidly to adjacent lymph nodes and distal organs. Each year, about 34,000 cases are reported in the U.S., and it has a very poor prognosis compared with other types of lung cancer. The 5-year survival rate is less than 5%. No therapeutic advances have been achieved against SCLC in 25 years, with topotecan being the only treatment option in the 2nd-line setting. A hallmark of cancer is its ability to evade an immune response. Nivolumab (Opdivo®) is a novel therapeutic that is intended to prevent immune tolerance of tumor cells. The drug's target is the programmed death-1 (PD-1) pathway, which acts as an immune checkpoint that downregulates T-cell activity. Nivolumab is a monoclonal antibody specific for the PD-1 receptor that purportedly blocks activation of this pathway. In most phase III trials, nivolumab is administered as an intravenous infusion, 3 mg/kg, once every 2 weeks. However, the dosage for treating SCLC has not been disclosed. Bristol-Myers Squibb, New York, NY Phase III trials (CheckMate 331 and 451) ongoing; FDA approved nivolumab for treating melanoma and nonsmall cell lung cancer (NSCLC)	Chemoradiation therapy Platinum-based agents (e.g., carboplatin, cisplatin) Topoisomerase inhibitors (e.g., etoposide, topotecan)	Increased overall survival Increased progression-free survival Improved quality of life
Oportuzumab monatox (Vicinium) for treatment of nonmuscle-invasive bladder cancer	Patients with high-grade nonmuscle-invasive bladder cancer (NMIBC) that is refractory to bacillus Calmette-Guérin (BCG) treatment	NMIBC is the 6th most common cancer diagnosed. It accounts for 70% to 80% of all bladder cancers and causes the deaths of about 16,000 patients in the U.S. each year. 1st-line therapy for NMIBC is BCG, which is not an effective treatment—it has a 1-year failure rate of 50% and a 5-year failure rate of 90%. A need exists for novel therapies for treating NMIBC, and no new effective drugs have been approved in the past 25 years. Oportuzumab monatox (Vicinium™) is a recombinant fusion protein consisting of a single-chain antibody fragment specific against the epithelial cell adhesion molecule (EpCAM) that is fused to a truncated form of *Pseudomonas aeruginosa*'s exotoxin A (ETA). Oportuzumab monatox targets tumor cells of epithelial origin by binding to overexpressed EpCAM and is then internalized. Once inside the cell, ETA dissociates from the antibody chain and exerts its cytotoxic activity. In clinical trials, 30 mg of oportuzumab monatox is instilled into the bladder via catheter. During the induction phase, patients are treated twice weekly for 6 weeks, then weekly for 6 weeks, and then in the maintenance phase, patients are treated every 2 weeks for 104 weeks. Viventia Bio, Inc., Winnipeg, Manitoba, Canada Phase III trial (VB4-845-02-IIIA) ongoing	Surgery (cystectomy) Radiotherapy combined with chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Platinum-based agents (e.g., cisplatin) Taxanes (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Paclitaxel-peptide drug conjugate (ANG1005) for treatment of glioblastoma	Patients with recurrent, high-grade glioma, which includes glioblastoma multiforme	High-grade gliomas can be difficult to treat and are often associated with a poor prognosis. The 5-year survival rate is less than 5%. In about 60% of patients in remission, gliomas develop resistance to temozolomide, leaving them with limited treatment alternatives. A need exists for effective interventions when the disease recurs. ANG1005 is a novel peptide-taxel derivative that has paclitaxel conjugated to Angiopep-2. This peptide interacts with the low-density lipoprotein receptor–related protein 1 (LRP-1), which allows ANG1005 to cross the blood-brain barrier and target cancer cells that express LRP-1 on their surface. In a clinical trial, ANG1005 is administered to patients, intravenously, 650 mg/m^2, once every 3 weeks. Angiochem, Montreal, Quebec, Canada Phase II trial (ANG1005-CLN03) ongoing; May 2014, FDA granted orphan drug status for treating glioma after granting fast-track status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., carmustine, cyclophosphamide, lomustine, nitrosourea, procarbazine, temozolomide) Angiogenesis inhibitors (e.g., bevacizumab) Immunotherapeutics (e.g., DCVax-L, HSPPC-96, rindopepimut [in development]) mTOR inhibitors (e.g., everolimus) PD-1 antibodies (e.g., nivolumab, pembrolizumab [in development]) Platinum-based drugs (e.g., carboplatin, cisplatin) Radiation therapy Vinca alkaloids (e.g., vincristine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ramucirumab (Cyramza) for treatment of urothelial bladder cancer	Patients with locally advanced or metastatic urothelial bladder cancer (UBC) whose disease has progressed after platinum-based chemotherapy	UBC includes disease of the ureters, urinary bladder, and urethra. About 90% of urothelial cancers begin in the bladder and have a 5-year survival rate of 85% when detected early. In contrast, the survival rate of advanced urothelial cancer is 14% for patients with lymph node–positive and metastatic disease. Ramucirumab (Cyramza®) is a novel monoclonal antibody that binds to the extracellular domain of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2), which is a receptor tyrosine kinase that acts as a central mediator of tumor angiogenesis. Available VEGF-pathway inhibitors include a monoclonal antibody specific for VEGF and small-molecule inhibitors of the kinase activity of VEGFR2 (and other receptor tyrosine kinases). Ramucirumab represents a novel mechanism of action for inhibiting VEGF-pathway signaling. Treatment is intended for disease that has progressed after standard 1st-line platinum-based regimens. In phase III trials, ramucirumab is administered intravenously, 8 mg/kg, once every 2 weeks. However, for UBC, patients will be treated intravenously with ramucirumab in combination with docetaxel every 21-day cycle. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trial (RANGE) ongoing	Surgery (cystectomy) Radiotherapy combined with chemotherapy with 1 or more of the following: Antimetabolites (e.g., 5-fluorouracil, gemcitabine) Platinum-based agents (e.g., cisplatin) Taxanes (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life
Sodium thiosulfate for prevention of cisplatin-mediated ototoxicity	Pediatric patients with newly diagnosed hepatoblastoma or any other malignancy amenable to treatment with cisplatin (germ cell tumor, medulloblastoma, neuroblastoma, osteosarcoma)	Platinum-based chemotherapy is used in the 1st-line setting for treating various types of cancer. Unfortunately, because platinum compounds are used systemically, they affect any dividing cells and cause serious adverse events. In pediatric patients with cancer; platinum-based chemotherapy causes ototoxicity, which can lead to deafness. Sodium thiosulfate (STS) is a water-soluble thiol with reducing activity that circulates only in the plasma and does not enter cells. Cisplatin usually exerts its anticancer activity during the first 2 hours after infusion; the remaining cisplatin stays in the plasma to be excreted or metabolized to reduce its activity. In plasma, STS inactivates cisplatin, which prevents it from causing hearing loss. In clinical trials, STS is administered intravenously, 16 g/m^2 or 533 mg/kg, 6 hours after cisplatin treatment, until regimen is complete. Fennec Pharmaceuticals, Inc., Research Triangle Park, NC Phase III trials (ACCL0431 and SIOPEL 6) ongoing	No other preventive agents exist for ototoxicity and hearing loss Hearing loss can be managed with devices (i.e., hearing aids, cochlear [inner ear] implants)	Prevented ototoxicity Prevented hearing loss

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tremelimumab for treatment of mesothelioma	Patients with mesothelioma who received 1st-line, pemetrexed-based therapy in combination with a platinum agent	About 3,000 cases of mesothelioma are diagnosed each year in the U.S. Mesothelioma is a malignant tumor that most commonly affects the protective lining (the pleura) surrounding the lungs. It is caused in about 85% of cases by exposure to asbestos fibers. Despite chemotherapy options for mesothelioma, the disease recurs in most patients. Targeted therapies are needed for treatment-resistant mesothelioma. Tremelimumab is a cytotoxic T-lymphocyte antigen 4 (CTLA-4)–targeted immunotherapy. By blocking the activity of CTLA-4, tremelimumab may increase antitumor cytotoxic activity (reduce immune tolerance to tumor cells). In clinical trials, tremelimumab is being tested in the 2nd-line setting, administered intravenously at an unspecified dosage to patients who are not responding to 1st-line pemetrexed plus platinum regimen. Medimmune LLC subsidiary of AstraZeneca (London, UK) Phase II trial (Tremelimumab) ongoing; Apr 2015, FDA granted orphan drug status	Radiation therapy Surgical resection Chemotherapy with 1 or more of the following: Antimetabolites (e.g., gemcitabine, pemetrexed, raltitrexed) Platinum-based agents (e.g., carboplatin, cisplatin, oxaliplatin) Topoisomerase inhibitor (i.e., irinotecan)	Increased overall survival Increased progression-free survival Improved quality of life
Veliparib for treatment of melanoma	Patients with unresectable stage III or IV metastatic melanoma	Unresectable metastatic melanoma is associated with a poor prognosis; available treatments lead to a 5-year survival rate of 15% to 20%. Veliparib (ABT-888) is a small-molecule inhibitor of poly adenosine diphosphate-ribose polymerase (PARP), an enzyme involved in DNA repair. By inhibiting PARP's DNA repair, veliparib may potentiate the anticancer activity of cytotoxic chemotherapy drugs whose mechanism of action induces DNA damage. In a phase II trial, veliparib is being tested at 20 and 40 mg, orally, twice daily, for 7 days every 28 days, in combination with intravenous temozolomide, 150 mg/m^2, for 5 days every 28 days. AbbVie, North Chicago, IL Phase II trial (M10-440) ongoing; Dec 2007, FDA granted orphan drug status	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., dacarbazine, temozolomide) B-RAF inhibitors (e.g., dabrafenib, vemurafenib) Immunotherapy (e.g., ipilimumab, nivolumab, pembrolizumab) MEK inhibitors (e.g., trametinib [cobimetinib; in development]) Platinum-based agents (e.g., carboplatin) Taxane agents (e.g., paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life

Table 18. AHRQ Priority Condition: 03 Cardiovascular Disease: 7 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous bone marrow–derived therapy system (CardiAMP) for heart failure	Patients with New York Heart Association functional class II or III heart failure who have chronic ischemic left ventricular dysfunction secondary to myocardial infarction, ventricular ejection fraction between 20% and 40%, and a Cell Potency Assay score of 3 as determined by Cell Analysis Core Lab results	Available heart failure therapies are intended to reduce symptoms and maintain quality of life. However, none has been shown to halt or reverse disease progression. CardiAMP therapy delivers autologous cells to the damaged heart muscle with the goal of improving exercise capacity. Clinicians first collect about 15 cc of bone marrow aspirate for proprietary Core Lab analysis to estimate a candidate's likelihood of successful cell therapy. Several days after laboratory results are returned, clinicians collect about 60 cc of bone marrow aspirate from an eligible patient to concentrate a proprietary dose of autologous bone marrow mononuclear cells and inject the cell product into the myocardium using the proprietary Helix needle-injection catheter. Patients are discharged the same day or the next day. BioCardia, Inc., San Carlos, CA Phase III trials ongoing	Aldosterone antagonists Angiotensin II receptor blockers Angiotensin-converting enzyme inhibitors Artificial hearts Beta blockers Digoxin Diuretics Heart transplantation Inotropes Ventricular-assist devices	Improved exercise and functional capacity Reduced heart failure progression Reduced mortality Improved quality of life
Broad-spectrum agent (PER977) for reversal of anticoagulants	Patients who have uncontrolled bleeding from direct and indirect factor Xa and IIa inhibitors (or other anticoagulants), including apixaban, dabigatran, edoxaban, and rivaroxaban; fondaparinux; and low-molecular-weight heparins and unfractionated heparins	A reversal agent that is effective for multiple anticoagulants could facilitate emergency treatment for uncontrolled bleeding. PER977 is a water-soluble, small-molecule, broad-spectrum anticoagulant-reversal agent that binds with direct and indirect factor Xa- and IIa- inhibitors, including apixaban, dabigatran, edoxaban, and rivaroxaban; fondaparinux; and low-molecular-weight heparins and unfractionated heparins. This binding allows rapid re-establishment of normal blood coagulation. PER977 does not bind to blood coagulation factors or other blood proteins. In clinical trials, the drug is administered as an intravenous injection at doses of 25–600 mg. Perosphere, Inc., Danbury, CT Phase II trials ongoing; Apr 2015, FDA granted fast-track status	Blood transfusion Protamine Prothrombin complex concentrates	Reduced major bleeding

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Caplacizumab for treatment of acquired thrombotic thrombocytopenic purpura	Patients in whom acquired thrombotic thrombocytopenic purpura (TTP) has been diagnosed	TTP is a rare disorder in which blood clots form in the small vessels throughout the body and consume a large volume of platelets available for blood clotting, increasing bleeding risk. Acquired TTP develops (usually in adults) when the spleen produces antibodies against the ADAMTS13 enzyme (i.e., von Willebrand factor–cleaving protease), which is involved in blood clotting. Acquired TTP may be triggered by other conditions, including pregnancy, cancer, HIV, lupus, and infections; by procedures, such as some surgeries, and blood and marrow stem cell transplant; by chemotherapy agents, such as ticlopidine, clopidogrel, and cyclosporine A; and by hormone therapy and estrogen. No drugs are indicated to treat the condition. Treatment relies on periodic plasmapheresis to remove antibodies that damage the ADAMTS13 enzyme and to replace circulating ADAMTS13 enzymes. Splenectomy may be performed to eliminate production of antibodies that block ADAMTS13 enzyme activity. Caplacizumab is a selective, bivalent anti–von Willebrand factor monoclonal antibody intended to treat TTP and thrombosis. The 1st-in-class agent could be the 1st drug approved for treating acquired TTP as an adjunct to plasma exchange. In clinical trials, the agent is evaluated as a 10 mg intravenous bolus injection prior to plasma exchange, followed by once- or twice daily subcutaneous injection, 10 mg, for a maximum of 90 days. Ablynx, Ghent, Belgium Phase II trials ongoing; FDA and European Medicines Agency granted orphan drug status in 2009	Corticosteroids Intravenous immune globulin Rituximab Surgery (splenectomy) Thrombopoietin receptor agonists (e.g., romiplostim, eltrombopag)	Reduced time to recovery Reduced relapse rate Fewer disease exacerbations Reduced need for plasmapheresis
Catheter-based renal denervation (Symplicity Spyral System) for uncontrolled hypertension	Patients with uncontrolled hypertension, defined as 24-hour average ambulatory systolic blood pressure between 140 and 170 mm Hg while receiving 3 standard antihypertensive medications	Uncontrolled or poorly managed hypertension increases the risk of ischemic stroke, heart failure, and severe vascular damage. Many patients have difficulty controlling blood pressure despite the use of multiple drugs. The renal sympathetic nervous system plays a key role in regulating overall blood pressure. Research has suggested that surgically severing the renal nerves could dramatically reduce blood pressure, but the surgical procedure was reportedly associated with high rates of perioperative morbidity, mortality, and severe long-term complications. The Symplicity Spyral™ multielectrode catheter is intended to reduce uncontrolled hypertension by incapacitating the renal nerves in a transcatheter procedure. The system consists of a proprietary generator and flexible, multielectrode catheter that is inserted through the femoral artery and threaded into the renal arteries. Once in place, the catheter tip delivers low-power radiofrequency energy to ablate the renal nerves. Medtronic, plc, Dublin, Ireland Phase II trials ongoing	Angiotensin II receptor blockers Angiotensin-converting enzyme inhibitors Beta blockers Calcium channel blockers Renin inhibitors Thiazide diuretics	Reduced blood pressure Reduced hypertension complications (e.g., myocardial infarction, stroke, aneurysm, heart failure, vessel-related vision loss)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mannan-binding lectin-associated serine protease-2 targeted antibody (OMS721) for treatment of atypical hemolytic uremic syndrome	Patients in whom atypical hemolytic uremia syndrome has been diagnosed	Atypical hemolytic-uremic syndrome affects about 1 in 500,000 people per year in the U.S. The condition is characterized by abnormal blood clotting in the kidney's small vessels, leading to hemolytic anemia, thrombocytopenia, severe hypertension, and kidney failure. The only FDA-approved therapy, eculizumab (Soliris®), has been linked to potentially fatal meningococcal infections and may increase patients' risk for other serious infections. OMS721 is a human monoclonal antibody targeting mannan-binding lectin-associated serine protease-2 (MASP-2), a proinflammatory protein that helps activate the lectin pathway of the immune complement system after tissue damage or infection. According to OMS721's developer, MASP-2 inhibition does not appear to interfere with the antibody-dependent classical complement activation pathway, which is a critical component of the acquired immune response to infection. OMS721 is intended to be self-administered via subcutaneous injection. Clinical trials have evaluated 3 dose levels. Omeros Corp., Seattle, WA Phase II trial ongoing; Jul 2015, FDA granted fast-track status	Eculizumab (Soliris®); only FDA-approved therapy Kidney dialysis Kidney transplantation Plasma infusion/exchange Vasodilators	Reduced kidney damage and failure Reduced need for kidney dialysis Reduced need for renal transplantation
Off-label alteplase (Cathflo Activase) for treatment of intraventricular hemorrhage	Patients in whom intraventricular hemorrhage (IVH) has been diagnosed	IVH occurs in about 45% of patients with spontaneous intracerebral hemorrhage (ICH) and is an independent factor associated with poor outcomes. Guidelines for treating spontaneous ICH from the American Heart Association and American Stroke Association make no recommendations for treating IVH in patients with ICH. However, guidelines cite early trials showing that although "intraventricular administration of rtPA in IVH appears to have a fairly low complication rate, the efficacy and safety of this treatment are uncertain." Recombinant tissue plasminogen activator (rt-PA; alteplase, Cathflo® Activase®) is a thrombolytic agent. Its use is proposed to facilitate clot lysis and evacuation of IVH with a ventricular drainage catheter instead of extraventricular drainage alone. Johns Hopkins University coordinating center, Baltimore, MD (Daniel F. Hanley, M.D., principal investigator) National Institute of Neurological Disorders and Stroke (funding source) Phase III trial ongoing; FDA approved alteplase as a 2.2 mg single-use vial in powder form for restoring function (defined as ability to withdraw blood) in central venous catheters; FDA approved alteplase in 50- or 100-mg single-use vials in powder form to treat ischemic stroke, acute myocardial infarction, and pulmonary embolism	No treatments for IVH are recommended other than cardiovascular, respiratory, and neurological supportive care to prevent worsening of disease	Reduced morbidity Reduced neurological impairment Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Perhexiline for treatment of hypertrophic cardiomyopathy with heart failure	Patients in whom heart failure and hypertrophic cardiomyopathy have been diagnosed	Hypertrophic cardiomyopathy is an inherited cardiac condition affecting about 1 in 500 people that results in reduced contractility of heart muscle. Decreased pumping efficiency causes the heart muscle to enlarge to compensate, thus consuming more energy and eventually leading to heart failure. More than 120,000 people in the U.S. have hypertrophic cardiomyopathy with moderate-to-severe heart failure symptoms.. Perhexiline is a carnitine palmitoyl-acyltransferase (CPT) inhibitor intended to block the heart's uptake of fatty acids as a fuel source, causing the heart to switch to glucose as a fuel source. This switch is believed to make the heart's energy production more efficient and may reduce heart failure symptoms. The drug is administered orally, up to 200 mg, daily. Heart Metabolics, Ltd., Dublin, Ireland Phase III trial to start Mar 2016 under FDA special protocol assessment; FDA granted orphan drug status	Alcohol septal ablation Amiodarone Beta blockers Calcium channel blockers Disopyramide Implantable cardioverter-defibrillator Surgical resection (septal myectomy, apical myectomy)	Improved exercised capacity Improved peak oxygen consumption Improved symptoms Improved quality of life

Table 19. AHRQ Priority Condition: 04 Dementia (including Alzheimer's Disease): 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts

Table 20. AHRQ Priority Condition: 05 Depression and Other Mental Health Disorders: 4 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Deep transcranial magnetic stimulation for treatment of post-traumatic stress disorder	Patients in whom post-traumatic stress disorder (PTSD) has been diagnosed	PTSD is a mental health disorder marked by experiencing recurrence (flashbacks, nightmares, and event-related negative thoughts), avoidance, and hyperarousal symptoms after a traumatic event. According to the National Institute of Mental Health, 6.8% of adult Americans will experience PTSD during their lifetimes. Many patients with PTSD do not respond adequately to prescribed drugs or psychotherapy; therefore, an unmet need exists for alternative treatments. Deep transcranial magnetic stimulation (TMS) is a safe, noninvasive intervention that uses a proprietary magnetic coil ("H coil") to stimulate deeper brain regions than traditional TMS. Research suggests that acquired impaired fear extinction underlies increased susceptibility to developing PTSD and that medial prefrontal cortex (mPFC) hypoactivity plays a role in fear-extinction impairment. Investigators hypothesize that in conjunction with psychotherapy, stimulating mPFC using deep TMS can facilitate fear extinction and produce a therapeutic effect, alleviating core symptoms of PTSD. In late-phase clinical trials, patients receive deep TMS stimulation to the mPFC during 3 weekly sessions for 4 weeks, coupled with brief exposure therapy, and 2 "booster" stimulation sessions administered at treatment weeks 5 and 9. Multiple investigators including: Brainsway Ltd., Jerusalem, Israel (manufacturer) Centre for Addiction and Mental Health, Toronto, Ontario, Canada (principal investigator site) Hadassah Ein Karem Medical Center, Jerusalem, Israel McLean Hospital, Belmont, MA Medical University of South Carolina, Charleston Phase III trial ongoing; Jan 2013, FDA approved deep TMS therapy for treating medically refractory major depressive disorder; deep TMS is approved in the European Union and Brazil for treating PTSD	Antidepressants (for PTSD and depression) Antipsychotics (for PTSD and anxiety, paranoia, or other mental health symptoms) Benzodiazepines (for PTSD and sleep or relaxation difficulty) Paroxetine Psychotherapy Sertraline	Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Intranasal esketamine for treatment-resistant major depressive disorder	Patients in whom treatment-resistant major depressive disorder (MDD) has been diagnosed	Fewer than half of patients with MDD achieve remission with approved antidepressant therapy, and available pharmacotherapies are often associated with undesirable side effects. Available options for treatment-resistant MDD are either surgically invasive (e.g., deep brain stimulation, vagus nerve stimulation) or must be performed under clinical supervision (e.g., transcranial magnetic stimulation [TMS], repetitive TMS). Esketamine is an enantiomer of ketamine, a widely used anesthetic that is also being investigated for rapid relief of severe, treatment-resistant depression and suicidal ideation. Based on preclinical and early-phase study data, esketamine purportedly has similar or better efficacy than ketamine for treating these indications. Developers also purport that, in a proprietary intranasal formulation, esketamine can be effectively self-administered with less abuse potential than ketamine. In clinical trials, esketamine is administered intranasally, twice weekly, 56 or 84 mg, as a monotherapy or adjunct to standard oral antidepressants (e.g., escitalopram, sertraline, venlafaxine). Janssen Research & Development, LLC, unit of Johnson & Johnson, New Brunswick, NJ Phase III trials ongoing; FDA granted fast-track status	Deep brain stimulation Electroconvulsive therapy Psychotherapy Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors TMS Tricyclic antidepressants Vagal nerve stimulation	Improved depression rating scale scores Rapid improvement in depression symptoms Reduced depression-related suicidal ideation Reduced depression symptom severity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Sodium benzoate (NaBen) for adjunct treatment of childhood-onset schizophrenia	Pediatric and adolescent patients in whom childhood-onset schizophrenia has been diagnosed	Childhood-onset schizophrenia is a rare, severe mental health disorder with an estimated prevalence between 1 in 10,000 (among patients with disorder onset during teenage years) and 1 in 40,000 (among patients with a disorder onset before age 13 years). Common symptoms include hallucinations and delusions, disorganized motor behavior, and social cognitive dysfunction; in children and adolescents, these symptoms can seriously disrupt development and social acclimation, isolating patients and caregivers from society at large. Existing pharmacotherapies for schizophrenia have limited efficacy among some patients and are associated with unwanted side effects in many patients. An unmet need exists for new, safe interventions. NaBen® is a prescription-strength formulation of sodium benzoate, a common food preservative that is also the sodium salt of naturally occurring benzoic acid. Recent studies demonstrate that *N*-methyl-D-aspartate receptor (NMDAR) hypofunctioning is a key factor in schizophrenia pathophysiology; hypothetically, improving NMDAR function could effectively treat this disorder. Several investigational schizophrenia drugs have attempted to directly target NMDAR neurotransmission, with limited success. In contrast, NaBen has a novel mechanism of NMDAR enhancement and schizophrenia therapy, inhibiting D-amino acid oxidase metabolism and indirectly augmenting NMDA functioning; researchers purport that this mechanism could allow NaBen to relieve several positive and negative schizophrenia symptoms. In clinical trials, NaBen tablets are administered orally, 500 mg, twice daily for at least 6 weeks, adjunct to standard antipsychotic medications. Hugo Moser Research Institute at Kennedy Krieger Institute, Baltimore, MD (clinical trial collaborator and primary investigator site) SyneuRx International (Taiwan) Corp., Taipei, Taiwan (developer and manufacturer) Phase II/III trial ongoing; Jul 2012, FDA granted orphan drug status; sodium benzoate is also an active ingredient in medications approved for treating urea cycle disorders and acute hyperammonemia and associated encephalopathy comorbid to urea-cycle deficiencies	Antidepressants Antipsychotics Cognitive behavior therapy Combination therapy Mood stabilizers (i.e.. lithium) Psychotherapy	Improved negative and positive schizophrenia symptoms Increased standard antipsychotic efficacy Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Sodium benzoate (NaBen) for adjunct treatment of schizophrenia	Patients in whom schizophrenia has been diagnosed	Schizophrenia is a severe mental health disorder estimated to affect about 1.1% of adult Americans. Common symptoms include hallucinations and delusions, disorganized motor behavior, and social cognitive dysfunction; these symptoms can be debilitating, leading to social exclusion or psychiatric intake. Existing pharmacotherapies for schizophrenia have limited efficacy among some patients and are associated with unwanted side effects in many patients. An unmet need exists for safe interventions that improve treatment efficacy for adults who have schizophrenia. NaBen® is a prescription-strength formulation of sodium benzoate, a common food preservative that is also the sodium salt of naturally occurring benzoic acid. Recent studies demonstrate that *N*-methyl-D-aspartate receptor (NMDAR) hypofunctioning is a key factor in schizophrenia pathophysiology; hypothetically, improving NMDAR function could prove effective for treating this disorder. Several investigational schizophrenia drugs have attempted to directly target NMDAR neurotransmission, with limited success. In contrast, NaBen has a novel mechanism of NMDAR enhancement and schizophrenia therapy, inhibiting D-amino acid oxidase metabolism and indirectly augmenting NMDA functioning; researchers purport that this mechanism could allow NaBen to relieve several positive and negative schizophrenia symptoms. In clinical trials, 500 mg NaBen tablets are administered orally, twice daily, for up to 42 weeks, adjunct to standard antipsychotic medications. SyneuRx International (Taiwan) Corp., Taipei, Taiwan Phase II/III trial ongoing; sodium benzoate is also an active ingredient in medications approved for treating urea cycle disorders and acute hyperammonemia and associated encephalopathy comorbid to urea-cycle deficiencies	Antidepressants Antipsychotics Cognitive behavior therapy Combination therapy Mood stabilizers (i.e., lithium) Psychotherapy	Improved positive and negative schizophrenia symptoms Increased standard antipsychotic efficacy Improved quality of life

Table 21. AHRQ Priority Condition: 06 Developmental Delays, Attention-Deficit/Hyperactivity Disorder, and Autism: 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts

Table 22. AHRQ Priority Condition: 07 Diabetes Mellitus: 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts

Table 23. AHRQ Priority Condition: 08 Functional Limitations and Disability: 39 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Aceneuramic acid for treatment of hereditary inclusion body myopathy	Patients in whom hereditary inclusion body myopathy (HIBM) has been diagnosed	HIBM is a rare, progressive, muscle-wasting disease that typically manifests in late adolescence or early adulthood. Patients lose skeletal muscle strength and are dependent on wheelchairs within 10–20 years of symptom onset. HIBM is caused by a mutation in the *GNE* gene, which encodes the enzyme that produces sialic acid and is necessary for muscle strength and function. No treatments to cure or delay progression of HIBM are available. Aceneuramic acid (UX001-CL301), an extended-release sialic acid, is intended to stabilize muscle strength. It is administered 3 times daily, orally, for a total of 6 g a day. Ultragenyx Pharmaceutical, Inc., Novato, CA Phase III trial ongoing; Oct 2011, FDA granted orphan drug status	No treatments are available	Sustained mobility Sustained muscle strength Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Adeno-associated virus delivery of follistatin (rAAV1.CMV.huFollistatin344) for treatment of Becker and Duchenne muscular dystrophies	Patients in whom Becker muscular dystrophy (BMD) or Duchenne muscular dystrophy (DMD) has been diagnosed	Epidemiological data suggest that nationwide, between 1 in 5,600 and 1 in 7,700 males aged 5–24 years have DMD or BMD. Available treatments are limited to improving symptoms without addressing their underlying cause. Patients who have DMD experience a shortened lifespan and require support from orthotic devices, while patients with BMD experience debilitating lower body muscle weakness. As these disorders progress, patients experience increased muscle weakness and atrophy, severely limiting their independence. An unmet need exists for interventions that can address underlying disease mechanisms and reduce patients' functional disability. rAAV1.CMV.huFollistatin344 is an experimental adeno-associated virus delivery of follistatin; in animal models and patients with BMD, preliminary research has demonstrated that this intervention effectively enhances skeletal muscle mass and strength. In clinical trials for treating DMD, patients are administered rAAV1.CMV.huFollistatin344 at a total dose of $2.4x10^{12}$ vector genome (vg) per kg, divided between gluteal muscle, quadriceps, and tibialis anterior injections. Researchers have also investigated similar dosing protocols for treating BMD. Milo Biotechnology, Cleveland, OH Nationwide Children's Hospital, Columbus, OH Phase I/II trial ongoing for treating DMD; Nov 2012, FDA granted orphan drug status for treating BMD and DMD	Beta-2 agonists Corticosteroids Orthotic devices Physical therapy Respiratory support devices	Improved muscle mass and strength Increased functional mobility Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Adeno-associated virus delivery of SGSH and SUMF1 cDNAs (SAF-301) for treatment of Sanfilippo syndrome type A	Patients in whom Sanfilippo syndrome type A (MPS IIIA) has been diagnosed	Sanfilippo syndrome A (MPS IIIA) is a rare, autosomal recessive, lysosomal storage disorder caused by a mutation to the gene that encodes the enzyme *N*-sulfoglycosamine sulfohydrolase (SGSH); it is the most severe form of mucopolysaccharidosis type III. Resulting deficiencies in SGSH lead to abnormal heparan sulfate accumulation and subsequent significant neurological disability and dramatically shortened life expectancy. No cure exists for MPS IIIA, and standard treatment is palliative; an unmet need exists for disease-modifying therapies for patients with this disorder. SAF-301 is an investigational adeno-associated virus delivery of SGSH and sulfatase modifying factor 1 (SUMF1) cDNA. SUMF1 is an enzyme that catalyzes the hydrolysis of sulfate esters; hypothetically, the combined administration of this enzyme and supplemental SGSH will ameliorate underlying biochemical causes of MPS IIIA. In clinical trials, SAF-301 is directly injected intracerebrally to both sides of the brain through 6 image-guided tracks, with 2 deposits per track, in a single surgical session. Alcyone Lifesciences, Inc., Lowell, MA (developmental partner) Lysogene, Neuilly-sur-Seine, France (original developer and orphan drug sponsor) Phase I/II extension trial ongoing; May 2013, FDA granted orphan drug status	Palliative care	Increased SGSH levels Reduced heparan sulfate accumulation Improved symptoms Reduced early mortality Improved quality of life
Anifrolumab for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	Investigators have not found a cure for SLE, and current treatments provide only partial relief of symptoms. Anifrolumab is an investigational monoclonal antibody that binds to subunit 1 of the type I interferon (IFN) receptor, inhibiting the activity of all type I IFN signaling, including IFN-alfa, IFN-beta, and IFN-omega. Converging research has implicated several IFN proteins in SLE etiology; hypothetically, drugs that broadly inhibit IFNs represent an effective therapy for SLE symptoms and disease progression. In clinical trials enrolling patients with SLE who are already on a stable SLE medication, anifrolumab is infused intravenously once monthly, at 1 of 2 dosages, for up to 48 weeks. AstraZeneca, London, UK Phase III trials ongoing	Belimumab Rituximab Rontalizumab	Reduced cutaneous manifestations of SLE Fewer disease flares Improved SLE responder index scores Reduced SLE-associated arthritic symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti–interferon-gamma antibody (NI-0501) for treatment of hemophagocytic lymphohistio-cytosis	Patients in whom hemophagocytic lymphohistio-cytosis (HLH) has been diagnosed	HLH is a rare and often fatal disease characterized by overactive T lymphocytes and macrophages. Patients with HLH may experience a severe inflammatory reaction and cytokine storm, resulting in death if untreated. Although the full mechanism of HLH is unknown, interferon-gamma plays a key role in the overactivation of the immune response. Available treatments may resolve a disease flare but do not prevent recurrences. Patients may be cured with a bone marrow transplant if a match is found. Fewer than 60% of patients who receive the standard of care survive. NI-0501 is a fully human monoclonal antibody against interferon gamma given at an unspecified dosage in clinical trials. It is administered with corticosteroids. Novimmune SA, Geneva, Switzerland Phase II trial ongoing for pediatric patients with primary HLH; FDA granted orphan drug status in 2010	Antineoplastics (e.g., etoposide) Corticosteroids (e.g., dexamethasone) Immunosuppressants (e.g., cyclosporine) Intravenous immunoglobulin	Fewer transfusions of red blood cells, platelets, and fresh frozen plasma Resolution of organ pathology Survival to bone marrow transplant Reduced mortality Improved quality of life
Arimoclomol for treatment of *SOD1* mutation–positive familial amyotrophic lateral sclerosis	Patients in whom familial amyotrophic lateral sclerosis (ALS) has been diagnosed	The average life expectancy of a patient with ALS is 3–5 years after diagnosis, and only 10% of patients survive for more than 10 years. Only 1 agent (riluzole) is FDA approved for treating ALS, and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function; novel therapies are urgently needed. Arimoclomol (BRX-345) is a novel drug under investigation for treating ALS. Research has demonstrated that arimoclomol activates molecular chaperones, stimulating cellular protein repair, and induces heat shock protein response; in animal models with superoxide dismutase 1 (*SOD1*) mutations mimicking ALS, arimoclomol administration is neuroprotective, alleviating oxidative stress and reducing protein aggregation biomarkers characteristic of ALS. More than 100 *SOD1* mutations are associated with familial ALS in humans, and investigators propose that arimoclomol may have similar treatment efficacy across these patients, who represent about 10% of all ALS cases. In clinical trials, arimoclomol is administered orally, 200 mg, 3 times daily. Massachusetts General Hospital, Boston University of Miami, Miami, FL Phase II/III trial ongoing; Mar 2005, FDA granted orphan drug status	Riluzole (Rilutek®) Supportive care	Delayed disease progression Reduced early mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Arylsulfatase A intrathecal enzyme replacement therapy (SHP611) for treatment of metachromatic leukodystrophy	Patients in whom metachromatic leukodystrophy (MLD) has been diagnosed	MLD is a rare, autosomal recessive, lysosomal storage disorder, usually caused by a deficiency in arylsulfatase A, an enzyme that degrades sulfatides. In developed countries, MLD has an estimated incidence of 1 in 100,000 live births. Lack of arylsulfatase A leads to accumulation of sulfatides in the brain, spinal cord, and peripheral nerves, resulting in diffuse neurological and nervous system dysfunction. The disorder is differentiated into 3 subtypes, late-infantile, juvenile, and adult, based on age of onset; symptom progression varies by onset, but is frequently characterized by balance and motor dysfunction, behavioral problems, difficulty speaking and swallowing, and seizures. No cure exists for MLD, and standard treatment is primarily palliative; bone marrow or cord blood transplants are effective for some patients, but only to slow disease progression. An unmet need exists for broadly effective, potentially disease-modifying therapies for MLD. SHP611 is a recombinant human arylsulfatase A enzyme replacement therapy, under investigation for treating MLD. This intervention is hypothesized to restore arylsulfatase A levels, addressing an underlying cause of severe MLD symptoms. In international clinical trials enrolling patients with late-infantile MLD, SHP611 is administered via intrathecal injection, using the Sophysa Soph-A-Port® Mini S device. Injections are delivered every other week for 38 weeks at 10, 30, or 100 mg doses. Shire, plc, Dublin, Ireland International phase I/II trials ongoing; Feb 2008, FDA granted orphan drug status	Bone marrow transplantation Cord blood transplantation Palliative care	Decreased sulfatide accumulation Delayed disease progression Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous CD34+ stem cell gene therapy for Wiskott-Aldrich syndrome	Patients in whom Wiskott-Aldrich syndrome (WAS) has been diagnosed	WAS is a rare, X-linked, recessive heritable immunodeficiency with an estimated U.S. incidence of 1 case per 250,000 live male births. WAS is caused by a specific mutation to the *WAS* gene, which normally encodes WAS protein (WASp); other *WAS* mutations lead to 2 WAS-related disorders, X-linked thrombocytopenia and X-linked congenital neutropenia. WAS is primarily characterized by eczema, immune deficiency, and thrombocytopenia (low platelet count); it affects multiple types of white blood cells, significantly increasing patients' risk of acquiring autoimmune and inflammatory disorders and some forms of cancer. Most standard treatments for WAS focus on managing primary symptoms and monitoring potential acquired malignancies; bone marrow transplantation has also been used in cases with available histocompatible matches, although this intervention increases risk and mortality rates. An unmet need exists for additional safe, effective treatments for patients with WAS. Autologous CD34+ stem cell therapy is an experimental treatment purported to safely address all primary and some secondary symptoms of WAS. In this intervention, patients' own CD34+ cells are transduced with lentiviral vector containing human *WAS* gene and then transplanted back to original donors. Autologous CD34+ stem cell gene therapy is being positioned as a 1st-line therapy for patients who lack compatible bone marrow donors. Fondazione Telethon, Rome, Italy (developer and named strategic collaborator) Généthon, Cedex, France (developer and clinical trial sponsor) GlaxoSmithKline, plc, Middlesex, UK (orphan drug status sponsor) IRCCS San Raffaele, Milan, Italy (strategic collaborator and clinical trial sponsor) San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), Milan, Italy (developer) International phase I/II trials ongoing; Apr 2010, FDA granted orphan drug status	Bone marrow transplant (in cases in which patients have compatible donors)	Reduced autoimmunity Reduced eczema Reduced thrombocytopenia-related bruising and bleeding Reduced severe acquired infections rate Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous CD34+ stem cell gene therapy (Lenti-D) for childhood cerebral adrenoleuko-dystrophy	Male pediatric and adolescent patients in whom childhood cerebral adrenoleuko-dystrophy (CCALD) or adrenoleuko-dystrophy has been diagnosed	Adrenoleukodystrophy is a rare, X-linked, recessive heritable disorder with an estimated nationwide incidence of 1 per 21,000 live male births; at least 7 phenotypes are known to occur in males. The disorder is caused by mutations to the *ABCD1* gene, which normally encodes peroxisomal membrane transporter protein ALD. *ABCD1* deficiencies cause patients to accumulate abnormally high levels of unbranched, saturated, very-long-chain fatty acids (VLCFAs) in their brains and adrenal cortexes; these levels can be used as a clinical biomarker for the disorder. Patients with adrenoleukodystrophy exhibit a range of symptoms, depending on phenotype. CCALD is the most severe phenotype and affects 30% to 40% of patients with adrenoleukodystrophy, with an onset between age 3 and 10 years; patients with CCALD experience demyelination and profound progressive neurological decline and, without treatment, are eventually left in a vegetative state. No cure exists for CCALD or other adrenoleukodystrophy phenotypes. Standard treatment for asymptomatic patients attempts to reduce VLCFA levels using Lorenzo's oil dietary therapy; for patients with CCALD and available histocompatible matches, bone marrow or stem cell transplants are treatment options. Unfortunately, fewer than 30% of patients have histocompatible matches, and allogenic transplants have potentially fatal side effects. An unmet need exists for well-tolerated, effective disease-modifying therapies for the majority of CCALD patients who lack histocompatible matches. Autologous CD34+ stem cell therapy is an experimental CCALD treatment purported to safely address symptoms and underlying causes of CCALD. In this intervention, patients' own CD34+ cells are transduced with proprietary lentiviral vector Lenti-D, containing components including functional human *ABCD1* gene, and then transplanted back to the original donors. Investigators hypothesize that a single autologous CD34+ stem cell therapy administration is sufficient to treat CCALD and enable patients to begin producing ALD protein. Bluebird Bio, Inc., Cambridge, MA Phase II/III trial ongoing; Apr 2012, FDA granted orphan drug status for treating general adrenoleukodystrophy	Histocompatible bone marrow transplant Histocompatible stem cell transplant Lorenzo's oil (4 parts glyceryl trioleate : 1 part glyceryl trierucate)	Delayed or halted CCALD progression Reduced functional disability Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Budesonide (Nefecon) for treatment of IgA nephropathy	Patients with immunoglobulin A (IgA) nephropathy who are at risk of end-stage renal disease and who have medically controlled blood pressure	IgA nephropathy is characterized by IgA accumulation in a patient's kidneys, which causes blood and protein to leak into urine. After 10–20 years, 25% to 50% of adult patients and 5% to 10% of pediatric patients develop total kidney failure and require dialysis or a kidney transplant. Available treatments target symptom management and slow progression. Budesonide (Nefecon) is a modified-release glucocorticoid that is designed act locally to avoid side effects associated with other glucocorticoids. It purportedly suppresses the gastrointestinal immune system when it is absorbed in the ileum and protects the kidneys. It is administered orally, 8 or 16 mg, daily. Pharmalink AB, Stockholm, Sweden Phase II trial ongoing; May 2010, FDA granted orphan drug status; FDA approved for treating Crohn's disease	Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers Corticosteroids Dialysis Kidney transplant	Decreased creatinine levels Decreased IgA levels Decreased protein in urine Delayed or prevented end-stage renal failure Improved quality of life
C20-D3-retinyl acetate for treatment of Stargardt's macular dystrophy	Patients in whom Stargardt's macular dystrophy has been diagnosed	Stargardt's macular dystrophy is a genetic eye disorder affecting a small area near the center of the retina, called the macula. It is most often caused by mutations in the *ABCA4* gene, which encodes Rim protein. Rim transports vitamin A to be recycled. In Stargardt's macular dystrophy, Rim is absent and vitamin A dimers accumulate in the eye, causing damage. It progresses to central and color vision loss and difficulty transitioning from light to dark. Disease prevalence is an estimated 1 in 8,000–10,000 individuals, and no treatment is available. C20-D3-retinyl acetate, also called C20-dueterated vitamin A or ALK-001, is an active form of vitamin A that does not form dimers and accumulate in the eye. It is intended to replace unrecycled vitamin A to continue proper functioning and halt disease progression. In clinical trials, it is administered once daily, orally, at an unspecified dose. Alkeus Pharmaceuticals, Inc., Boston, MA Phase II trial ongoing; Sept 2010, FDA granted orphan drug status	No treatment is available	Halted progression of central vision loss Improved functional status Improved vision Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Characterized oral desensitization immunotherapy (AR101) for severe pediatric and adolescent peanut allergies	Pediatric and adolescent patients in whom a severe peanut allergy has been diagnosed	Experts estimate that at least 1% of all American children are allergic to peanuts, marked by hypersensitivity to peanut proteins; up to half of patients with a peanut allergy react to peanut protein levels equivalent to as low as 30% of a single peanut kernel. Peanut allergies tend to be lifetime indications, with fewer than 25% of children outgrowing their allergies. Peanut protein cross-contamination most commonly occurs in restaurants and classrooms, placing patients at risk of severe, potentially fatal symptoms including anaphylaxis, asthma, hives, and cardiac arrest during regular activities. No cure exists for peanut allergies or any other food allergies; standard treatment is emergency epinephrine administration, usually via an auto-injector, to treat anaphylaxis after allergen exposure. An unmet need exists for nonemergency therapies for treating patients who have severe peanut allergies. AR101 is an investigational formulation of peanut flour and other pharmaceutical components, intended to desensitize younger patients with severe peanut allergies. Purportedly, AR101 administration sufficiently desensitizes patients' immune systems so that accidental peanut exposure does not result in severe anaphylactic reactions. In clinical trials, AR101 is administered orally, ingested with other foods, with escalating dosing from 0.5 to 300 mg. The manufacturer's proposed initial desensitization regimen lasts 20 weeks, and the drug is intended for chronic use to maintain desensitization. Aimmune Therapeutics, Inc. (formerly Allergen Research Corp.), Brisbane, CA Phase II extension trial ongoing; Jun 2015, FDA granted breakthrough therapy status; Sept 2014, FDA granted fast-track status	No direct comparators have been identified; standard therapy for severe peanut allergies is emergency epinephrine treatment (e.g., EpiPen® auto-injector)	Reduced risk of severe accidental anaphylactic response Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Dalfampridine (Ampyra) for treatment of walking deficit after ischemic stroke	Patients with a stable walking deficit due to an ischemic stroke	Rehabilitation therapy after ischemic stroke can take weeks to months. Patients may need rehabilitation to become as independent as possible and attain the best possible quality of life. Rehabilitation does not reverse brain damage incurred during stroke but can help to teach patients new ways of performing tasks to compensate for residual damages. Some patients may require ongoing rehabilitation to maintain and refine skills. The degree of restored function varies by individual and depends on the neurologic damage caused by the stroke. Improved techniques and technologies for stroke rehabilitation are needed. Oral dalfampridine, extended release, is a potassium channel blocker proposed to treat walking deficit after ischemic stroke. Stroke trials are evaluating the drug at 7.5 or 10 mg, taken twice daily.The drug is contraindicated contraindicated in patients with a history of seizures or with moderate to severe renal impairment because of increased risk of seizures. Acorda Therapeutics, Inc., Ardsley, NY Phase III trials ongoing; FDA approved for treating walking deficit in patients with multiple sclerosis	Functional electrical stimulation Physical therapy (with or without manual or powered exercise equipment) to strengthen motor skills and improve mobility Transcranial magnetic stimulation	Improved post-stroke walking ability Improved quality of life
Delayed-release halofuginone (HT-100) for treatment of Duchenne muscular dystrophy	Patients in whom Duchenne muscular dystrophy (DMD) has been diagnosed	DMD is an X-linked recessive disorder and is the most common of the 9 recognized types of muscular dystrophy, with an estimated worldwide prevalence of 1 in 3,600 males. Available treatments for DMD are limited to reducing symptoms without addressing their underlying cause. Patients experience a shortened lifespan and require additional support from orthotic devices. An unmet need exists for effective therapies to treat severe symptoms in patients with DMD. HT-100 is an investigational oral molecule whose active ingredient is delayed-release halofuginone, an approved veterinary antibiotic. Halofuginone is also a demonstrated antifibrotic, inhibiting collagen alpha1(I) gene (*COL1A1*) expression and collagen synthesis. Investigators hypothesize that HT-100 may function similarly for treating DMD, reducing scar tissue, inflammation, and muscle damage commonly observed in patients, and also promoting muscle regeneration. In preliminary clinical trials, HT-100 is administered in single or multiple doses, at 1 of 5 dose levels. Akashi Therapeutics, Inc., Cambridge, MA Phase I/II trial ongoing; Oct 2011, FDA granted orphan drug status; Jul 2014, FDA granted fast-track status	Increased muscle regeneration Reduced fibrosis and inflammation Improved quality of life	Beta-2 agonists Corticosteroids Orthotic devices Physical therapy Respiratory support devices

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ectodysplasin-A1 replacement molecule (EDI200) for treatment of X-linked hypohidrotic ectodermal dysplasia	Patients in whom X-linked hypohidrotic ectodermal dysplasia (XLHED) has been diagnosed	XLHED is a rare genetic disorder caused by mutations to ectodysplasin A (*EDA*), ectodysplasin A receptor (*EDAR*), and EDAR-associated death domain (*EDARADD*) genes; estimated worldwide XLHED prevalence is 1 in 17,000. Mutations to *EDA*, *EDAR*, or *EDARADD* result in deficient levels of ectodysplasin-A1 (EDA-A1) protein, a transmembrane protein important in regulating ectodermal development. EDA-A1 deficiencies eventually lead to aberrant development of skin, hair, nails, teeth, and sweat glands; characteristic symptoms include reduced ability to sweat (hypohidrosis), reduced hair growth (hypotrichosis), and absent or misshapen teeth (hypodontia). Although patients with XLHED may live into adulthood, younger patients are at increased risk for potentially fatal hyperthermia and respiratory infections. No cure exists for XLHED, and standard care is palliative, usually addressing severe chronic skin and dental issues. EDI200 is an investigational recombinant fusion protein intended to replace deficient EDA-A1 protein in certain patients who have XLHED. Purportedly, EDI200 binds to EDAR, activating signalling pathways normally mediated by EDA-A1; investigators hypothesize that early treatment with EDI200 can prevent or alleviate XLHED developmental symptoms. In clinical trials, patients are administered 5 doses of EDI200 over 3 weeks, at a dose of 3 or 10 mg/kg. Edimer Pharmaceuticals, Cambridge, MA Phase II trial ongoing with neonate patients; Jan 2006, FDA granted orphan drug status; Jun 2012, FDA granted fast-track status	Palliative care	Increased functional EDA protein Reduced early mortality Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Edaravone for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	ALS is a progressive disorder marked by neurodegeneration of nerve cells in the brain and spinal cord. A 2014 report calculated that nationwide ALS prevalence is about 3.9 cases per 100,000 Americans. The average life expectancy of a patient with ALS is 3–5 years after diagnosis, and only 10% of patients survive for more than 10 years. Only 1 agent (riluzole) is FDA approved for treating ALS, and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function; novel therapies are urgently needed. Edaravone (TW001, MCI-186) is an investigational antioxidant and free radical scavenger, originally developed and approved in Japan to aid patients' recovery after brain ischemia. Investigators hypothesize that edaravone's demonstrated facility for protecting against oxidative stress may offer a viable mechanism for preventing or delaying motor neuron degeneration characteristic of ALS. In initial clinical trials, treatment cycles consist of two 60 mg edaravone ampoules (MCI-186) injected intravenously once daily for 10 days, followed by 14 observation days; patients complete 8 treatment cycles. An oral formulation (TW001) is also being prepared for clinical trials. Mitsubishi Tanabe Pharma Corp. subsidiary of Mitsubishi Chemical Holdings Corp., Tokyo, Japan (original developer and IV clinical trial sponsor) Treeway B.V., Rotterdam, the Netherlands (oral formulation developer) Phase III Japanese trial ongoing for MCI-186 formulation; Apr 2015, FDA granted orphan drug status to TW001 formulation	Riluzole Supportive care	Delayed disease progression Improved cognitive and motor degeneration symptom Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Epicutaneous patch desensitization therapy (Viaskin Peanut Patch) for severe peanut allergies	Patients in whom a severe peanut allergy has been diagnosed	Experts estimate that at least 1% of all American children are allergic to peanuts, marked by hypersensitivity to peanut proteins; up to half of patients with a peanut allergy react to peanut protein levels equivalent to as low as 30% of a single peanut kernel. Peanut allergies tend to be lifetime indications, with fewer than 25% of children outgrowing their allergies. Peanut protein cross-contamination most commonly occurs in restaurants and classrooms, placing patients at risk of severe, potentially fatal symptoms including anaphylaxis, asthma, hives, and cardiac arrest during regular activities. Presently, no cure exists for peanut allergies or any other food allergies; standard treatment is emergency epinephrine administration, usually via auto-injector, to treat anaphylaxis after allergen exposure. An unmet need exists for nonemergency therapies for treating patients who have severe peanut allergies. The Viaskin® Peanut Patch is an epicutaneous, yet nontransdermal, formulation of peanut proteins, intended to desensitize patients who have severe peanut allergies. Viaskin's manufacturer hypothesizes that the drug, which targets skin and lymph node Langerhans cells, sufficiently desensitizes T helper cell type 2 (Th2)-oriented allergen responses so accidental peanut exposure does not result in severe anaphylactic reactions. In clinical trials enrolling adolescents and adults, 1 patch is applied to a patient's skin every 24 hours for up to 30 months; individual patches are worn for a full day, and contain a maximum dose of 250 mcg peanut protein. Viaskin's manufacturer is examining the drug's efficacy as a chronic treatment and as a discrete therapy in a sustained allergen response–suppression trial design. Assistance Publique – Hôpitaux de Paris, Paris, France (trial sponsor) DBV Technologies, Bagneux, France (manufacturer and developer) Consortium of Food Allergy Research (CoFAR), various American research hospitals and universities (trial sponsor) National Institute of Allergy and Infectious Diseases, Bethesda, MD (trial sponsor) Multiple phase II trials ongoing; Feb 2012, FDA granted fast-track status	No approved direct comparators have been identified; standard therapy for severe peanut allergies is emergency epinephrine treatment (e.g., EpiPen® auto-injectors)	Reduced risk of severe accidental anaphylactic response Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Exon 44 skipping therapy (BMN 044) for treatment of Duchenne muscular dystrophy	Patients with Duchenne muscular dystrophy (DMD) and a dystrophin gene mutation caused by deletions of exons 43, 45, 38–43, 40–43, 42–43, or 45–54	DMD is an X-linked recessive disorder and is the most common of the 9 recognized types of muscular dystrophy, with an estimated worldwide prevalence of 1 in 3,600 males. Available treatments for DMD are limited to reducing symptoms without addressing their underlying cause. Patients experience a shortened lifespan and require additional support from orthotic devices. BMN 044 is an antisense oligonucleotide that induces exon skipping of exon 44. Antisense oligonucleotides skip defective exons (small RNA sequences that code for sections of protein) with high specificity, purportedly treating DMD by correcting the errant reading frame and allowing normal protein to be produced. Based on genetic studies, about 6% of patients with DMD have a form treatable by inducing exon 44 skipping. In clinical trials, BMN 044 is infused intravenously, up to 9 mg/kg weekly, or injected subcutaneously, up to 6 mg/kg weekly. BioMarin Pharmaceutical, Inc., San Raphael, CA Phase I/II and II trials ongoing; Nov 2009, FDA granted orphan drug status	Beta-2 agonists Corticosteroids Orthotic devices Physical therapy Respiratory support devices	Decreased muscle degeneration Decreased need for supportive devices Improved symptoms Reduced early mortality Improved quality of life
Exon 45 skipping therapy (BMN 045) for treatment of Duchenne muscular dystrophy	Patients with Duchenne muscular dystrophy (DMD) and a dystrophin gene mutation caused by deletions of exon 44, 46, 46–47, 46–48, 46–49, or 46–51	DMD is an X-linked recessive disorder and is the most common of the 9 recognized types of muscular dystrophy, with an estimated worldwide prevalence of 1 in 3,600 males. Available treatments for DMD are limited to reducing symptoms without addressing their underlying cause. Patients experience a shortened lifespan and require additional support from orthotic devices. BMN 045 is an antisense oligonucleotide that induces exon skipping of exon 45. Antisense oligonucleotides skip defective exons (small RNA sequences that code for sections of protein) with high specificity, purportedly treating DMD by correcting the errant reading frame and allowing normal protein to be produced. Based on genetic studies, about 8% of patients with DMD have a form treatable by inducing exon 45 skipping. In clinical trials, BMN 045 is injected subcutaneously, up to 9 mg/kg, weekly. BioMarin Pharmaceutical, Inc., San Raphael, CA Phase IIb trials ongoing; Jan 2013, FDA granted orphan drug status	Beta-2 agonists Corticosteroids Orthotic devices Physical therapy Respiratory support devices	Decreased muscle degeneration Decreased need for supportive devices Improved symptoms Reduced early mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ganaxolone for adjunctive treatment of protocadherin 19 female epilepsy	Female patients in whom protocadherin 19 (PCDH19) female epilepsy has been diagnosed	PCDH19 female epilepsy is a rare, X-linked disorder caused by a mutation to the protocadherin 19 (*PCDH19*) gene, which normally encodes a delta-2 protocadherin protein purported to function as a calcium-dependent cell-adhesion neural protein. Diagnostic screenings suggest that up to 10% of females who experience seizures before age 5 have this mutation; nationwide, PCDH19 female epilepsy has an estimated prevalence of 15,000 to 30,000 patients. Researchers hypothesize that a mutation to the *PCDH19* gene causes defective GABAergic signaling in patients, leading to characteristic symptoms including early-onset seizure clusters, cognitive delays, and psychiatric symptoms. Anticonvulsant medications have shown limited efficacy for treating PCDH19 female epilepsy, but no available drug is consistently effective for reducing seizures, and some patients have disease that is resistant to standard medications; an unmet need exists for additional safe, effective treatments for this disorder. Ganaxolone is a 1st-in-class synthetic neurosteroid and positive allosteric modulator of the GABA-A receptor, under investigation for treating PCDH19 female epilepsy. In preclinical studies and early-phase clinical trials, ganaxolone was well tolerated and had demonstrated anxiolytic and anticonvulsant properties. In ongoing clinical trials, ganaxolone is administered as an oral capsule adjunct to standard anticonvulsants, at dosages up to 1,800 mg, daily, or 63 mg/kg, daily, for up to 26 weeks. Marinus Pharmaceuticals, Inc., Radnor, PA Phase II trial ongoing; Mar 2015, FDA granted orphan drug status; ganaxolone is also under investigation for treating focal onset epileptic seizures and behavioral symptoms of fragile X syndrome	Benzodiazepines Clobazam Phenytoin Potassium bromide	Fewer seizures Improved quality of life
Glucosylceramide synthase inhibitor (GZ/SAR402671) for treatment of Fabry disease	Patients with Fabry disease who have not received enzyme replacement therapy	Fabry disease is a genetic disorder characterized by cellular buildup of globotriaosylceramide (GL-3), a type of fat, which causes a wide range of symptoms and can lead to heart attack, stroke, and kidney damage. Available enzyme replacement therapies for the disease are expensive and have been subject to recent shortages. Substrate reduction therapy using GZ/SAR402671 is intended to inhibit glucosylceramide synthase, the enzyme that produces GL-3. In a clinical trial, the drug is administered orally, once daily, at an unspecified dose. Genzyme subsidiary of Sanofi, Paris, France Phase II trials ongoing; Apr 2015, FDA granted fast-track status	Enzyme replacement therapy Palliative treatment	Decreased GL-3 levels Improved cardiac outcomes Improved renal function (e.g., glomerular filtration rate) Reduced mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Hepatocyte growth factor–like molecule (BB3) for treatment of delayed graft function after kidney transplantation	Patients with poor renal function after kidney transplantation using a cadaveric donor	Delayed graft function (DGF) is a form of acute renal failure most commonly defined as the use of dialysis within 1 week of kidney transplantation. It is likely due to ischemia or reperfusion injury when a cadaveric donor organ is used. DGF is associated with an inflammatory reaction that can be debilitating and life threatening, because it increases the risk of organ loss. DGF incidence has increased in recent years, likely because of increased organ donations after cardiac death instead of just brain death. BB3 is a small molecule with hepatocyte growth factor–like activity, which is involved in angiogenesis, tissue repair, and reducing deposition of extracellular matrix. It is administered at a dosage of 2 mg/kg by intravenous infusion within 24 hours after transplant and then daily for 3 days. Angion Biomedica Corp., Uniondale, NY Phase III trial ongoing; FDA granted orphan drug and fast-track statuses	No treatments are available	Faster kidney function after transplantation Reduced risk of kidney loss Reduced use of dialysis Improved survival Improved quality of life
Human retinal progenitor cells (ReN003) for treatment of retinitis pigmentosa	Patients in whom retinitis pigmentosa (RP) has been diagnosed	No medications are available to restore lost vision or halt progression of vision loss that occurs with the inherited disorder RP. Human retinal progenitor cells (hRPCs) may preserve existing photoreceptors to prevent further degradation of the retina. In preclinical studies, hRPCs engrafted into the photoreceptor layer and matured into functional photoreceptor cells. In patients with RP, this has the potential to restore visual function. ReN003, an hRPC cell line, is administered by subretinal injection. ReNeuron Group, plc, Guildford, UK, in partnership with Schepens Eye Research Institute, Boston, MA, and Massachusetts Eye and Ear Infirmary, Boston Phase I/II ongoing; FDA granted orphan drug and fast-track statuses	Argus II retinal prosthesis system	Improved visual acuity Increased independence Reduced visual deterioration Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Luspatercept for treatment of beta-thalassemia	Patients in whom beta-thalassemia has been diagnosed	Patients with beta-thalassemia have a mutation in the gene that encodes beta-globin. Patients who are homozygous for mutated beta-globin have thalassemia major, which causes severe anemia. They may rely on chronic blood transfusions for survival. To combat the effects of iron overload due to chronic transfusions, patients must also undergo nightly iron chelation. A cure for beta-thalassemia—an allogeneic hematopoietic stem cell transplant from a matched sibling donor—is available only to children. About 75% of patients do not have this option, and those who do face significant risk of morbidity and mortality. Luspatercept is a modified activin receptor type IIB fusion protein that acts as a ligand trap for members of the TGF-beta superfamily. It stimulates differentiation and maturation of erythrocyte precursors in a way that is distinct from erythropoietin. It is a powder dissolved in water and administered at a dose of 3,000 or 6,000 mg, twice daily, orally. Acceleron Pharma Inc., Cambridge, MA, and Celgene Corp., Summit, NJ Phase II trials ongoing; May 2015, FDA granted fast-track status for 2 indications: patients who are transfusion-dependent or transfusion-independent	Allogeneic stem cell transplant Chronic blood transfusions	Improved organ function Reduced dependence on blood transfusions Reduced incidence of iron overload Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multitargeted ammonia removal agent (OCR-002, L-ornithine phenylacetate) for treatment of hyperammonemia and resultant hepatic encephalopathy	Patients in whom hyperammonemia and resultant hepatic encephalopathy (HE) have been diagnosed	HE is a treatable, primarily neuropsychiatric disorder frequently observed in patients with acute liver failure or chronic liver cirrhosis whose livers cannot convert ammonia to urea. Instead of clearing through the liver, ammonia and byproducts accumulate in the blood and affect cognitive function; coma or death can result from severe HE. Standard therapies focus on reducing patients' plasma ammonia levels and risk of renal failure; although several medications are recommended, these drugs have varying inter- and intrapatient efficacy as well as undesirable side effects. Additional, effective, well-tolerated treatments for HE are needed. L-ornithine phenylacetate (OCR-002) is an investigational ammonia-scavenging compound purported to treat HE by rapidly lowering elevated systemic ammonia levels. In contrast to other HE medications, OCR-002 has multiple ammonia-lowering mechanisms: the drug indirectly stimulates the removal of ammonia, as glutamine; promotes direct ammonia excretion, as phenylacetylglutamine; and modulates glutaminase, an ammonia-generating enzyme, in human gut. In clinical trials enrolling hospitalized patients with hyperammonemia and an acute episode of HE, OCR-002 is intravenously infused at dosages up to 10 g over 24 hours, for 5 days, as an adjunct to standard care; the manufacturer is also developing an oral OCR-002 formulation for treating patients who have HE and chronic liver cirrhosis. Ocera Therapeutics, Inc., Durham, NC, and Palo Alto, CA Phase II and IIb trials ongoing; in 2010, FDA granted fast-track and orphan drug statuses to OCR-002 for treating hyperammonemia and resultant HE in patients with acute liver failure or acute-on-chronic liver disease	Dietary modification General nitrogen-removing drugs (e.g., nonspecific antibiotics, polysaccharides) Hemodialysis (reserved for severe hyperammonemia cases) Lactulose Rifamixin Urea cycle function-modifying drugs (e.g., sodium benzoate, sodium phenylacetate)	Improved neurocognitive symptoms Reduced plasma ammonia levels Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label adalimumab for treatment of mucopolysaccharidoses	Patients in whom mucopolysaccharidosis type I (MPS I), type II (MPS II), or type VI (MPS VI) has been diagnosed	Mucopolysaccharidoses are a group of rare, inherited metabolic disorders caused by mutations that lead to absence or dysfunction in 1 or more of 11 lysosomal enzymes, which normally degrade various glycosaminoglycans, the building blocks of bone, cartilage, connective tissue, cornea, and joint fluid. Patients with mucopolysaccharidoses exhibit abnormal development, stiffening, and pain in these structures, along with increased risk of respiratory, cardiovascular, and cognitive symptoms. Severe mucopolysaccharidoses may require corrective surgery or enzyme replacement therapy, while milder cases result in focal or diffuse joint pain and stiffening that limits functional mobility. An unmet need exists for effective, well-tolerated nonsurgical treatments to alleviate patients' symptoms. Adalimumab is a tumor necrosis factor (TNF)-inhibiting anti-inflammatory monoclonal antibody approved to treat indications including rheumatoid arthritis and Crohn's disease. The drug is demonstrated to reduce pain, swelling, and stiffness in these disorders; investigators hypothesize that it may have similar efficacy for treating symptoms in patients with certain mucopolysaccharidoses, including type I (Hurler-Scheie syndrome variants), type II (Hunter syndrome), and type VI (Maroteaux-Lamy syndrome). In clinical trials for treating mucopolysaccharidoses, adalimumab is injected subcutaneously every other week for 16 treatment weeks, 20 mg (for patients weighing between 15 kg and 30 kg) or 40 mg (for patients weighing at least 30 kg). Adalimumab may potentially be used adjunct to enzyme replacement therapies or as a sole pharmacotherapy. Los Angeles Biomedical Research Institute, Los Angeles, CA Phase II/III trial ongoing; FDA approved for treating several indications including Crohn's disease, rheumatoid arthritis, and ulcerative colitis	Palliative care	Reduced joint pain, stiffness, and swelling Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label pentoxifylline for treatment of severe acute pancreatitis	Patients in whom severe acute pancreatitis has been diagnosed	Severe acute pancreatitis is an inflammatory process in which pancreatic enzymes digest the gland, causing severe pain and life-threatening complications (e.g., shock, pulmonary failure, renal failure, gastrointestinal bleeding, multiorgan system failure). The condition may cause severe pain and require treatment in an intensive care unit. Standard treatment manages symptoms using analgesics, antibiotics, nutritional support, and fluid resuscitation. Some patients may require surgery to remove gallstones, necrotic tissue, or abscesses. No treatments are available that address the inflammatory reaction causing pancreatitis. Pentoxifylline is a tumor necrosis factor alpha inhibitor that may reduce inflammation and the innate immune response triggering pancreatitis. It is administered orally, 400 mg, 3 times daily, for up to 3 days. Mayo Clinic, Rochester, MN, and National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD Phase III trial ongoing	Supportive care Surgery	Fewer complications Reduced length of hospital stay Reduced length of intensive care unit stay Reduced pain Shorter pancreatitis duration
Olipudase alfa (GZ402665) for treatment of Niemann-Pick disease type B	Patients in whom mild acid sphingomyelinase deficiency (ASMD) has been diagnosed Patients in whom Niemann-Pick disease type B has been diagnosed	ASMD is an extremely rare, inherited lysosomal storage spectrum disorder caused by mutations in the *SMPD1* gene that lead to deficiencies in the enzyme acid sphingomyelinase; patients with Niemann-Pick disease type A (NPA) or type B (NPB) are considered to have ASMD. Worldwide, about 1,200 patients have received a diagnosis of ASMD. Acid sphingomyelinase deficiencies cause sphingomyelin accumulation in cells, leading to cell death and major organ malfunction. Patients with NPB may survive into adulthood, but can exhibit complications including enlarged livers and spleens, cardiovascular stress, and heart disease; NPA is a more severe neurologic indication and is often fatal between ages of 2 and 4 years. No cure exists for ASMD, and standard therapy is palliative; an unmet need exists for disease-modifying interventions. Olipudase alfa is an investigational recombinant human acid sphingomyelinase enzyme replacement therapy designed to supplement acid sphingomyelinase deficiencies in patients with the NPB form of ASMD. In clinical trials, olipudase alfa is administered intravenously every 2 weeks, 1 or 3 mg/kg, for 52 weeks, with an optional 4-year extension treatment period. Genzyme subsidiary of Sanofi, Paris, France Phase I/II (pediatric patients) and phase II/III trials (adult patients) ongoing; Jun 2015, FDA granted breakthrough therapy status for treating NPB	Palliative care	Reduced mortality Improved symptoms Reduced sphingomyelin accumulation Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oral *Oxalobacter formigenes* therapy (Oxabact) for primary hyperoxaluria	Patients in whom primary hyperoxaluria (PH) has been diagnosed	PH is an extremely rare, autosomal recessive, inherited metabolic disorder caused by a deficiency of 1 of 3 enzymes—alanine-glyoxylate aminotransferase (AGXT), glyoxylate reductase/hydroxypyruvate reductase (GRHPR), or 4-hydroxy-2-oxoglutarate aldolase 1 (HOGA1)—that normally convert glyoxylate into glycine or glycolate. As a result of these deficiencies, excess glyoxylate accumulates and is converted to oxalate; excess oxalate then combines with calcium, forming calcium oxalate deposits. Calcium oxalate, in turn, is the main component of kidney stones and is also hazardous to other organs. Researchers have identified 3 types of PH, differentiated by the underlying mutation; type 1 PH is caused by *AGXT* mutations, type 2 PH is caused by *GRHPR* mutations, and type 3 PH is caused by *HOGA1* mutations. Standard PH therapies attempt to prevent calcium oxalate deposition using vitamin B_6 supplements, neutral phosphates, and diuretics, or by dietary modifications including increased fluid intake and reduced oxalate, salt, sugar, and animal protein consumption. However, PH often leads to kidney stone formation before age 10, along with significantly elevated risk of end-stage renal disease. Severe organ damage due to PH may require kidney dialysis or organ transplantation, which can be curative interventions for some patients with type 1 PH. However, an unmet need exists for additional, nonsurgical PH therapies. Oxabact® is a proprietary composition of live *Oxalobacter formigenes*, a naturally occurring, nonpathogenic human gut bacteria. Because this bacteria efficiently and exclusively uses oxalate as an energy source, investigators hypothesize that it could be the basis of a safe, effective treatment for reducing kidney stones characteristic of PH. In clinical trials, Oxabact is administered for 6 weeks as an oral enteric-coated capsule, taken twice daily with meals, at a minimum dosage of $1x10^9$ cfu. OxThera AB, Stockholm, Sweden Various members of the ELIMOX project (European FP7 research consortium) Phase I/II and II trials ongoing; Mar 2006, FDA granted orphan drug status	For milder cases: Dietary modification Diuretics Neutral phosphate medications Vitamin B_6 supplements For more severe cases: Kidney dialysis Organ transplant	Reduced calcium oxalate deposition Reduced dietary restrictions Reduced risk of organ failure Reduced mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ozanezumab for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	ALS is a progressive disorder marked by neurodegeneration of nerve cells in the brain and spinal cord. A 2014 report calculated that ALS prevalence is about 3.9 cases per 100,000 Americans. The average life expectancy of a patient with ALS is 3–5 years after diagnosis, and only 10% of patients survive for more than 10 years. Only 1 agent (riluzole) is FDA approved for treating ALS, and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function; novel therapies are urgently needed. Ozanezumab is an investigational monoclonal antibody to Nogo A protein. Nogo A is an isoform of reticulon-4, a protein encoded by the RTN4 gene that inhibits central nervous system–specific neurite outgrowth. Researchers propose that ozanezumab treatment will block Nogo A's functionality, protecting neuromuscular junctions and facilitating repair and reconnection of motor neuron axons damaged by ALS. In clinical trials, ozanezumab is intravenously infused, 15 mg/kg, administered every 2 weeks for 48 weeks. GlaxoSmithKline, plc, Middlesex, UK Phase II trial completed; Jul 2009, FDA granted orphan drug status	Riluzole (Rilutek®) Supportive care	Improved respiratory capacity Increased functional independence Increased muscle strength Increased progression-free survival Improved quality of life
Pegylated carboxyhemo-globin bovine (Sanguinate) for treatment of sickle cell disease	Patients in whom sickle cell disease (SCD) has been diagnosed	SCD is an autosomal recessive disorder that affects about 100,000 people in the U.S. and can present as sickle cell anemia and sickle beta-0 thalassemia. Increased disease prevalence is seen in people of African and Mediterranean descent; about 1 in 500 African-American children have sickle cell anemia. In SCD, sickled red blood cells are more susceptible to oxidative damage and inappropriate adhesion, which can lead to vaso-occlusive crisis (VOC). VOC causes severe pain by obstructing vasculature and requires hospitalization. Patients may progress to thromboembolic events, stroke, organ failure, or early death. VOC is typically managed with hydration and pain medication but cannot be halted. The only FDA-approved treatment for SCD, hydroxyurea, can reduce VOC incidence but is not effective in about 1/3 of adult patients. Pegylated carboxyhemoglobin bovine (Sanguinate™) is a carbon monoxide releasing/oxygen transfer agent with vasoconstrictive properties. It purportedly aids in bringing oxygen to oxygen-deprived cells and tissues for treating VOCs, acute chest syndrome, leg ulcers, and strokes associated with SCD. It is administered as 1 dose at 320 mg/kg by transfusion over 2 hours. Prolong Pharmaceuticals, LLC, South Plainfield, NJ Phase II trial ongoing; Apr 2015, FDA granted orphan drug status	Allogeneic hematopoietic stem cell transplantation Analgesics Blood transfusion Hydroxyurea Statins Supplemental oxygen	Fewer hospitalizations and rehospitalizations Reduced health disparities in African Americans Reduced occurrence of acute chest syndrome Reduced severity and duration of VOCs Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Purified staphylococcal protein A (PRTX-100) for treatment of immune thrombocytopenia	Patients in whom immune thrombocytopenia (ITP) has been diagnosed	ITP is a bleeding disorder in which blood does not clot properly due to low platelet counts. The disorder is hypothesized to be caused by an abnormal autoimmune response, sometimes associated with a recent viral infection, in which patients' immune systems attack platelets. Patients with ITP commonly exhibit purpura (purple bruises caused by small blood vessel bleeds) and petechiae (bleeding resulting in pinpoint red or purple skin dotting), and are at increased risk of excessive nose bleeds, hematomas, and potentially fatal bleeding in the brain; female patients with ITP may also experience unusually heavy menstrual bleeding. Most ITP cases are not fatal, but can require lifestyle changes; adults with severe cases of ITP may opt for pharmacotherapy or splenectomy, although these interventions have attendant side effects and inconsistent efficacy. An unmet need exists for safe, effective treatments for adult patients with ITP. PRTX-100 is an investigational highly purified form of staphylococcal protein A (SpA), an immunoglobulin binding protein derived from *Staphylococcus aureus* cell walls. Studies demonstrate that PRTX-100 binds to B lymphocytes and macrophages, modulating immune processes; purportedly, this activity enables PRTX-100 to reduce immune system–mediated platelet destruction, addressing an underlying cause of ITP. In clinical trials, PRTX-100 is infused intravenously 4 times weekly, up to 24 mcg/kg, over 30–60 minutes. Protalex, Inc., Florham Park, NJ Phase I/II trial ongoing; Jun 2015, FDA granted orphan drug status	Anti-Rh (D) immunoglobulin Corticosteroids Immunosuppressants (azathioprine, cyclophosphamide) Intravenous immune globulin (IVIG) Intravenous platelet transfusion Rituximab Splenectomy Thrombopoietin receptor agonists (eltrombopag [Promacta®] and romiplostim [Nplate®])	Increased platelet counts Reduced abnormal bleeding Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Recombinant human beta-glucuronidase (UX003) for treatment of Sly syndrome	Patients in whom mucopolysaccharidosis type VII (MPS VII) has been diagnosed	MPS VII, also known as Sly syndrome, is a rare, autosomally inherited metabolic disorder, with an estimated worldwide incidence of 1 in 250,000 newborns. Sly syndrome is caused by mutations in the *GUSB* gene, which normally encodes the beta-glucuronidase. Beta-glucuronidase is a lysosomal enzyme essential for glycosaminoglycan breakdown; absent or insufficient beta-glucuronidase leads to accumulation of dangerous levels of glycosaminoglycans. Sly syndrome symptoms are similar to those observed in Hurler syndrome (MPS type I) and have a wide spectrum of severity, broadly affecting bone, tissues, and organs including brain, heart, liver, and spleen. No cure exists for the disorder, and severe forms are fatal at birth or infancy due to hydrops fetalis; many patients who survive to adolescence or adulthood experience fatal heart disease or airway obstruction. UX003 is an investigational enzyme replacement therapy purported to treat the underlying cause of Sly syndrome by providing exogenous beta-glucuronidase. In clinical trials, UX003 is administered as an intravenous liquid-buffered saline formulation at a dosage of 4 mg/kg every 2 weeks. Ultragenyx Pharmaceutical Inc., Novato, CA Multiple phase III trials, including pivotal trial, ongoing; Feb 2012, FDA granted orphan drug status	Bone marrow transplant (experimental therapy)	Improved symptoms Reduced mortality Improved quality of life
Resolaris for treatment of facioscapulo-humeral muscular dystrophy	Patients in whom facioscapulo-humeral muscular dystrophy (FSHD) has been diagnosed	FSHD is a rare, autosomally dominant inherited genetic disorder primarily caused by contraction of a repeat on chromosome 4 and a toxic gain of function of the *DUX4* gene. The disorder has an estimated worldwide prevalence between 1 and 3 in 25,000. FSHD symptoms usually manifest before adulthood and primarily affect the muscles in the face, shoulder blades, and upper arms. Although life expectancy is normal, progression often leads to severe disability. No cure exists for FSHD, and outside of experimental therapies, only palliative care is available to patients. Resolaris (ATYR1940) is an investigational physiocrine-based protein therapy purported to treat underlying causes of FSHD. Physiocrines are hypothesized to function as cell- and physiological state–specific extracellular signaling molecules that can serve as systemic biological drugs for various diseases, including FSHD. In clinical trials, Resolaris is administered intravenously, up to 3 mg/kg, weekly. aTyr Pharma, Inc., San Diego, CA International phase Ib/II trial ongoing; Apr 2015, FDA granted orphan drug status	Palliative care	Delayed or prevented severe symptoms Reduced FSHD-related loss of function Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Resunab for treatment of systemic sclerosis	Patients in whom systemic sclerosis has been diagnosed	Systemic sclerosis is an autoimmune connective tissue disease marked by vasculopathy, skin thickening due to collagen accumulation, autoantibody formation, and inflammation leading to fibrosis in skin and internal organs. In the U.S., systemic sclerosis has an estimated prevalence of 2.4 patients per 10,000 persons; incidence rates are increased among women in mid-to-late childbearing years, African Americans, and Choctaw Native Americans. Patients who have the limited cutaneous form of systemic sclerosis have fairly high survival rates but are at increased risk of developing pulmonary arterial hypertension within 20 years; however, patients with diffuse cutaneous systemic sclerosis have a 10-year survival rate of 50% to 55%. A cure for systemic sclerosis has not been found, and standard conventional-dose immunosuppressive therapy has limited efficacy in either preventing disease progression or reducing mortality rates. Resunab™ is a novel synthetic medication under investigation for treating systemic sclerosis. Preclinical research has demonstrated that Resunab is a preferential agonist of immune cell CB2 receptors. It binds to these receptors and triggers inflammation resolution, a multifaceted process that reduces immune-mediated inflammation and tissue injury; this action offers a potential therapy for improving inflammation and other systemic sclerosis symptoms. In clinical trials, Resunab is administered orally, at 5, 20, or 40 mg doses, daily, for 28 days, followed by 40 mg, daily, for an additional 56 days. Corbus Pharmaceuticals Holdings, Inc., Norwood, MA Phase II trial ongoing; Jun 2015, FDA granted orphan drug status; Aug 2015, FDA granted fast-track status; Resunab is also under investigation for treating cystic fibrosis	Combined autologous hematopoietic stem cell transplant and high-dose immunosuppressive therapy Low-dose immunosuppressive therapy Symptom-based palliative pharmacotherapy (nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme inhibitors)	Delayed disease progression Reduced mortality Improved skin fibrosis and inflammation Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Sublingual thin film apomorphine (APL-130277) for acute treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed Patients in whom PD with consistent daily "off" episodes has been diagnosed	Up to 1 million Americans have a diagnosis of PD, and about 60,000 new cases are diagnosed yearly. Worldwide, 7 million to 10 million patients have a diagnosis of PD. The most frequently prescribed treatment for PD is levodopa (L-dopa), which can be effective but also has severe side effects such as dyskinesia. Dosages must be frequently monitored and adjusted. Patients with PD experience "on" times when L-dopa reduces symptoms and "off" times when medication becomes ineffective and symptoms worsen before the next dose is administered. Treatments that can reduce the "off" times could improve quality of life and management of PD. APL-130277 is a thin film formulation of apomorphine, a nonselective dopamine agonist previously approved as an injectable PD therapy. APL-130277's manufacturer purports that sublingual apomorphine has an improved delivery route, with rapid, durable action that increases "on" times and reduces "off" times with fewer treatment-related adverse events than injectable apomorphine. Additionally, APL-130277 can be self-administered by patients, even during "off" episodes. In clinical trials enrolling patients with PD taking stable doses of carbidopa/L-dopa, APL-130277 thin film is self-administered at doses of 10, 15, 20, 25, 30, or 35 mg for acute treatment of up to 5 daily "off" episodes. Cynapsus Therapeutics, Inc., Toronto, Ontario, Canada Pivotal phase III trial ongoing	Apomorphine (injectable) Carbidopa-levodopa (enteral suspension) Carbidopa-levodopa (oral) Levodopa (oral) Pramipexole Rasagiline Selegiline	Increased "on" times with associated increased levodopa efficacy Rapidly reduced "off" times associated with decreased treatment efficacy Reduced motor fluctuations Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tocilizumab (Actemra) for treatment of systemic sclerosis	Patients in whom systemic sclerosis has been diagnosed	Systemic sclerosis is an autoimmune connective tissue disease marked by vasculopathy, skin thickening due to collagen accumulation, autoantibody formation, and inflammation leading to fibrosis in skin and internal organs. In the U.S., systemic sclerosis has an estimated prevalence of 2.4 patients per 10,000 persons; incidence rates are increased among women in mid-to-late childbearing years, African Americans, and Choctaw Native Americans. Patients who have the limited cutaneous form of systemic sclerosis have fairly high survival rates but are at increased risk of developing pulmonary arterial hypertension within 20 years; however, patients with diffuse cutaneous systemic sclerosis have a 10-year survival rate of 50% to 55%. A cure for systemic sclerosis has not been found, and standard conventional-dose immunosuppressive therapy has limited efficacy for either preventing disease progression or reducing mortality rates. Additionally, no definitive disease cause has been identified, although interleukin-6 (IL-6) has recently been implicated. Tocilizumab (Actemra) is a humanized monoclonal antibody that targets the IL-6 receptor. Elevated levels of IL-6 are hypothesized to indicate systemic sclerosis. Tocilizumab purportedly reduces the dosage of corticosteroids needed to treat systemic sclerosis and may reduce relapse rates in patients who are receiving tapered corticosteroid doses. In clinical trials, patients are administered tocilizumab, injected subcutaneously, 162 mg, weekly, for up to 96 weeks. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trial ongoing; Jun 2015, FDA granted breakthrough therapy status; tocilizumab is also under study for treating giant cell arteritis and polymyalgia rheumatica	Combined autologous hematopoietic stem cell transplant and high-dose immunosuppressive therapy Low-dose immunosuppressive therapy Symptom-based palliative pharmacotherapy (nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme inhibitors)	Delayed disease progression Reduced disease-related mortality Reduced skin fibrosis Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Triheptanoin for treatment of fatty acid oxidation disorders	Patients in whom a fatty acid oxidation disorder (FAOD) has been diagnosed	FAODs are a group of rare, genetic metabolic disorders characterized by absent or malfunctioning enzymes required to oxidize fatty acids, an essential secondary source of energy after glucose is expended. If not accurately diagnosed and treated from birth, these enzyme deficiencies can lead to severe symptoms, including aberrant mood and appetite, extreme sleepiness, hypoglycemia, muscle weakness, and heart failure. Aside from dietary modifications, which have inconsistent efficacy, no treatments exist for FAOD. Triheptanoin (UX007) is a purified synthetic triglyceride purported to treat FAOD by providing supplemental, medium-length, odd-chain fatty acids that can be metabolized to increase intermediates used in Krebs cycle energy generation. Researchers hypothesize that triheptanoin also has a secondary property for treating FAOD, because it can be converted to glucose when patients' glucose levels are low. In clinical trials for treating FAOD, triheptanoin is administered as an orally ingested oil, at dosages equivalent to up to 20% of individual patients' caloric requirements. Baylor Research Institute, Dallas, TX (original developer and clinical trial sponsor) Ultragenyx Pharmaceutical, Inc., Novato, CA (in-licensee and commercialization clinical trial sponsor) Multiple phase II trials ongoing; Apr 2015, FDA granted orphan drug status; triheptanoin is also under investigation for treating other indications, including glucose transporter type-1 deficiency syndrome	Ketogenic diet	Improved energy production Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Triheptanoin for treatment of glucose transporter type-1 deficiency syndrome	Patients in whom glucose transporter type-1 deficiency syndrome (G1D) has been diagnosed	G1D is a rare, autosomal dominant inherited disorder caused by mutations to the *SLC2A1* gene, which normally encodes the glucose transporter 1 (GLUT1) protein. Mutated SLC2A1 leads to deficiencies in brain glucose, because GLUT1 protein is essential for transporting glucose across the blood-brain barrier. Patients with G1D frequently exhibit developmental delays, medication-refractory infantile seizures, microcephaly, spasticity, and movement disorders. Although the majority of patients with G1D respond positively to ketogenic dietary treatment, about 1/3 of patients are unresponsive to available interventions. Triheptanoin (UX007) is a purified synthetic triglyceride purported to have anaplerotic activity, treating G1D by providing primary and secondary tricarboxylic acid cycle metabolites that can cross the blood-brain barrier and be converted to glucose. In clinical trials for treating G1D, triheptanoin is administered as an orally ingested oil, taken 4 times daily with food, at dosages equivalent to up to 35% of individual patients' total caloric intake. The maximum tested daily dose is 100 mg triheptanoin oil. Institut National de la Santé Et de la Recherche Médicale (INSERM), Paris, France (clinical trial sponsor) Ultragenyx Pharmaceutical Inc., Novato, CA (in-licensee and commercialization clinical trial sponsor) University of Texas Southwestern Medical Center (UTSMC), Dallas (clinical trial sponsor) Phase I/II and II trials ongoing; Oct 2014, FDA granted orphan drug status; triheptanoin is also under investigation for treating other indications, including fatty acid oxidation disorders	Ketogenic diet Thioctic acid (experimental)	Improved blood glucose transport Reduced G1D-related paroxysmal symptoms Reduced seizures Improved quality of life

Table 24. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 7 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Brincidofovir for prevention of cytomegalovirus disease after kidney transplantation	Patients who received a kidney transplant and can be cytomegalovirus (CMV) seronegative or seropositive	CMV reactivation is a significant cause of morbidity and mortality after organ transplant. Brincidofovir (CMX001) is intended to be a broad-spectrum antiviral for treating or preventing life-threatening double-stranded DNA (dsDNA) viral diseases, including CMV. It has also been tested for efficacy against adenovirus, smallpox, and Ebola virus disease. Brincidofovir combines the manufacturer's phospholipid intramembrane microfluidization (PIM) conjugate technology with cidofovir, a cytosine nucleoside inhibitor of viral DNA polymerase. PIM technology covalently modifies the cidofovir molecule so that it mimics a naturally occurring phospholipid metabolite that can use natural uptake pathways to increase intracellular concentrations of the drug and achieve oral availability. Additionally, brincidofovir is purported to be significantly more potent in inhibiting viral DNA synthesis than cidofovir. Dosage is not specified for 2 ongoing phase III trials. In phase III trials for other indications (adenovirus, CMV/stem cell transplants), patients are receiving brincidofovir orally, twice weekly; dosage varies. Chimerix, Inc., Durham, NC Phase III trials ongoing; Oct 2014, FDA granted fast-track status for CMV, adenovirus, and smallpox indications	Cidofovir (off label) Ganciclovir Valganciclovir	Decreased rate of organ rejection Reduced CMV viral load Reduced mortality Shorter time to symptom resolution Shorter hospital stays
Iclaprim for treatment of acute bacterial skin and skin structure infection	Patients in whom an acute bacterial skin and skin structure infection (ABSSSI) has been diagnosed	ABSSSIs are primarily caused by the pathogens *Staphylococcus aureus* and *Streptococcus pyogenes*. These infections can be treated with antibiotics, but drug resistance is common, particularly in *S. aureus.* Methicillin-resistant *S. aureus*, or MRSA, is found in about 60% of hospitals in the U.S. Vancomycin is a glycopeptide antibiotic that inhibits bacterial cell wall synthesis and is used for front-line treatment of ABSSSI caused by *S. aureus* and other gram-positive bacteria; however, drug-resistant strains have emerged. Iclaprim is a novel diaminopyrimidine that inhibits bacterial dihydrofolate reductase (DHFR) and is active against methicillin-, trimethoprim-, and vancomycin-resistant strains. In phase III trials, patients will likely receive iclaprim, intravenously, for 10–14 days at an unspecified dose. Motif Bio, plc, London, UK Phase III trials planned; FDA granted fast-track and qualified infectious disease product statuses	Antibiotics (e.g., cephalosporins, glycopeptides)	Increased clinical cure rate Decreased bacterial resistance Shorter hospitalizations Decreased rates of hospital-acquired infection

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Iclaprim for treatment of hospital-acquired bacterial pneumonia	Patients in whom hospital-acquired bacterial pneumonia has been diagnosed	Hospital acquired infections (HAIs) are a group of infections that are a major cause of morbidity and mortality in the U.S.; they collectively cause about 100,000 deaths annually. Hospital-acquired pneumonia (HAP) accounts for 15% to 20% of all HAIs in the U.S. Most HAPs are caused by bacteria (HABP), and pathogens may be either gram negative (such as *Pseudomonas aeruginosa*) or gram positive (such as *Staphylococcus aureus*). HABP is treated with a variety of antibiotics, depending on time to onset of HABP and/or risk factors for antibiotic resistance. Drug resistance to front-line therapies is common. Iclaprim is a novel diaminopyrimidine that inhibits bacterial dihydrofolate reductase (DHFR) and is active against methicillin-, trimethoprim-, and vancomycin-resistant bacterial strains. In phase III trials, patients would likely receive iclaprim, intravenously, for 10–14 days at an unspecified dose. Motif Bio, plc, London, UK Phase III trials planned; FDA granted fast-track and qualified infectious disease product statuses	Antibiotics (typically combination therapy) Aspiration of subglottic secretions Upright or semi-upright patient positioning to reduce risk of aspiration	Increased clinical cure rate Decreased bacterial resistance Shorter hospitalizations Decreased HAI rates
Monoclonal antibody (MEDI3902) for prevention of *Pseudomonas aeruginosa*–related hospital-acquired bacterial pneumonia	Patients who are hospitalized and are at high risk for acquiring *P. aeruginosa*–related bacterial pneumonia (HABP), including those receiving mechanical ventilation	*P. aeruginosa* is a highly drug-resistant gram-negative bacterial pathogen that causes serious hospital-acquired infections (HAIs) including hospital-acquired bacterial pneumonia (HABP). An estimated 51,000 *P. aeruginosa* infections occur each year in a hospital setting in the U.S.; *P. aeruginosa* causes up to 24% of pneumonia cases in mechanically-ventilated patients, and infection may be fatal. These infections can be treated with antibiotics, but drug resistance is common. About 13% of hospital-acquired *P. aeruginosa* infections are caused by multidrug-resistant bacteria. Multidrug-resistant *P. aeruginosa* was recently given a “serious” threat level in the U.S. Centers for Disease Control’s antibiotic resistance threat report. MEDI3902 is a monoclonal antibody (mAb) that blocks *P. aeruginosa* infection by targeting 2 bacterial proteins (PcrV secretion protein; Psl exopolysaccharide). It may be used alone or in combination with antibiotics against *P. aeruginosa*. Medimmune LLC subsidiary of AstraZeneca, London, UK Phase I trial ongoing; Sept 2014, FDA granted fast-track status	Antibiotics (combination therapy, then de-escalating to monotherapy) Aspiration of subglottic secretions Upright or semi-upright patient positioning to reduce risk of aspiration	Increased survival Decreased bacterial resistance Shorter hospitalizations Decreased HAI rates

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ombitasvir/ paritaprevir/ ritonavir (Technivie) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Interferon (IFN)-free direct-acting antiviral (DAA) regimens have been FDA approved only for patients with HCV genotypes 1, 2, and 3, but no DAA regimen had been approved for treating genotype 4, which affects about 10% of the HCV-infection population. Ombitasvir/paritaprevir/ritonavir (Technivie) is an IFN-free regimen intended to improve treatment success and tolerability in patients with chronic HCV genotype 4 without cirrhosis. Ombitasvir is an NS5A inhibitor; paritaprevir is an NS3/4A HCV protease inhibitor; and ritonavir is a CYP3A protease inhibitor. The treatment consists of a fixed-dose combination of ombitasvir (25 mg) and paritaprevir/ritonavir (150/100 mg), administered orally, once daily, with weight-based ribavirin (1,000 or 1,200 mg in divided doses, twice daily) for 12 weeks. AbbVie, North Chicago, IL Enanta Pharmaceuticals, Inc., Watertown, MA FDA approved Jul 2015 for use in combination with RBV for treating chronic HCV genotype 4 infection without cirrhosis	Other DAA regimens	Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 12 weeks) Decreased need for liver transplant Improved quality of life
Relebactam in combination with imipenem/cilastatin (MK-7655A) for treatment of complicated bacterial infection	Patients who are hospitalized and who have complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI), or hospital-acquired or ventilator-associated bacterial pneumonia (HABP or VABP)	Hospital-acquired infections (HAIs) are a group of infections that are a major cause of morbidity and mortality in the U.S.; they collectively cause about 100,000 deaths annually. Bacterial resistance to existing antibiotic therapies is common; an unmet need exists for new antibiotics to treat these infections. Relebactam (MK-7655) is an investigational beta-lactamase inhibitor that is being investigated together with imipenem/cilastatin (Primaxin®), which is an FDA-approved combination beta lactam (carbapenem) antibiotic, for treating 3 HAIs: cIAI, cUTI, and HABP/VABP. The investigational combination of these 3 antibiotics is called MK-7655A. In a phase III trial, patients are receiving MK-7655A, intravenously, once every 6 hours. Duration of treatment depends on the infection type. Dosage depends on renal function; patients receive either imipenem/cilastatin 200 mg plus relebactam 100 mg or imipenem/cilastatin 500 mg plus relebactam 250 mg. Merck & Co., Inc., Whitehouse Station, NJ Phase III trial ongoing; Sept 2014, FDA granted qualified infectious disease product and fast-track statuses	Antibiotics (e.g., colistimethate sodium, imipenem/cilastatin)	Decreased morbidity Decreased mortality Shorter hospital stays

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Taurolidine-citrate-heparin (Neutrolin) for prevention of catheter-related bloodstream infection and thrombosis	Patients who are undergoing hemodialysis through a central venous catheter (CVC) Patients with cancer who are receiving total parenteral nutrition (TPN) through a CVC	About 425,000 catheter-related bloodstream infections (CRBSIs) occur each year in the U.S., with a mortality rate of 20% to 25%. Patients who have CVCs are also susceptible to thrombosis. These conditions may be prevented by treating catheters with antimicrobial and/or anticoagulant agents (catheter lock solutions), but no agents are approved for use in the U.S. Taurolidine-citrate-heparin (Neutrolin) is a combination catheter lock solution being developed for preventing infection, thrombosis, and biofilm formation in patients who have a CVC and are undergoing hemodialysis or in patients with cancer who have a CVC and are receiving TPN. Taurolidine (3.5%) is a taurine (amino acid) derivative with antimicrobial activity against gram-positive and gram-negative bacteria, as well as *Candida* species; citrate (3.5%) also has antimicrobial activity. Heparin (1,000 U/mL) is used as an anticoagulant. CorMedix, Inc., Bedminster, NJ Phase III trial planned; Jan 2015, FDA granted qualified infectious disease product and fast-track statuses	Antibiotics (off-label; e.g., ciprofloxacin, minocycline, rifampin, vancomycin) Citrate Heparin Taurolidine Urokinase	Reduced CRBSI incidence Reduced mortality Improved patient health outcomes

Table 25. AHRQ Priority Condition: 10 Obesity: 2 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Obalon intragastric balloon for treatment of obesity	Patients in whom overweight or obesity has been diagnosed, with a body mass index (BMI) of 27–40 kg/m^2 who have been unable to lose weight through a supervised diet and behavior modification program	Modifications to diet and exercise are frequently inadequate for reducing weight in patients who are severely overweight or obese. Intermediate interventions between invasive surgery and lifestyle changes and drugs could fill a therapeutic gap. The Obalon intragastric balloon is intended to reduce stomach capacity, thereby increasing satiety with less food, for up to 3 months. The balloon is contained in a capsule connected to a thin tube. With a glass of water, the patient swallows the capsule with the tube attached. Over several minutes, the capsule dissolves to release the deflated balloon. After confirming balloon placement on x-ray, the physician inflates it with inert gas to a 250 cc through the tube and then removes the tube through the mouth. Balloon placement takes about 15 minutes and purportedly does not require sedation. The balloon remains in the stomach for up to 12 weeks and then must be removed endoscopically through the mouth. The manufacturer purports that up to 3 gastric balloons can be placed together, in subsequent procedures, to reduce the amount of food a patient can consume. Obalon Therapeutics, Carlsbad, CA Pivotal trial ongoing; FDA premarket approval application submission anticipated by Dec 2015	Adjustable gastric banding Bariatric surgery (e.g., gastric bypass, sleeve gastrectomy) Liraglutide (Saxenda®) Lorcaserin (Belviq®) Naltrexone/bupropion (Contrave®) Orbera™ intragastric balloon Orlistat (Xenical®) Phentermine/ topiramate (Qsymia®) ReShape™ Integrated Dual Balloon System VBLOC Maestro® vagus nerve blocking	Decreased comorbidities (e.g., prediabetes, high blood pressure) Increased weight loss Improved quality of life
Orbera intragastric balloon for treatment of obesity	Patients in whom obesity has been diagnosed, with a body mass index (BMI) of 30–40 kg/m^2 who have been unable to lose weight through a supervised diet and behavior modification program	Modifications to diet and exercise are frequently inadequate for reducing weight in patients who are severely overweight or obese. Intermediate interventions between invasive surgery and lifestyle changes and drugs could fill a therapeutic gap. The Orbera™ intragastric balloon is a silicon balloon designed to reduce stomach capacity, thereby increasing satiety with less food, for up to 6 months. A physician places the deflated balloon in the stomach endoscopically using local anesthesia and mild sedation and fills it with 400–700 cc of sterile saline through a self-sealing valve. Endoscopic placement takes up to 30 minutes. When removal is desired, the device is deflated endoscopically, captured with an endoscopic snare tool, and removed through the mouth. Apollo Endosurgery, Inc., Austin, TX Pivotal trial complete; Aug 2015, FDA approved “for use as an adjunct to weight reduction for adults with obesity with Body Mass Index (BMI) of ≥ 30 and ≤ 40 kg/m^2 and is to be used in conjunction with a long-term supervised diet and behavior modification program designed to increase the possibility of significant long-term weight loss and maintenance of that weight loss.” The device is indicated for a maximum of 6 months placement in adults for whom conservative weight loss measures were unsuccessful.	Adjustable gastric banding Bariatric surgery (e.g., gastric bypass, sleeve gastrectomy) Liraglutide (Saxenda®) Lorcaserin (Belviq®) Naltrexone/bupropion (Contrave®) Orlistat (Xenical®) Phentermine/ topiramate (Qsymia®) ReShape™ Integrated Dual Balloon System VBLOC Maestro® vagus nerve blocking	Decreased comorbidities (e.g., prediabetes, high blood pressure) Increased weight loss Improved quality of life

Table 26. AHRQ Priority Condition: 11 Peptic Ulcer Disease and Dyspepsia: 2 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Esophageal cytology collection system (Cytosponge) for diagnosis of Barrett's esophagus	Patients who have symptoms suggestive of gastroesophageal reflux disease who may be at risk of Barrett's esophagus	Although relatively rare, esophageal cancer can be fatal. Barrett's esophagus increases risks for developing esophageal cancer. The discomfort and inconvenience of periodic endoscopy to monitor Barrett's esophagus can discourage some patients from adhering to followup schedules; periodic endoscopy also increases monitoring costs. New interventions are needed to improve patient compliance and lower costs. The Cytosponge® is intended to be a less invasive alternative to endoscopy for evaluating symptoms suggestive of gastroesophageal reflux disease or Barrett's esophagus. A patient swallows a gelatin-coated compressed mesh sponge attached to a string. Stomach acids dissolve the gelatin and release the sponge. A clinician uses the string to withdraw the mesh, which collects an esophageal tissue sample during removal. Medtronic, plc, Dublin, Ireland Unphased, observational, single-group studies ongoing; FDA 510(k) cleared Nov 2014 for "use in the collection and retrieval of surface cells in the esophagus"	Upper endoscopy	Improved patient comfort Reduced diagnostic cost
External myoelectric monitoring (G-Tech patch) to identify gastrointestinal disorders	Patients with gastrointestinal symptoms of uncertain cause	Available gastrointestinal imaging tests are often labor intensive and require use of radioactive tracers. Further, testing, such as endoscopy or barium swallow exams, cannot measure gut motility or electrical activity over an extended period. The G-Tech patch is intended to noninvasively monitor electrical activity in the stomach, intestines, and colon to help physicians diagnose gastrointestinal disease. The system comprises 3 wireless electrodes worn as disposable patches on the abdomen for several days. The electrodes send collected data to a smartphone via Bluetooth low-energy transmission. The smartphone application sends patient data to a secure cloud-based database for physician review. Based on findings, a physician may order additional testing as needed.. G-Tech Medical, Inc., Mountain View, CA Observational feasibility study ongoing	Barium x-ray Blood tests Computed tomography Flexible sigmoidoscopy Lactose tolerance tests Stool tests Symptomatic criteria (Rome, Manning criteria)	Improved diagnostic accuracy Reduced use of unnecessary diagnostic tests

Table 27. AHRQ Priority Condition: 12 Pregnancy, Including Preterm Birth: 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts

Table 28. AHRQ Priority Condition: 13 Pulmonary Disease, Asthma: 4 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
High-dose nitric oxide (AIT-CF) for adjunctive treatment of cystic fibrosis	Patients in whom cystic fibrosis (CF) has been diagnosed	No curative treatments exist for CF. Molecular treatments are being developed to reduce the mucus buildup and exacerbations that are hallmarks of the disease. Patients are also treated with antibiotics to manage infections. Treatments providing improved CF symptom management are needed. Nitric oxide (NO) is a naturally produced gas that has antimicrobial properties and has demonstrated efficacy against a broad spectrum of microbes, including those that are drug-resistant. NO also promotes smooth muscle relaxation of bronchi and has mucolytic activity. AIT-CF is a proprietary, high-dose NO formulation and delivery system being developed for treating CF. AIT-CF is delivered directly to the lungs, at 160 ppm, using positive air pressure and integrated monitoring. In a phase I/II trial, patients are receiving AIT-CF for 30 minutes, 3 times daily, for a total of 10 working days. Advanced Inhalation Therapies, Ltd., Rehovot, Israel Phase I/II trial ongoing; Sept 2014, FDA granted orphan drug status	Antibiotics Mucolytics	Improved lung function Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Inhaled ciprofloxacin dry powder for treatment of bacterial infection–related bronchiectasis	Patients in whom bronchiectasis (BE) related to bacterial infection has been diagnosed	BE is characterized by dilated bronchi, airway inflammation, and bacterial colonization and affects about 110,000 people in the U.S. Chronic bacterial infection is common and may contribute to increased symptoms, decreased quality of life, and worsened forced expiratory volume in 1 second (FEV_1) values. No licensed antibiotic therapies are available for patients who have chronic bacterial infection and BE; oral, inhaled, or intravenous antibiotics are used off label and do not always improve patient outcomes. Ciprofloxacin dry powder for inhalation (DPI) is an investigational formulation of the FDA-approved broad-spectrum fluoroquinolone antibiotic ciprofloxacin, which blocks the activity of bacterial DNA topoisomerases. Ciprofloxacin DPI is intended for treating patients who have BE and chronic bacterial infection and is directly delivered to the airways. In phase III trials, patients are receiving ciprofloxacin DPI 32.5 mg, twice a day, in cycles of 14 days on/14 days off or 28 days on/28 days off, for 48 weeks. Bayer HealthCare Pharmaceuticals unit of Bayer AG, Leverkusen, Germany Phase III trials ongoing; FDA granted orphan drug and qualified infectious disease product statuses	Antibiotics (off-label; e.g., combination cephalosporin/ aminoglycoside, ciprofloxacin, low-dose gentamycin, tobramycin)	Shorter length of therapy Simplified dosing Improved adherence to treatment Fewer adverse events Reduced overall cost of treatment
Lebrikizumab for treatment of idiopathic pulmonary fibrosis	Patients in whom idiopathic pulmonary fibrosis (IPF) has been diagnosed	IPF is a progressive, debilitating disease characterized by inflammation and scarring (fibrosis) in the lungs, with a median survival time from diagnosis of 2–5 years; 5-year survival rate is about 20%. 2 approved treatments are available to slow disease progression, however they do not cure IPF. Lebrikizumab is a humanized monoclonal antibody designed to block the activity of interleukin-13 (IL-13), a cytokine that is produced by T-helper type 2 (Th2) cells and is a strong inducer of tissue fibrosis. Inhibiting IL-13 could slow the progression of IPF. In a phase II trial, patients are receiving lebrikizumab, subcutaneously, once every 4 weeks, at an unspecified dose. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase II trial ongoing; Mar 2015, FDA granted orphan drug status; lebrikizumab is also being developed for treating moderate to severe asthma	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Methotrexate Nintedanib Penicillamine Pirfenidone Pulmonary rehabilitation Supplemental oxygen	Improved lung function measured by forced vital capacity Improved ability to perform activities of daily living Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Monoclonal antibody (SAR156597) for treatment of idiopathic pulmonary fibrosis	Patients in whom idiopathic pulmonary fibrosis (IPF) has been diagnosed	IPF is a progressive, debilitating disease characterized by inflammation and scarring (fibrosis) in the lungs, with a median survival time from diagnosis of 2–5 years; 5-year survival rate is about 20%. 2 approved treatments are available to slow disease progression; however, they do not cure IPF. SAR156597 is a tetravalent, bispecific monoclonal antibody designed to simultaneously block the activity of interleukin-4 (IL-4) and interleukin-13 (IL-13), 2 cytokines that are produced by T-helper type 2 (Th2) cells and are strong inducers of tissue fibrosis. Inhibiting IL-4 and IL-13 could slow the progression of IPF. In a phase II trial, patients are receiving SAR156597, subcutaneously, once or twice weekly for 52 weeks at an unspecified dose. Sanofi, Paris, France Phase II trial ongoing; Sept 2011, FDA granted orphan drug status	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Methotrexate Nintedanib Penicillamine Pirfenidone Pulmonary rehabilitation Supplemental oxygen	Improved lung function measured by forced vital capacity Improved ability to perform activities of daily living Slowed disease progression Improved quality of life

Table 29. AHRQ Priority Condition: 14 Substance Abuse: 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts

Table 30. AHRQ Priority Condition: 15 Cross-Cutting: 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts

Section 3. Interventions Tracked but Archived Since Last Update: 25 Interventions

Table 31. AHRQ Priority Condition: 01 Arthritis and Nontraumatic Joint: 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason

Table 32. AHRQ Priority Condition: 02 Cancer: 12 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Capsule endoscopy (PillCam Colon 2) for colorectal cancer screening	Patients who require further evaluation after incomplete colonoscopy	In about 10% of colonoscopy procedures, colon imaging is incomplete—not technically possible despite adequate bowel preparation—potentially missing colorectal cancers and adenomatous polyps. Followup screening with a next-generation pill camera (PillCam Colon 2) represents a new option for this patient population. The device consists of a light-emitting diode and 2 miniature cameras on either end of a 12-by-33 mm pill. The 2 cameras are intended to enable better image capture as the device travels the intestinal tract. After ingestion by the patient, the pill camera sends up to 35 frames per second of data to a recorder worn by the patient over the course of about 10 hours; data are subsequently analyzed by a physician. Given Imaging, Ltd., Yoqneam, Israel, a subsidiary of Covidien, plc., Dublin, Ireland; in 2015, Covidien was acquired by Medtronic, plc, Dublin, Ireland FDA cleared under the 510(k) de novo classification process in Jan 2014 for “detection of colon polyps in patients after an incomplete optical colonoscopy with adequate preparation, and a complete evaluation of the colon was not technically possible”	Barium enema Computed tomography colonography Repeat dual- or triple-camera colonoscopy	Improved colorectal cancer/adeno-matous polyp sensitivity Improved colorectal cancer/adeno-matous polyp specificity	Experts’ comments indicated that the intervention offers only incremental improvement over other options and has no high-impact potential

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Everolimus (Afinitor) for treatment of advanced HER2-positive breast cancer	Patients in whom advanced HER2-positive breast cancer has been diagnosed	Although HER2-targeted therapies such as trastuzumab and lapatinib have improved outcomes for patients with HER2-positive advanced breast cancer, not all patients have disease that responds to these therapies. Everolimus (Afinitor®) is a small-molecule inhibitor of the protein mTOR, which is a central regulator of cell growth. Everolimus targets a novel cellular pathway compared with other HER2-targeted therapies. Using everolimus to inhibit mTOR by everolimus has been demonstrated to be effective in treating multiple cancer types (e.g., renal cell carcinoma, astrocytoma). In clinical trials, everolimus was administered orally, 5 mg, daily, in combination with vinorelbine and trastuzumab. Novartis International AG, Basel, Switzerland Phase III trials (BOLERO-1 and BOLERO-3) ongoing	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine, pemetrexed) HER2-targeted antibodies (e.g., ado-trastuzumab emtansine, pertuzumab, trastuzumab) HER2-targeted kinase tyrosine inhibitors (e.g., afatinib, lapatinib) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloid (e.g., vinorelbine)	Increased progression-free survival Increased overall survival Improved quality of life	Phase III BOLERO-3 trial showed incremental improvement while the phase III BOLERO-1 trial missed its primary endpoint; everolimus is no longer in the 2015 Novartis pipeline

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Ex vivo expanded cord blood (StemEx) for allogeneic bone marrow transplant treatment of hematologic malignancies	Patients with hematologic malignancies who need a bone marrow transplant and for whom no suitable matched donor is available	Individuals being treated for hematologic malignancies may receive high-dose chemotherapy (myeloablative therapy) followed by a bone marrow transplant to reconstitute their ability make healthy blood cells. Perfectly matched bone marrow donors are not available for all patients who could benefit from transplantation, because of the difficulty in identifying perfectly matched donors. Although an exact match is needed for adult marrow transplants to avoid complications from graft-versus-host disease (GVHD), cord blood reportedly causes significantly less GVHD; however, the number of stem cells in cord blood is not large enough to provide complete bone marrow engraftment. StemEx is a graft of stem cells and progenitor cells isolated from a single unit of cord blood. Stem cells and progenitor cells are enriched ex vivo by means of copper chelation, which reduces the availability of copper and purportedly promotes cell proliferation over differentiation. The enriched cell population is then infused into the patient along with the remainder of the cord blood unit in an effort to enable the patient to make healthy blood cells after myeloablative therapy. Gamida Cell, Ltd., Jerusalem, Israel, in partnership with Teva Pharmaceutical Industries, Ltd., Petah-Tikva, Israel Phase II/III trial ongoing; FDA granted orphan drug status for use as hematopoietic support in patients with recurrent or refractory hematologic malignancies who are receiving high-dose chemotherapy, in patients with chronic myeloid leukemia, and in patients with myelodysplastic syndromes	Pooled unexpanded cord blood transplant Unexpanded cord blood transplant	Increased overall survival Improved bone marrow engraftment rate Improved neutrophil recovery rate Improved platelet recovery rate	In Jul 2013, company announced that FDA would require a phase III randomized controlled trial to support approval; no such trial has been initiated in the subsequent 2 years; no longer meets horizon scanning criteria for tracking

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
High-intensity focused ultrasound (Ablatherm system) for treatment of localized prostate cancer	Patients in whom localized prostate cancer has been diagnosed	High-intensity focused ultrasound (HIFU) is a noninvasive treatment under study for treating prostate cancer. HIFU ablates tissue by using sound waves to generate heat within a small, focused area, leaving surrounding tissue unaffected. The noninvasive and targeted nature of HIFU has the potential to reduce side effects associated with invasive procedures and radiation therapy and, unlike those procedures, may also be repeated in the event of local recurrence. HIFU ablation is performed in a 1–3 hour outpatient procedure. The most advanced clinical trial of the Ablatherm® HIFU system in the U.S. is studying its use in treating patients who have localized prostate cancer and have not undergone prostate cancer treatment. EDAP TMS S.A., Lyon, France Phase II/III trial met primary endpoint; FDA accepted premarket approval application Mar 2013; Jul 2014, FDA's Gastroenterology & Urology Devices panel voted 9-0 against the device's effectiveness, 5-3 against its safety (with 1 abstention) 8-0 (with 1 abstention) that risks outweigh the benefits; Nov 2014, FDA sent a "not approvable" letter to the company; in subsequent discussions, FDA recommended the company seek clearance of Ablatherm HIFU through a direct de novo 510(k) process rather than a premarket approval application, which could speed its clearance	Brachytherapy External beam radiation Observation Other HIFU systems (in development) Radical prostatectomy	Increased overall survival Increased progression-free survival Improved quality of life	Experts' comments indicated the technology has no high-impact potential because of other available treatments, FDA status, and the fact that no trial has compared it to optimal standard treatments; only 1 small comparative trial has been ongoing to compare it to cryosurgery and that trial's status has not been updated in 1½ years

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
High-intensity focused ultrasound (Sonablate system) for treatment of localized prostate cancer	Patients in whom localized prostate cancer has been diagnosed	High-intensity focused ultrasound (HIFU) is a noninvasive treatment under study for treating prostate cancer. HIFU ablates tissue by using sound waves to generate heat within a small, focused area, leaving surrounding tissue unaffected. The noninvasive and targeted nature of HIFU has the potential to reduce side effects associated with invasive procedures and radiation therapy and, unlike those procedures, may also be repeated in the event of local recurrence. HIFU ablation is performed in a 1–3 hour outpatient procedure. The most advanced clinical trial of the Sonablate system in the U.S. is studying its use in treating patients who have localized prostate cancer that has recurred after initial therapy with external beam radiation therapy. SonaCare Medical, LLC (formerly USHIFU, LLC), Charlotte, NC Phase III trial ongoing for prostate cancer; system available in Europe since 2001; Oct 2014, FDA issued a “not approvable” letter to the premarket application submission reviewed by FDA’s advisory panel; Mar 2015, FDA allowed a marketing application submission via the direct de novo 510(k) process	Brachytherapy External beam radiation Observation Other HIFU systems (in development) Radical prostatectomy	Increased overall survival Increased progression-free survival Improved patient quality of life	Experts’ comments indicated the technology has little high-impact potential because of other treatment options
Ipilimumab (Yervoy) for treatment of metastatic hormone-refractory prostate cancer	Patients in whom metastatic, chemotherapy-naïve castration-resistant prostate cancer (CRPC) has been diagnosed	Men with progressive metastatic CRPC have a poor prognosis and few treatment options. Ipilimumab (Yervoy™) is a 1st-in-class targeted anticytotoxic T-lymphocyte antigen 4 therapy; it is intended to block the activity of cytotoxic T-lymphocyte antigen 4, which could lead to increased antitumor cytotoxic activity (reduce immune tolerance to tumor cells). Ipilimumab is administered by intravenous infusion, 10 mg/kg. Treatment consists an induction phase (4 doses, 1 every 3 weeks) followed by a maintenance phase (1 dose every 12 weeks). Bristol-Myers Squibb, New York, NY Sept 2013, company announced phase III trial did not meet its primary endpoint of improving overall survival in patients who had previously undergone docetaxel therapy; Aug 2015, company announced phase III trial did not meet its primary endpoint of improving overall survival in patients who were chemotherapy naïve	Abiraterone Docetaxel Enzalutamide Radium-223 Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life	Development halted in the U.S. after 2 phase III trials failed to demonstrate an improvement in overall survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Ipilimumab (Yervoy) for treatment of small cell lung cancer	Patients in whom extensive-disease small cell lung cancer (SCLC) has been newly diagnosed	Patients with advanced SCLC have extremely low survival rates with current treatments. Ipilimumab (Yervoy™) is a cytotoxic T-lymphocyte antigen 4 (CTLA-4)-targeted immunotherapy previously approved for treating metastatic melanoma. By blocking the activity of CTLA-4, ipilimumab may increase antitumor cytotoxic activity and reduce immune tolerance to tumor cells. This agent is being tested as a 1st-line treatment in combination with etoposide and platinum therapy. Ipilimumab is administered intravenously, 10 mg/kg, once every 3 weeks for 4 doses, then once every 12 weeks beginning at week 24. Bristol-Myers Squibb, New York, NY Phase III trial ongoing	Chemotherapy with 1 or more of the following: ALK inhibitors if ALK-mutant (e.g., ceritinib, crizotinib) Angiogenesis inhibitors (e.g., bevacizumab, ramucirumab) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., pemetrexed, gemcitabine) EGFR inhibitors if *EGFR*-mutant (e.g., afatinib, erlotinib) PD-1 antibodies (e.g., nivolumab [pembrolizumab; in development]) Platinum-based agents (e.g., carboplatin, cisplatin) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloids (e.g., vinblastine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life	Development halted for treating SCLC because the phase III Study-156 trial failed to meet its primary endpoint

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Ramucirumab (Cyramza) for treatment of metastatic colorectal cancer	Patients in whom metastatic colorectal cancer (CRC) has been diagnosed	Current 2nd-line treatments for metastatic CRC are of limited efficacy, and the median overall survival of these patients is less than 1 year. Ramucirumab (Cyramza) is a novel monoclonal antibody that binds to the extracellular domain of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2), which is a receptor tyrosine kinase that acts as a central mediator of tumor angiogenesis. Available inhibitors of the VEGF pathway include a monoclonal antibody specific for VEGF and small-molecule inhibitors of the kinase activity of VEGFR2 (and other receptor tyrosine kinases). Therefore, ramucirumab represents a novel mechanism of action for inhibiting VEGF-pathway signaling. Treatment is intended for patients whose disease has progressed after standard 1st-line chemotherapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. In clinical trials for CRC, ramucirumab is intravenously administered, 8 mg/kg, once every 2 weeks as an adjunct to the standard 2nd-line FOLFIRI (folinic acid [leucovorin], 5-fluorouracil, and irinotecan) regimen. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trial (RAISE) ongoing; Apr 2015, FDA approved in combination with FOLFORI for treating CRC in the 2nd-line setting	Chemotherapy with 1 or more of the following: Angiogenesis inhibitors (e.g., bevacizumab) Antimetabolites (e.g., 5-fluorouracil, capecitabine) EGFR antibodies (e.g., cetuximab, panitumumab) FOLFIRI FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin) Multikinase inhibitors (e.g., regorafenib) Platinum-based agents (e.g., oxaliplatin) Topoisomerase inhibitors (e.g., irinotecan)	Increased overall survival Increased progression-free survival Improved quality of life	Experts' comments indicated this agent has little high-impact potential because of the numerous other treatments available for this patient group

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Selumetinib for treatment of metastatic uveal melanoma	Patients in whom advanced uveal melanoma has been diagnosed	Uveal melanoma arises from melanocytes within the choroid of the eye. In 50% of patients, the cancer metastasizes and has a poor outcome, with a median survival of less than 12 months. Although radiotherapy is used to treat advanced cutaneous melanoma, no effective therapy has been found for patients with metastatic uveal melanoma. The mitogen-activated protein kinase (MAPK)/extracellular signal–regulated kinase (ERK) pathway is a central regulator of cellular responses to growth signals. Aberrant activity of this pathway has been implicated in the development of many cancer types. The MAPK kinase (MEK) is a protein kinase that plays a role in this pathway by controlling activation of ERK; therefore, inhibiting MEK activity could inhibit cancer cell growth and/or survival. Selumetinib (AZD6244, ARRY-142886) is a MEK inhibitor under study for treating uveal melanoma. In clinical trials, it is administered orally, 75 mg, twice daily, indefinitely until disease progression or intolerable toxic effects. AstraZeneca, London, UK Phase III trial (SUMIT) ongoing; Apr 2015, FDA granted orphan drug status	Gamma knife therapy Radiotherapy Surgery Thermotherapy	Increased overall survival Increased progression-free survival Improved quality of life	Development halted by manufacturer because the phase III SUMIT trial failed its primary endpoint of improving progression-free survival and patients manifested a greater rate of adverse events

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Sirolimus (Rapamune) for treatment of lymphangio-leiomyomatosis	Patients with lymphangio-leiomyomatosis (LAM)	LAM is a low-grade metastatic neoplasm that targets the lungs, and it almost exclusively affects women. LAM is characterize by proliferation of smooth muscle cells in lungs, bronchioles, alveolar septa, perivascular spaces, and lymphatics. The proliferation obstructs airways and is associated with abdominal tumors, cystic destruction of the lung, and pleural effusions. It occurs sporadically in about 5 of 1 million people and in 30% to 40% of women who have another disease, tuberous sclerosis complex. Even though infiltrating smooth muscle cells have a benign appearance, they bear a biallelic-inactivating mutation in the *TSC* genes. This defect causes mTOR to be constitutively active, which regulates cellular functions such as growth, motility, and survival. Sirolimus (Rapamune®) is an mTOR inhibitor demonstrated to restore homeostasis in *TSC*-defective cells and has the potential to improve lung function in patients with LAM. In clinical trials, 2 mg of sirolimus is administered to patients orally, daily, for 1 year. Pfizer, Inc., New York, NY Phase III trials (MILES and MIDAS) ongoing; May 2015, FDA approved for treating LAM after accepting a supplemental new drug application and granting priority review status in Feb 2015; sirolimus is also approved as an immunosuppressant to prevent organ rejection following transplant	Estrogen inhibitors (e.g., tamoxifen, toremifene) Estrogen receptor inhibitors (e.g., fulvestrant) Lung transplant	Increased overall survival Increased progression-free survival Improved quality of life	Since 2011, sirolimus has been used off label for treating lymphangio-leiomyomatosis; thus, its FDA approval will have little high-impact potential

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Sorafenib (Nexavar) for treatment of breast cancer	Patients in whom metastatic or locally advanced/ unresectable, HER2-negative breast cancer has been diagnosed; patients must have received up to 2 chemotherapies that included at least 1 anthracycline	Improved therapy options are needed for patients with advanced breast cancer that has progressed on or is refractory to standard chemotherapies. Sorafenib (Nexavar®) is a multiple kinase inhibitor (VEGFR, PDGFR, and Raf kinases) that targets the MAP kinase pathway to inhibit tumor cell proliferation and angiogenesis. In a trial of patients with advanced breast cancer, sorafenib is administered orally, 600 mg, daily, in combination with capecitabine. Bayer AG, Leverkusen, Germany, and Onyx Pharmaceuticals, a subsidiary of Amgen, Inc., Thousand Oaks, CA Phase III trial (RESILIENCE) ongoing; FDA approved for treating kidney and liver cancer, indications for which it is typically administered at a dosage of 400 mg, twice daily	Chemotherapy with 1 or more of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine, pemetrexed) PARP inhibitors (e.g., BMN 673, niraparib, olaparib [in development]) PD-1 antibodies (e.g., pembrolizumab [in development]) Taxanes (e.g., docetaxel, nab-paclitaxel, paclitaxel) Vinca alkaloid (e.g., vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life	The phase III RESILIENCE trial failed its primary endpoint; sorafenib for this breast cancer indication is not part of the 2015 Bayer pipeline
Urocidin for treatment of nonmuscle-invasive bladder cancer	Patients in whom nonmuscle-invasive bladder cancer (cancer on the surface of the bladder) has been diagnosed	Treatments that can provide better outcomes and reduce rates of recurrence are needed for patients with bladder cancer. Urocidin™ is a mycobacterial cell-wall DNA complex proposed to create a localized immune response. The mechanism of action is unclear. In clinical trials, urocidin is administered to patients who did not respond to bacillus Calmette-Guérin (BCG) treatment. Urocidin is administered by transurethral catheter directly into the bladder, 8 mg, weekly. Telesta Therapeutics, Inc., Belleville, Ontario, Canada Phase II/III trial complete; FDA granted fast-track status in 2006; Jun 2015, company filed a biologics license application with FDA	BCG treatment Cystectomy Intravesical chemotherapy Radiation therapy	Avoided cystectomy Increased overall survival Increased progression-free survival Improved quality of life	Experts' comments deemed this to have no high-impact potential because it offers only an incremental effect for treating bladder cancer

Table 33. AHRQ Priority Condition: 03 Cardiovascular Disease: 3 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Autologous bone marrow stem cells (Ixmyelocel-T) for treatment of critical limb ischemia	Patients in whom critical limb ischemia (CLI) has been diagnosed	Outcomes for patients with CLI are poor, and many patients require amputation. This intervention represents a novel treatment modality for this condition. Tissue repair cell (Ixmyelocel-T) technology consists of bone marrow extracted from the patient, expanded over the course of 12 days at the manufacturer's facility using the company's proprietary process, and reinfused into the patient 14 days after extraction. The formulation includes monocytes, macrophages (intended to destroy dead tissue, stimulate regeneration, and reduce inflammation), mesenchymal stem cells (intended to promote angiogenesis), and endothelial progenitor cells (intended to promote blood vessel lining and generate cardiovascular tissue). Vericel Corp., Cambridge, MA Phase II trial ongoing, FDA granted fast-track status	Percutaneous angioplasty and stenting Pharmacotherapy (e.g., cilostazol, pentoxifylline) Surgery	Regenerated tissue Improved circulation Reduced need for amputation Reduced morbidity and mortality	Company announced "a strategic change in its research and development programs" to refocus clinical development of ixmyelocel-T for treating dilated cardiomyopathy

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Electrical stimulation of carotid baroreceptors (Barostim neo Legacy system) for treatment-resistant hypertension	Patients in whom severe, drug-resistant hypertension has been diagnosed	Many pharmacotherapies are available for treating hypertension, and typically 3 types of drugs are used in conjunction to try to lower blood pressure. Yet, many cases of hypertension are not controlled with these interventions, and because such treatment-resistant hypertension is associated with high morbidity (e.g., end-organ damage) and mortality, novel interventions are warranted. Baroreceptors in the aortic arch and the carotid sinuses are fibers that act as natural blood pressure sensors and control nervous system activity that affects the heart, kidneys, and peripheral blood vessels. When baroreceptors are stimulated by an increase in blood pressure, sympathetic efferent nerves are inhibited. Signaling by sympathetic efferent nerves typically increases blood pressure through its effects on cardiac, renal, and vasomotor targets. Therefore, blocking sympathetic nervous system activity in response to elevated blood pressure, combined with a simultaneous increase in parasympathetic activity, can act as a negative-feedback loop to stabilize blood pressure by reducing heart rate and fluid volume and dilating arteries. The Barostim neo Legacy system uses a pacemaker-like implantable pulse generator, inserted subcutaneously near the clavicle, to continuously deliver electrical signals to baroreceptors in both the left and right carotid arteries in the neck, via 2 carotid sinus leads. Device voltage can be titrated by physicians, via an external programmer, until the patient reaches a predetermined hemodynamic endpoint or the maximum dose is reached. The Neo System has 1 carotid sinus lead, and implantation requires only a unilateral incision. The company purports that this and the smaller lead design lead to a shorter procedure time and a greater patient safety profile than its 1st-generation Rheos system. CVRx, Inc., Minneapolis, MN Dec 2014, FDA granted humanitarian device exemption for use in patients with resistant hypertension who were previously implanted with the Rheos Carotid Sinus Leads Models 1010R, 1010L, 1014L, or 1014R	Optimal medical management	Fewer cardiovascular events Reduced hypertension Reduced mortality Reduced stoke incidence Improved quality of life	Experts' comments deemed this to have no high-impact potential because FDA gave device a humanitarian device exemption to enable only U.S. patients who had been defined as responders to the previous generation system, Rheos Carotid Sinus Lead System, to receive it—fewer than 300 patients

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Ultrasound (ClotBust-ER) for treatment of acute ischemic stroke	Patients in whom acute ischemic stroke has been diagnosed	Although stroke is a leading cause of death in the U.S., only a single drug, tissue plasminogen activator (tPA), is approved for neuroprotection. It is effective only when administered within a narrow window of symptom onset, and only a very small percentage of patients experiencing an acute stroke receive tPA because most do not present for treatment within the necessary time frame. Transcranial ultrasound is a new treatment intended to dissolve blood clots causing ischemic stroke. However, technical challenges are associated with administering transcranial ultrasound, and sonographers capable of detecting occluded cerebral artery segments are available only in specialized stroke centers or emergency departments. ClotBust™-ER is a hands-free ultrasound device that employs multiple transducers operating at 2 MHz. It is intended to deliver therapeutic ultrasound energy to the vessel occlusion in the brain to treat ischemic stroke in patients eligible for intravenous thrombolytic therapy. The system includes multiple ultrasound transducers mounted on an adjustable head frame worn by the patient while the sonographer administers therapeutic ultrasound in the principal regions where the majority of vessel occlusions in the brain occur. Because the transducers self-align based on anthropometric landmarks, they do not need to be aimed by a trained sonographer. Cerevast Therapeutics, Inc., Redmond, WA Phase III trial terminated	Anticoagulant therapy (e.g., tPA [alteplase], aspirin) as indicated by patient history and time of presentation for care	Improved clot lysis Reduced stroke-related morbidity and mortality	Trial was terminated with no further information reported; company Web site is no longer live

Table 34. AHRQ Priority Condition: 04 Dementia (including Alzheimer's Disease): 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason

Table 35. AHRQ Priority Condition: 05 Depression and Other Mental Health Disorders: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Avatar system for treatment of auditory hallucinations in schizophrenia	Patients in whom schizophrenia has been diagnosed	Of 1.4 million people in the U.S. who have schizophrenia with auditory hallucinations, 10% do not respond to available psychopharmaceuticals. Furthermore, despite an apparently high response to medication, 80% of individuals with schizophrenia are functionally unable to work. Thus, new treatments for schizophrenia are urgently needed. The avatar computer-based system exposes patients with treatment-resistant disease to an avatar that looks, speaks, and sounds like the voices they hear in their heads. The therapist (who is hidden) controls what the avatar says. During the sessions, the patient must learn to tolerate and fight back against the avatar's frightening voice and messages. Avatar therapy purportedly reduces the frequency and severity of patients' auditory hallucinations; it is administered across seven 30-minute sessions. University College London, London, UK Institute of Psychiatry, King's College London, London, UK Pilot study completed	Cognitive behavior therapy Cognitive remediation Computerized cognitive training	Improved symptoms Improved functioning Improved quality of life	No data or clinical trial updates have been identified since a 2013 *BMJ* proof-of-concept paper was published

Table 36. AHRQ Priority Condition: 06 Developmental Delays, Attention-Deficit/Hyperactivity Disorder, and Autism: 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason

Table 37. AHRQ Priority Condition: 07 Diabetes Mellitus: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Insulin pump integrated with low-glucose suspend monitoring system (MiniMed 530G with Enlite) for treatment of diabetes requiring exogenous insulin	Patients with type 1 or type 2 diabetes mellitus (T1DM or T2DM) who require insulin and are highly motivated to use a closed-loop system and monitor its function	Nearly 26 million children and adults in the U.S., or 8.3% of the population, have diabetes mellitus, and about 5% of these are cases of T1DM. In about 7.0 million of all those with diabetes, the disease remains undiagnosed. In 2010, clinicians diagnosed 1.9 million new cases of diabetes in U.S. people aged 20 years or older. Treatment requires a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and for T1DM and some cases of type 2 diabetes, taking insulin. Patients who require daily insulin may someday benefit from a closed-loop system, termed an artificial pancreas device system (APDS). An APDS consists of an insulin pump, a real-time glucose monitor, and a sensor to detect glucose levels and automatically adjust and deliver appropriate insulin doses. Various manufacturers have made components required for the artificial pancreas; however, no single manufacturer has yet succeeded in creating a total closed-loop system. The MiniMed® 530G system with Enlite® sensor is a low-glucose-suspend system considered to be the 1st step towards an APDS. The system includes an insulin pump and sensor to continuously monitor glucose levels. The pump can deliver insulin constantly as well as in bolus doses to compensate for meals. The Enlite sensor is a replaceable component that detects blood glucose levels. The device features a threshold (low-glucose) suspend system that automatically stops insulin delivery when preset glucose levels are detected. Medtronic, plc, Dublin, Ireland FDA approved Sept 2013	Insulin modifications Islet cell transplantation Pancreas transplantation	Halted or delayed progression of secondary complications Reliable glycemic control at desired levels Reduced risk of acute and nighttime hypoglycemia Reduction in postprandial (after meal) hyperglycemia Improved quality of life	FDA approved 2 years ago; no longer meets horizon scanning criteria for tracking

Table 38. AHRQ Priority Condition: 08 Functional Limitations and Disability: 3 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Bioartificial liver system (ELAD System) as bridge to recovery or liver transplantation	Patients in whom acute liver failure has been diagnosed	Extracorporeal bioartificial liver support system (Extracorporeal Liver Assist Device [ELAD®]) is intended to replace lost liver functions, such as synthesis of metabolic enzymes and key proteins. The cell-based liver support system adds a "bioreactor" filter to standard liver dialysis systems that temporarily removes blood from the body to remove circulating toxins. ELAD incorporates cultured human hepatocytes in bioreactor cartridges as part of a dialysis-like system. It functions as a bridge while a transplant candidate awaits a donor liver. The device is regulated as a combination biologic by FDA's Division of Cellular, Tissue and Gene Therapy in the Center for Biologics Evaluation and Research. Trials are testing the device in acute liver failure; fulminant hepatic failure; acute or chronic hepatitis, including acute alcoholic hepatitis; and alcohol-induced liver decompensation. Vital Therapies, Inc., San Diego, CA Phase III trials suspended for alcohol-induced liver decompensation (VT-208), acute alcoholic hepatitis (VT-210), and fulminant hepatic failure (VT-212); FDA granted orphan status for acute liver failure; company anticipates meeting with FDA for potential restructuring of development program after failure to meet primary endpoints in VT-208 trial	Antibiotics Lactulose Liver transplant	Improved rate of 30-day transplant-free survival Increased time to progression of end-stage liver disease	Phase III trial (VT-208) failed to meet endpoints, and all other phase III trials halted; developer plans to meet with FDA to determine whether new trials should proceed; no further trials planned as of Sept 2015

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Droxidopa (Northera) for treatment of symptomatic neurogenic orthostatic hypotension	Patients with Parkinson's disease, multiple system atrophy, and/or pure autonomic failure who are at risk of neurogenic orthostatic hypotension (nOH)	nOH is a chronic condition purportedly caused by an underlying neurogenic disorder, such as Parkinson's disease, multiple system atrophy, or pure autonomic failure. Symptoms include dizziness, lightheadedness, blurred vision, fatigue, and fainting episodes upon standing. Treatment has included pharmacotherapy, which does not achieve an adequate response in many patients. Droxidopa (Northera™) is a norepinephrine precursor that allows reuptake of norepinephrine into peripheral nervous system neurons, stimulating receptors for vasoconstriction and providing physiologic improvement in symptomatic nOH. Dose is titrated according to symptom response from 100 to 600 mg total, daily. Administered orally, up to 3 times daily. Chelsea Therapeutics International, Ltd., subsidiary of H. Lundbeck a/s, Valby, Denmark Phase III trials completed; FDA approved Feb 2014 for treating "symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy."	Diet and lifestyle modifications Pharmacotherapy (e.g., midodrine hydrochloride)	Decreased confusion from reduced cerebral circulation Decreased nOH Decreased risk of falling	Experts' comments deemed in Sept 2014 that this intervention had no potential for high impact unless more data became available; after another year of tracking, no new trials are ongoing and no new data are anticipated

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Intraoral tongue-drive computerized system to maneuver electric wheelchairs	Patients with quadriplegia	The Tongue Drive System (TDS) is a computerized, tongue-operated, assistive neurotechnology. It consists of a lentil-sized, magnetic tracer-stud that is affixed to the tongue, most commonly by piercing. In spinal cord injuries, the tongue is generally spared from injury because it is innervated by nerves from the brain and not the spinal cord. The tongue is also strong and does not fatigue easily. The magnetic tracer-stud creates a magnetic field around the pierced glossal area detected by a wireless headset. The headset transmits information to a smartphone carried by the patient. The smartphone can then transmit information to a wheelchair or computer, commanding these devices to perform tasks such as wheelchair movement or daily computer tasks (e.g., email). This system can be recharged via a USB after 2 days of continuous use. A standby mechanism allows patients to perform daily tasks, such as eating, sleeping, and conversing, without unnecessary TDS use. Patients must undergo training with the TDS for the computer program to appropriately interpret and calibrate tongue movement, allowing proper control of the patient wheelchair and computer device. The TDS will likely cost between $6,000 and $7,000 in addition to an electric wheelchair. Georgia Institute of Technology, Atlanta Pilot trial and unphased trials completed; developer predicts TDS ready for market in 2016	Comparators depend on severity of spinal cord paralysis Chin control wheelchair Head control wheelchair “Sip and puff” wheelchair Speech control wheelchair Tongue keyboard controller wheelchair	Improved aesthetics of device Improved communication speed Improved mobility Improved wheelchair function and control Improved quality of life	Last study was completed in 2013; no further evidence of continued development or a manufacturing partner has been found

Table 39. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 4 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Brincidofovir for prevention of BK virus reactivation after kidney transplantation	Patients who recently received a kidney transplant	About 1/3 of people have latent BK virus in the urogenital tract, which can result in kidney complications when patients are immunosuppressed after receiving a kidney transplant. No therapies are available to prevent BK virus reactivation. Brincidofovir (CMX001) is purportedly a broad spectrum antiviral for treating or preventing life-threatening double-stranded DNA (dsDNA) viral diseases. Brincidofovir combines the manufacturer's PIM (phospholipid intramembrane microfluidization) conjugate technology with cidofovir, a selective inhibitor of viral DNA polymerase and an approved antiviral agent for treating cytomegalovirus infection. PIM technology covalently modifies the cidofovir molecule so that it mimics a naturally occurring phospholipid metabolite that can use natural uptake pathways to achieve oral availability. Additionally, brincidofovir is purported to be significantly more potent in inhibiting viral DNA synthesis than cidofovir. In clinical trials, brincidofovir is being administered orally, 100 mg, twice weekly, for up to 24 weeks. Chimerix, Inc., Durham, NC Phase III trial ongoing; FDA granted fast-track status; also under study for preventing cytomegalovirus infection after hematopoietic stem cell transplant	Standard immunosuppres-sion followed by low-dose immunosuppres-sion	Reduced rate of BK virus nephropathy Reduced rate of post-transplant complications	Development for this indication appears halted; drug is being studied for other indications, such as prevention of cytomegalovirus after hematopoietic stem cell transplantation
Rapid antigen test (ReEBOV) for diagnosis of Zaire Ebola virus infection	Patients suspected of having Ebola Zaire virus infection	No FDA-cleared diagnostic tests are available for detecting Ebola Zaire virus (*Zaire ebolavirus*) in clinical specimens. The ReEBOV™ Antigen Rapid Test is a point-of-care test intended to detect the presence of Ebola Zaire virus (detected in the West Africa outbreak in 2014) in fingerstick whole blood, plasma, or serum specimens from patients with signs and symptoms of Ebola virus infection in conjunction with epidemiological risk factors. ReEBOV purportedly detects the presence of Ebola virus proteins in the blood sample within 15–25 minutes and is intended for use when a rapid test is more appropriate than use of an authorized nucleic acid test, which purportedly is more sensitive in detecting the Ebola Zaire virus but requires specialized testing facilities and takes 12–24 hours to arrive at a result. Corgenix Medical Corp., Broomfield, CO FDA issued an emergency use authorization Feb 2015 to test for the presumptive presence of Ebola Zaire virus (detected in the West Africa outbreak in 2014)	Nucleic acid-based detection	Improved disease containment Earlier treatment and improved outcomes	10 diagnostic tests received emergency use authorization within a short time to address the unmet need in late 2014 and the 1st half of 2015; the topic no longer meets horizon scanning criteria for tracking

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Recomodulin for treatment of severe sepsis with coagulopathy	Patients in whom severe sepsis with coagulopathy has been diagnosed	Patients with sepsis with coagulopathy exhibit disseminated microthrombi that can cause organ dysfunction and death. About 30% of patients with sepsis develop disseminated intravascular coagulation, which doubles the risk of death. Recomodulin® (ART-123) is recombinant, human soluble, thrombomodulin alpha. Thrombomodulin purportedly modulates fibrinolysis, which is impaired by the inflammation and endothelial injury that occur during sepsis. It also purportedly activates protein C, which modifies the inflammatory and coagulant response at several different levels. Treatment with exogenous thrombomodulin could help relieve signs of sepsis with coagulopathy. In clinical trials, ART-123 has been administered intravenously, 0.06 mg/kg, daily, up to a maximum daily dose of 6 mg, for 6 days. Asahi Kasei Corp., Tokyo, Japan Phase III trial ongoing	Coagulation factor concentrates or cryoprecipitate Plasma	Reduced episodes of life-threatening bleeding Reduced mortality	No evidence of development in more than 3 years
Silicone-based condom (ORIGAMI Anal Condom) to prevent HIV infection during receptive anal intercourse	Individuals engaging in anal intercourse	HIV remains a chronic illness associated with high morbidity and mortality in the absence of effective treatments. HIV-drug resistance, high lifelong cost of therapy, and adverse events suggest that prophylactic HIV measures to prevent infection should be pursued for individuals at high risk of infection. The ORIGAMI Anal Condom™ is purportedly the 1st silicone-based condom designed for receptive anal intercourse. The condom is made of medical grade silicone, which is intended to improve the safety of receptive anal sex with respect to the transmission of HIV. The manufacturer purports latex condoms are not designed for the vigor of anal intercourse. Silicone is also purported to have a novel and improved feel compared with the feel of latex condoms and might increase condom use. The condom is intended to be inserted into the anus similar to female condoms. Origami Condoms of California, Culver City, CA Manufacturer projects regulatory approval by late 2015	Latex condoms Harm reduction campaigns Preexposure prophylaxis (tenofovir/ emtricitabine)	Reduced transmission and incidence of HIV Increased patient satisfaction Increased use of condoms during receptive anal intercourse	Formulation changed to latex, similar to other condoms; intervention is now incremental

Table 40. AHRQ Priority Condition: 10 Obesity: 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason

Table 41. AHRQ Priority Condition: 11 Peptic Ulcer Disease and Dyspepsia: 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason

Table 42. AHRQ Priority Condition: 12 Pregnancy, Including Preterm Birth: 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason

Table 43. AHRQ Priority Condition: 13 Pulmonary Disease, Asthma: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
School-based preventive asthma care technology (SB-PACT) program for management of asthma in school children	School children in whom asthma has been diagnosed	Children in inner city areas are more likely to have their asthma poorly controlled. The School-Based Preventive Asthma Care Technology (SB-PACT) program comprises directly observed administration of preventive asthma treatments in school, combined with the use of a Web-based technology that helps coordinate systematic symptom screening, electronic report generation, and medication authorization from providers. University of Rochester School of Medicine and Dentistry, Rochester, NY Pilot study completed; SB-TEAM followup study (n=400) recruiting	Standard care	Fewer days missed from school Increased symptom-free days Improved symptoms at night Reduced rescue medication use Reduced exhaled nitric oxide (inflammation)	A research project by the university in schools; has not been further expanded after 2 years of tracking in horizon scanning

Table 44. AHRQ Priority Condition: 14 Substance Abuse: 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason

Table 45. AHRQ Priority Condition: 15 Cross-Cutting: 0 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason