AHRQ Healthcare Horizon Scanning System – Status Update

Horizon Scanning Status Update: July 2014

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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. HHSA290201000006C). 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 is also a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research can 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 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 Institute 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. Three and a half years have passed since initiation of the system in December 2010. The horizon scanning 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, breakthrough therapy, or innovation pathway statuses 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 from implementation of 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 are presented first as "Currently Tracked Interventions," followed by "Interventions Added Since Last Update," and then by "Interventions Tracked but Archived Since Last Update" during the 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 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 *P*opulation, *I*ntervention, potential *C*omparators to the intervention, and potential *O*utcomes 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 in phase III trials for drugs unless they have a special status, in which

case phase II is accepted; in phase II or III trials for devices; and for which pilot information is available for 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 the topics selected for advancement.

Once topic profiles are developed, comments are sought from up 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 the experts suggest that an intervention is unlikely to address or meet an unmet need or to have an 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, 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).

Since we began populating the horizon scanning system in December 2010, we have uploaded about 19,000 leads into the system. Our analysts have reviewed them, and from these, about 2,000 topics have been initially identified and moved through the system. This Status Update report contains 491 identified interventions we are tracking, which includes 26 new topics entered into the system during this reporting period. We archived 48 topics during this reporting period, for a net of 443 interventions for tracking going forward. The reason for archiving each topic is provided in its respective priority-area table of archived topics. 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, four priority areas comprise 76 percent of the interventions (including programs) being tracked. Interventions related to cancer account for about 39% (173/443) of tracked topics this reporting period. The other priority areas with the most tracked topics in descending order of number of topics are as follows: functional limitations and disability (18%, 78/443), cardiovascular diseases (10%, 46/443), and infectious diseases (9%, 40/443).

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% (106/443) of topics being tracked in the system.

In terms of overall types of interventions, about 87% (rounded to the nearest percent) fall into one of two general categories, and the proportions of topics in these categories have changed only slightly since initial reporting: about 73% of topics are pharmaceuticals/biotechnologies (i.e., drugs, vaccines, biologics) and about 14% are implanted or external devices used to treat a condition. About 4% are technologies intended to screen, diagnose, identify risk, identify blood markers or gene mutations, or monitor a disease state (these are devices, assays, imaging modalities). About 3% of topics are surgeries and procedures. About 2% are innovative programs, services, or care delivery practices, and another 2% involve information technology, information systems, or applications used in treating, managing, or monitoring patients. About 0.6% are assistive technologies (e.g., prostheses).

Section 1. Currently Tracked Interventions: 465 Interventions

Table 1. AHRQ Priority Condition: 01 Arthritis and Nontraumatic Joint Disease: 13 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 trials for ankylosing spondylitis, it is being administered in 20 or 30 mg doses. Celgene Corp., Summit, NJ Phase III trial ongoing; approved Mar 2014 for treating adults who have active psoriatic arthritis	Corticosteroids Disease-modifying antirheumatic drugs Nonsteroidal anti-inflammatory drugs Physical therapy Sulfasalazine (Azulfidine) Tumor necrosis factor inhibitors	Reduced signs and symptoms Improved mobility Improved quality of life
Autologous conditioned serum for treatment of osteoarthritis (knee and back)	Patients in whom osteoarthritis (OA) has been diagnosed	No regenerative treatments are approved by the U.S. FDA for patients with OA. Autologous conditioned serum (ACS) consists of serum collected from the patient that has components purported to be regenerative or protective—such as interleukin (IL)-1Ra, which is believed to dampen IL-1-mediated inflammation—isolated from the sample. The conditioned serum is re-injected into the arthritic joint. By specifically enriching for desired molecules, not simple fractionation/concentration, ACS purportedly has different effects from those of platelet-rich plasma therapy. ACS is administered as intra-articular injections in combination with physical therapy and an anti-inflammatory diet. NY Spine Medicine, Schottenstein Pain & Neurology, New York, NY Pilot studies completed; procedure currently diffusing in the U.S.	Analgesics Autologous mesenchymal stem cells Lifestyle modification Physical therapy Platelet-rich plasma Viscosupplementation	Reduced pain Increased range of motion Increased tissue regeneration Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous mesenchymal stem cells for treatment of joint osteoarthritis	Patients in whom osteoarthritis (OA) has been diagnosed	No regenerative treatments are FDA approved for patients with OA. Treating osteoarthritic joints with mesenchymal stem cells (MSCs) derived from the patient might have potential to restore large cartilage defects found in patients with OA. MSCs are adult stem cells that retain the ability to differentiate into a number of cell types, including chondrocytes, which are the cells responsible for maintaining cartilage. MSCs can be isolated from various tissues including bone marrow, synovium, periosteum, skeletal muscle, and adipose tissue. Some protocols add growth factors and other substances, such as antibiotics, to differentiate and expand the MSCs before reinfusion back into the patient. MSCs that are more than minimally manipulated (i.e., that add growth factors or other substances and undergo culture expansion) are subject to FDA approval. MSCs are administered by intra-articular injection and can be used alone or in combination with other OA treatment including platelet-rich plasma infusions and prolotherapy. CellTex Therapeutics Corp., Houston, TX IntelliCell Biosciences, Inc., New York, NY (IntelliCell™) Regenerative Sciences, Inc., Broomfield, CO (Regenexx-SD™) Various OA treatment centers Phase II trials recruiting	Analgesics Autologous conditioned serum Lifestyle modification Physical therapy Platelet-rich plasma Viscosupplementation	Reduced pain Increased range of motion Increased tissue regeneration Improved quality of life
Autologous platelet-rich plasma therapy for treatment of joint osteoarthritis	Patients in whom knee osteoarthritis (OA) has been diagnosed	No regenerative treatments are FDA approved for patients with OA. Viscosupplementation purportedly provides temporary relief and short-term function for some patients, but long-term, nonsurgical treatments are needed. Platelet-rich plasma (PRP) therapy involves collecting, separating, and concentrating autologous platelets from a patient's blood. This is usually performed at a community blood bank (e.g., American Red Cross Blood Services) or a hospital's own blood bank. The PRP is re-infused in an outpatient setting at the desired anatomic site (i.e., knee). PRP purportedly contains and releases (through degranulation) at least 7 different growth factors that are intended to stimulate bone and soft-tissue healing. It is administered as an intra-articular injection at various time intervals. Many orthopedic practices Regenerative Sciences, Inc., Broomfield, CO Phase III trials ongoing	Analgesics Autologous conditioned serum Lifestyle modification Mesenchymal stem cells Physical therapy Viscosupplementation	Reduced pain Increased range of motion Increased tissue regeneration 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 IL-17 receptor–mediated signaling and improving psoriatic arthritis symptoms. In clinical trials, brodalumab is being given via subcutaneous injection every 2 weeks, 140 or 210 mg, for 16 weeks. Amgen, Inc., Thousand Oaks, CA 5 phase III trials ongoing	Apremilast Corticosteroids DMARDS (e.g., methotrexate, sulfasalazine) Immunosuppressants (e.g., azathioprine, cyclosporine, leflunomide) Nonsteroidal anti-inflammatory drugs Tumor necrosis factor-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 (SI-6603) 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 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 clinical trials, condoliase is administered at 1.25U as a single local injection. Seikagaku Corp., Tokyo, Japan Phase III trial recruiting	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
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 17, which is thought to contribute to psoriatic arthritis pathogenesis. In the ongoing UNCOVER-2 trial, ixekizumab is being given by subcutaneous injection in two 80 mg injections at week 0, followed by weekly 80 mg injections until week 12. Eli Lilly and Co. Indianapolis, IN 5 phase III trials ongoing (including SPIRIT-P1, UNCOVER-2, UNCOVER-3); 1 phase II trial ongoing	Apremilast Corticosteroids DMARDS (e.g., methotrexate, sulfasalazine) Immunosuppressants (e.g., azathioprine, cyclosporine, leflunomide) Nonsteroidal anti-inflammatory drugs 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 are purported to 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 trial ongoing	High tibial osteotomy Joint distraction Mesenchymal stem-cell therapy Nonsteroidal anti-inflammatory drugs 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 (RDEA594) 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	Only 30% to 40% of gout patients respond adequately to allopurinol. Lesinurad (RDEA594) is a selective urate transporter inhibitor. Inhibition leads to uric acid excretion to reduce uric acid and crystal formation, potentially alleviating symptoms of acute gout. Lesinurad can be used as monotherapy or in combination with allopurinol. In clinical trials, dosage is 200 or 400 mg, orally, once daily. Ardea Biosciences, Inc., acquired Jun 2012 by AstraZeneca, London, UK Phase III trials ongoing	Colchicine Nonsteroidal anti-inflammatory drugs Steroids Allopurinol Febuxostat Probenecid	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 clinical trials, masitinib is administered orally, 3 or 6 mg/kg, daily. AB Science S.A., Paris, France Phase II/III trial recruiting	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
Secukinumab 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 spin and can cause vertebrae in to fuse together; there is no known cure. Treatments focus on reducing inflammation, improving mobility, and decreasing pain, but are not effective for all patients. 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 associated with ankylosing spondylitis, pathology could be blocked while minimizing the systemic immunosuppression associated with tumor necrosis factor (TNF) blockers, which are often used in treatment. Administered subcutaneously, 75 or 150 mg, monthly. Novartis International AG, Basel, Switzerland Phase III trials ongoing	Corticosteroids Disease-modifying antirheumatic drugs Ixekizumab (in development) Nonsteroidal anti-inflammatory drugs Physical therapy Sulfasalazine (Azulfidine) TNF inhibitors	Improved mobility Improved quality of life Reduced pain and other symptoms
Secukinumab 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 is a monoclonal antibody antagonist for interleukin-17 (IL-17) purportedly involved in developing delayed-type hypersensitivity reactions. It purportedly does so by increasing chemokine production, which promotes the recruitment of 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. The drug is administered subcutaneously, 150 mg, monthly. Novartis International AG, Basel, Switzerland Phase III trials completed (ERASURE and FIXTURE); phase IIIb trial ongoing comparing secukinumab to ustekinumab (Stelara)	Apremilast Corticosteroids DMARDS (e.g., methotrexate, sulfasalazine) Immunosuppressants (e.g., azathioprine, cyclosporine, leflunomide) Nonsteroidal anti-inflammatory drugs Tumor necrosis factor-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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Secukinumab 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 is 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 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. Administered subcutaneously, 75 or 150 mg, monthly, with a 10 mg/kg loading dose. Novartis International AG, Basel, Switzerland Phase III trials ongoing	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

Table 2. AHRQ Priority Condition: 02 Cancer: 175 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, has optioned development rights in North America Multiple academic research institutions including Case Comprehensive Cancer Center, Cleveland, OH; Emory University, Atlanta, GA; St. Joseph's Hospital and Medical Center, Phoenix, AZ; University of California, San Francisco (investigators) 1 phase III trial completed, numerous phase I, II, and III trials ongoing; FDA granted orphan drug status; commercially available as Gliolan® in Europe	Standard surgical resection without fluorescence assistance	Increased overall survival Increased progression-free survival Improved quality of life
90Y-clivatuzumab tetraxetan for treatment of pancreatic cancer	Patients with metastatic pancreatic cancer who have received at least 2 prior therapies, including at least 1 gemcitabine-containing regimen	Only about 5% of patients with pancreatic cancers have disease that responds to the current standard of care (gemcitabine chemotherapy), and the prognosis for these patients is very poor. 90Y-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 yytrium-90 using the chelator tetraxetan. In clinical trials, 90Y-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 ongoing; FDA granted orphan drug and fast-track status	Various chemotherapies including 1 or more of the following: 5-Fluorouracil Capecitabine Erlotinib Gemcitabine Leucovorin Oxaliplatin Nab-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
Ado-trastuzumab emtansine (Kadcyla) for treatment of breast cancer	Patients in whom metastatic HER2-positive breast cancer has been diagnosed	Patients with advanced HER2-positive breast cancer have a poor prognosis with current treatment options. Ado-trastuzumab emtansine (Kadcyla®, formerly trastuzumab-DM1) is a combination of an HER2-specific antibody (trastuzumab, Herceptin®) and a cytotoxic microtubule inhibitor (DM1, mertansine). This combination is intended to enable preferential delivery of a highly cytotoxic agent to cells expressing HER2 to produce the same (or better) results as HER2 inhibition plus chemotherapy, but with reduced side effects. This agent is administered intravenously, at 3.6 mg/kg, every 3 weeks. F. Hoffmann-La Roche, Ltd., Basel, Switzerland FDA approved Feb 2013 for treating HER2-positive metastatic breast cancer in patients who previously received trastuzumab and a taxane; 1st antibody-drug conjugate approved for treating breast cancer; additional phase III trials ongoing in adjuvant setting and 1st-line and 3rd-line treatment of metastatic disease	Lapatinib plus capecitabine Trastuzumab plus chemotherapy (e.g., paclitaxel, docetaxel, vinorelbine, capecitabine) Trastuzumab plus lapatinib	Increased overall survival Increased progression-free survival Improved quality of life
Afatinib (Gilotrif) for treatment of 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 ongoing	Various combination or monotherapy regimens including: 5-fluorouracil Bleomycin Cetuximab Cisplatin Docetaxel Gemcitabine Ifosfamide Methotrexate Paclitaxel 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
Afatinib (Gilotrif) for treatment of metastatic breast cancer	Patients in whom advanced HER2-positive breast cancer has been diagnosed	Patients with advanced HER2-positive breast cancer have a poor prognosis with current 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; these receptor tyrosine kinases are overexpressed in breast cancers (about 20% of patients). Targeted EGFR-like receptor inhibition in these cancers has a high relative success rate. Although multiple receptor tyrosine kinase inhibitors are available, afatinib is unique in that its inhibition is irreversible. In a phase III clinical trial in HER2-positive breast cancer, afatinib (once daily oral dose) is administered in combination with intravenous vinorelbine (25 mg/m^2 once weekly). Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trial ongoing	Ado-trastuzumab emtansine Lapatinib plus capecitabine Trastuzumab plus chemotherapy (e.g., paclitaxel, docetaxel, vinorelbine, capecitabine) Trastuzumab plus lapatinib	Increased overall survival Increased progression-free survival Improved quality of life
Afatinib (Gilotrif) for treatment of nonsmall cell lung cancer	Patients in whom nonsmall cell lung cancer (NSCLC) has been diagnosed and who have certain EGFR mutations	The 5-year survival rate for patients with advanced NSCLC is less than 15% with current treatments. Afatinib (Gilotrif™) is a small-molecule, irreversible ErbB inhibitor. It inhibits both epidermal growth factor receptor (EGFR; HER1) and HER2 receptor tyrosine kinases. These receptor tyrosine kinases are mutated and overexpressed in NSCLC in about 10% of patients; targeted EGFR-like receptor inhibition in these cancers has a relatively high success rate. Although other EGFR inhibitors are available, afatinib is unique in that its inhibition is irreversible. Within the *EGFR* gene mutations present in about 10% of NSCLCs, the majority are *EGFR* exon 19 deletions or exon 21 L858R substitutions. The product labeling indicates that afatinib is taken orally at a once-daily dosage of 40 mg. Boehringer Ingelheim, GmbH, Ingelheim, Germany FDA approved Jul 2013 for 1st-line treatment of metastatic NSCLC in patients whose tumors harbor specific types of *EGFR* gene mutations as detected by the FDA-approved companion diagnostic test (therascreen EGFR RGQ PCR Kit, QIAGEN, Manchester Ltd., UK)	1st-line: Combination chemotherapy (e.g., pemetrexed plus cisplatin) Targeted immunotherapy (e.g., bevacizumab, cetuximab, erlotinib) 2nd-line: Erlotinib Single agent chemotherapy (e.g., docetaxel, 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
Aldoxorubicin for treatment of soft tissue sarcoma	Patients with unresectable or metastatic soft tissue sarcoma who have undergone at least 1 prior 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	Dacarbazine Doxorubicin Gemcitabine plus docetaxel Ifosfamide Pazopanib	Increased overall survival Increased progression-free survival Improved quality of life
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. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase II trial ongoing; phase III trial registered, not yet recruiting; FDA granted breakthrough therapy status	Docetaxel Gemcitabine Pemetrexed Platinum doublet Targeted immunotherapy (e.g., bevacizumab, erlotinib)	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 a treatment intended to stimulate an immune response against the patient's pancreatic cancer cells. The 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. In current clinical trials, HyperAcute®-Pancreas is administered by injection in combination with standard of care chemoradiation. Clinical trials are testing this intervention in surgically resected and unresectable/borderline resectable pancreatic cancers. 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 ongoing under FDA special protocol assessment; trials examining use in surgically resected and unresectable disease; FDA granted fast-track and orphan drug statuses	Standard chemoradiation regimens (including systemic chemotherapy such as FOLFIRINOX, 5-fluorouracil, gemcitabine, and/or nab-paclitaxel)	Increased overall survival Increased progression-free survival Improved quality of life
Alisertib for treatment of peripheral T-cell lymphoma	Patients in whom relapsed/refractory peripheral T-cell lymphoma (PTCL) has been diagnosed	Current treatment options for relapsed/refractory PTCL are largely palliative and generate responses in fewer than 50% of patients (with the exception of brentuximab vedotin for the anaplastic large cell lymphoma [ALCL] subtype). Alisertib is an Aurora A kinase inhibitor under study for treating PTCL. Aurora A kinase is an important regulator of the mitotic spindle and is required for progression through the mitotic phase of the cell cycle. Inhibiting Aurora A has been shown to cause mitotic errors, potentially leading to aneuploidy, apoptosis, and cellular senescence. Alisertib is administered orally, 50 mg, twice daily. Millennium Pharmaceuticals, Inc., subsidiary of Takeda Pharmaceutical Co., Ltd., Osaka, Japan Phase III trial ongoing	Alemtuzumab Bortezomib Brentuximab vedotin (ALCL subtype only) Cyclosporine (angioimmunoblastic T-cell lymphoma subtype only) Denileukin diftitox Gemcitabine Pralatrexate Radiation therapy Romidepsin	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	Although a number of treatments have been applied to CRCA, many patients do not respond to treatment. CRCA may limit patients' tolerance of further treatment, directly affecting survival. 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). 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 has the potential to address both the appetite and metabolic (e.g., proinflammatory) aspects of CRCA. In clinical trials, it is administered at a dosage of 100 mg, orally, daily. Helsinn Healthcare S.A., Lugano/Pazzallo, Switzerland Phase III trials ongoing	Anti-cytokine antibodies Appetite stimulants (e.g., cannabinoids, corticosteroids, cyproheptadine) Progesterone derivatives Dietary counseling Melanocortin antagonists Metabolic disturbance modulators (e.g., pentoxifylline, thalidomide)	Improved lean body mass Improved muscle strength Increased body weight Increased overall survival Improved quality of life
Anastrozole (Arimidex) for prevention of breast cancer in postmenopausal women at elevated risk of breast cancer	Postmenopausal women at risk of developing breast cancer	Breast cancer is the most common form of cancer diagnosed in women, and approaches to reducing the incidence of the disease in postmenopausal women at high risk are sought. Anastrozole (Arimidex®) is an aromatase inhibitor that blocks production of estrogen, known to be a major driver of breast cancer development in high risk women. Anastrozole is approved for treating breast cancer in both the adjuvant and locally advanced/metastatic disease settings; however, the efficacy of aromatase inhibitors as chemopreventive agents has not been clearly established. In the preventive setting, anastrozole is administered to postmenopausal women at high risk for up to 5 years at a dosage of 1 mg, once daily, in an oral tablet. Cancer Research UK, London, and Medical Research Council of Australia, Canberra, Australia (Marketed by AstraZeneca, London, UK, as a breast cancer treatment) Phase III trial ongoing	Exemestane Raloxifene Tamoxifen	Decreased risk of developing breast cancer

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti-GD2 monoclonal antibody (ch14.18) for treatment of 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, ch14.18, 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 ch14.18 antibody purportedly targets neuroblastoma cells via antibody-dependent, cell-mediated cytotoxicity. In clinical trials, ch14.18 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. United Therapeutics Corp., Silver Spring, MD, in collaboration with the National Cancer Institute, Bethesda, MD Phase III trials ongoing; FDA and European Medicines Agency (EMA) granted orphan drug status; EMA granted approval in Dec 2013; company submitted biologics license application to FDA in Apr 2014	Isotretinoin	Increased overall survival Increased progression-free survival Improved quality of life
Anti-PD-1L monoclonal antibody (MPDL3280A) for treatment of advanced non-small cell lung cancer	Patients with locally advanced or metastatic non-small 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. 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. MPDL3280A 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, MPDL3280A is administered as a 1,200 mg intravenous infusion on day 1 of a 21-day cycle. Hoffmann-La Roche (Basel, Switzerland) Phase III trial ongoing	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
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 ongoing; Sept 2013, company announced phase III trial had failed to meet 1st co-primary endpoint of increasing disease-free survival; trial continues to assess 2nd co-primary endpoint of overall survival	Granulocyte-macrophage colony stimulating factor Interferon-alpha Interleukin-2 Radiation therapy	Increased overall survival Increased progression-free survival Improved quality of life
Autologous dendritic cell immunotherapy (AGS-003) for treatment of renal cell carcinoma	Patients in whom advanced or metastatic renal cell carcinoma (RCC) has been diagnosed	Approximately 14,000 deaths are attributable to kidney cancer in the U.S. each year. AGS-003 is a personalized immunotherapy in which dendritic cells 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 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 ongoing	Axitinib Bevacizumab (with interferon alfa) Everolimus Interleukin-2 Pazopanib Sorafenib Sunitinib 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
Autologous dendritic cell immunotherapy (DCVax-L) for glioblastoma multiforme	Patients in whom unilateral glioblastoma multiforme has been diagnosed	Glioblastoma multiforme is difficult to treat and associated with a very poor patient prognosis. New therapies that improve survival and slow disease progression 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 trials ongoing; Mar 2014, manufacturer announced that phase III trial's Data Safety Monitoring Board recommended that trial continue after an interim review of safety data; interim review for efficacy pending	Bevacizumab (under investigation) Other immunotherapeutics (in development, e.g., HSPPC-95, ICT107) Radiation therapy Surgical resection (with or without carmustine wafer) Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life
Autologous dendritic cell immunotherapy (ICT-107) for treatment of glioblastoma multiforme	Patients in whom glioblastoma multiforme (GBM) has been diagnosed who have undergone surgical debulking	GBM is difficult to treat and associated with a very poor patient 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 autologous 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; company is finalizing a phase III protocol for discussion with FDA, possibly during summer 2014; FDA granted orphan drug status in 2010	Bevacizumab (under investigation) Other immunotherapeutics (in development, e.g., DCVax-L, HSPPC-95) Radiation therapy Surgical resection (with or without carmustine wafer) 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
Automated breast ultrasound (Invenia automated breast ultrasound system, formerly called somo.v) for screening dense breast tissue	Women with dense breast tissue who are undergoing screening mammography	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, the presence of dense breast tissue limits the accuracy of screening mammography, and screening mammography's sensitivity for tumors in women with dense breast tissue is as low as 30% to 50%. Ultrasound imaging has been used for some time in breast imaging; however, it is not routinely used for screening asymptomatic women in the U.S. The somo.v automated breast ultrasound system generates 3-dimensional images of the breast in an automated fashion. The system is under study as an adjunct to conventional mammographic screening in women with dense breast tissue. General Electric Co., Fairfield, CT This device received FDA premarket approval in Sept 2012 under the device name Somo.v, made by U Systems, which was subsequently acquired by GE, and the ABUS was renamed Invenia. The device is indicated as "an adjunct to mammography for breast cancer screening in asymptomatic women for whom screening mammography findings are normal or benign (bi-rads assessment category 1 or 2), with dense breast parenchyma (bi-rads composition/density 3 or 4) and have not had previous clinical breast intervention. The device is intended to increase breast cancer detection in the described patient population." Several PMA supplements have been approved for the system since 2012.	Screening mammography alone Screening magnetic resonance imaging Manual breast ultrasound	Increased breast cancer sensitivity and specificity Improved positive and negative predictive values
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, as 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 ongoing; FDA granted fast-track status	Docetaxel Erlotinib Paclitaxel 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
Bcl-2 inhibitor (ABT-199) for treatment of chronic lymphocytic leukemia	Patients with relapsed or refractory chronic lymphocytic leukemia (CLL) who have undergone at least 1 prior chemotherapy regimen	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. 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, ABT-199 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; FDA granted orphan drug status in 2012	Various chemoimmunotherapy regimens, including rituximab plus bendamustine	Increased overall survival Increased progression-free survival Improved quality of life
Beta glucan immunomodulator (Imprime PGG) 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 ongoing	Cetuximab monotherapy Regorafenib	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
Bevacizumab (Avastin) for treatment of ovarian cancer	Patients in whom advanced or recurrent ovarian cancer has been diagnosed	Ovarian cancer is the 2nd deadliest cancer after pancreatic cancer; no new 1st-line treatment options have been developed in the past decade. Bevacizumab (Avastin®) is a monoclonal antibody that binds vascular endothelial growth factor (VEGF) and prevents the interaction of VEGF with its receptors (Flt-1 and KDR) on the surface of endothelial cells. By preventing the interaction of VEGF with its receptors, bevacizumab prevents the proliferation of endothelial cells and the formation of new blood vessels needed to nourish growing tumors. This agent is on the market for several other indications and is being tested in the 1st- and 2nd-line settings in combination with standard chemotherapy. In clinical trials for treating ovarian cancer, bevacizumab is administered at 15 mg/kg, intravenously, on day 1 of each 3-week cycle. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland, and National Cancer Institute, Bethesda, MD Multiple phase III trials ongoing; in Jun 2014, the manufacturer released phase III trial (AURELIA) data showing improved progression-free survival and overall response rate, but not overall survival; UK National Institute for Health and Care Excellence announced in May 2013 it would not recommend use for ovarian cancer; in Nov 2013 approved for use in Japan	Combination chemotherapy including 1 or more of the following: Carboplatin Gemcitabine Paclitaxel Paclitaxel monotherapy Pegylated liposomal doxorubicin Topotecan	Increased overall survival Increased progression-free survival Improved quality of life
Blinatumomab 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 relapsed/refractory ALL have been developed in 30 years; 5-year survival for this patient population is only 7%. Blinatumomab 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 who are newly diagnosed or have relapsed/refractory disease. Amgen, Inc., Thousand Oaks, CA Phase III trials ongoing as adjunct to standard chemotherapy for newly diagnosed disease and as monotherapy for relapsed/refractory disease; FDA granted orphan drug status and breakthrough therapy status	Newly diagnosed ALL: CALGB 8811 Larson regimen Linker 4-drug regimen Hyper-CVAD with or without rituximab MRC UKALLXII/ECOG2993 regimen Relapsed/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
Buparlisib for treatment-refractory metastatic 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 frequently 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 in combination with the anti-estrogen drug fulvestrant. It is administered orally, 100 mg, daily. Novartis International AG, Basel, Switzerland Phase III trials ongoing; also under study for treating endometrial cancer, glioblastoma, HER2-positive breast cancer, melanoma, nonsmall cell lung cancer, prostate cancer, and urothelial cancer	Everolimus plus exemestane Fulvestrant monotherapy	Increased overall survival Increased progression-free survival Improved quality of life
Cabozantinib (Cometriq) for treatment of castration-resistant prostate cancer	Patients with castration-resistant prostate cancer (CRPC) that may include bone metastases	Median overall survival for patients with CRPC is only about 18 months. No treatments for CRPC are available that target MET, which may be responsible for prostate cancer drug resistance in patients treated with current receptor tyrosine kinase inhibitors. Cabozantinib (Cometriq®) is an oral, 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. Finally, VEGF and MET also appear to stimulate osteoclasts and osteoblasts, thus showing potential for treating bone metastasis. 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 trials, it is administered at a 100 mg dose, once daily. Exelixis, Inc., South San Francisco, CA Phase II and phase III trials ongoing; Mar 2014 interim analysis by Independent Data Monitoring Committee recommended that phase III COMET-1 trial proceed for final analysis	Abiraterone Cabazitaxel Denosumab Docetaxel Enzalutamide Radium-223	Reduced bone metastasis Reduced bone pain 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 received previous 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; 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 ongoing; 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	Axitinib Bevacizumab Everolimus Interleukin 2 Pazopanib Sorafenib Sunitinib Temsirolimus	Increased overall survival Increased progression-free survival Improved quality of life
Cancer stem cell–inhibitor (BBI608) for treatment of colorectal cancer	Patients with pretreated, unresectable, advanced colorectal cancer (CRC) who received prior treatment with a thymidylate synthase inhibitor and whose disease was 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) or in combination with best supportive care (phase II). Boston Biomedical, Inc., Cambridge, MA owned by Sumitomo Dainippon Pharma of Osaka, Japan Phase II and III trials ongoing	Best supportive care Regorafenib	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
Capsule endoscopy (PillCam COLON 2) for colorectal cancer screening	Patients who require further evaluation after incomplete colonoscopy	In approximately 10% of colonoscopy procedures colon imaging is incomplete because complete evaluation of the colon was 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 track. 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, Yoqne'am, Israel FDA cleared for marketing 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/adematous polyp sensitivity Improved colorectal cancer/adematous polyp specificity
Ceritinib (Zykadia) for treatment of nonsmall cell lung cancer	Patients in whom ALK mutation–positive, advanced or metastatic nonsmall cell lung cancer (NSCLC) has been diagnosed	The 5-year survival rate for patients with NSCLC is less than 15%, and patients whose disease progresses following 1st-line chemotherapy have few treatment options. ALK is an oncogenic tyrosine kinase that was identified in gene fusions that caused activation of ALK in lymphoma. Ceritinib (LDK378) inhibits ALK activity; in NSCLC tumors that are driven by constitutive ALK activity, it may reduce tumor growth and survival. Ceritinib may provide a treatment option for patients whose NSCLC has progressed after treatment with the ALK inhibitor crizotinib. In clinical trials, ceritinib is provided as a once-daily, oral dose of 750 mg. Novartis International AG, Basel, Switzerland FDA approved Apr 2014 for treating locally advanced or metastatic NSCLC that is ALK-positive as detected and has progressed after crizotinib treatment; Phase III trials ongoing in previously treated and untreated NSCLC; FDA granted breakthrough therapy status Mar 2013	1st-line: Combination chemotherapy (e.g., pemetrexed plus cisplatin) Crizotinib Other targeted immunotherapy (e.g., bevacizumab, cetuximab, erlotinib) 2nd-line: Erlotinib Single-agent chemotherapy (e.g., docetaxel, 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
Cobimetinib for treatment of melanoma	Patients in whom BRAF mutation-positive metastatic melanoma has been diagnosed	Patients with BRAF mutation–positive melanoma frequently demonstrate a response to BRAF inhibitors; however, these responses are typically short in duration. MEK is a kinase that functions downstream of BRAF in the pathway driving melanoma pathogenesis in BRAF mutation–positive melanoma. Dual inhibition of BRAF and MEK may increase the duration of response to agents targeting the RAS/RAF/MEK/ERK pathway. Cobimetinib is an orally administered MEK inhibitor under study in combination with the BRAF inhibitor vemurafenib. In trials, cobimetinib is administered at an oral dose of 60 mg, once a day on days 1–21 of each 28-day treatment cycle. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trial ongoing; Jul 2014, manufacturer announced that phase III trial met its primary progression free survival endpoint	Dabrafenib Ipilimumab Trametinib Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life
Combination eflornithine/sulindac (CPP-1X) 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 the 1st 3 years after surgery. Investigators are examining a new therapy 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 ongoing	No commonly used chemopreventive agent exists for preventing colorectal cancer recurrence Compounds under investigation include: Aspirin Calcium supplements Curcumin Nonsteroidal anti-inflammatory drugs 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
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 following 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 prior to day 1 of cycle 1; then custirsen 640 mg weekly every 21-day cycle. OncoGenex Pharmaceuticals, Inc., Bothell, WA Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel Phase III trial ongoing	Docetaxel Erlotinib Pemetrexed Platinum doublet (plus or minus bevacizumab)	Increased overall survival Increased progression-free survival Improved quality of life
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 treatment with 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. OncoGenex Pharmaceuticals, Inc., Bothell, WA Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel Phase III trials (AFFINITY and SYNERGY) ongoing; FDA granted fast-track status; Apr 2014 top-line data from SYNERGY trial indicated that custirsen did not meet primary endpoint of improving overall survival	Abiraterone Cabazitaxel Docetaxel Enzalutamide Radium-223 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
Cyclin-dependent kinase 4/6 inhibitor (LEE011) for treatment of 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. 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 first-line setting for advanced disease. In clinical trials, LEE011 is administered as a once daily, oral dose of 600 mg, on days 1–21 of each 28-day cycle. Novartis International AG, Basel, Switzerland Phase III trial ongoing	Anastrozole Abemaciclib (in development) Fluoxymesterone Fulvestrant High-dose estrogen Letrozole Palbociclib (in development) Progestin Tamoxifen Toremifene	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 NSCLC 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. It 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. In clinical trials, dacomitinib is administered in a once-daily, oral dose of 45 mg. Treatment settings include: 1st-line treatment of patients with activating mutations in EGFR; 2nd-line treatment of patients after chemotherapy; and 2nd-line or 3rd-line treatment of patients previously treated with an EGFR inhibitor. Pfizer, Inc., New York, NY Phase III trials ongoing; in Jan 2014, Pfizer announced that dacomitinib had failed to meet primary endpoint in the 2nd-line setting after chemotherapy and in the 2nd-line or 3rd-line setting after EGFR inhibitor; Pfizer is re-evaluating results “to better understand the effects of dacomitinib in molecularly defined subgroups of patients with advanced NSCLC.”	Afatinib Erlotinib	Increased overall survival Increased progression-free survival Improved quality of life
Daratumumab for treatment of multiple myeloma	Patients in whom relapsed/refractory multiple myeloma has been diagnosed	Patients with relapsed/refractory multiple myeloma who have undergone treatment with 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 is purported to lead to multiple myeloma cell death through antibody-dependent, cell-mediated cytotoxicity and complement-dependent cytotoxicity. Patients are intended to have undergone prior treatment with both a protease inhibitor and an immunomodulatory drug before receiving this treatment. Daratumumab is administered by intravenous infusion at a dosage of 16 mg/kg and is being tested in combination with lenalidomide and dexamethasone or in combination with bortezomib and dexamethasone. Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ Phase III trials registered, not yet recruiting; FDA granted breakthrough therapy status May 2013	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

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 at a dosage of 25 mg/kg, intravenously, 4 times per day. Gentium S.p.A., a majority owned indirect subsidiary of Jazz Pharmaceuticals, Inc., Dublin, Ireland Phase III trial ongoing; FDA granted orphan drug and fast-track status; new drug application submitted Jul 2011; FDA issued a refuse to file response and the company withdrew the application in Aug 2011, stating that it would work to address issues and resubmit; received marketing authorization from European Commission in Oct 2013	Analgesia Diuresis Renal replacement therapy Transfusion	Increased overall survival Improved quality of life
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. This agent is already approved for preventing skeletal-related events in patients with established bone metastases from solid tumors. Preclinical data suggest that RANKL inhibition may also 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 trial ongoing, enrollment complete	Various chemotherapy regimens	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
Dinaciclib for treatment of chronic lymphocytic leukemia	Patients with chronic lymphocytic leukemia (CLL) who have undergone prior chemotherapy and/or chemoimmuno-therapy or whose disease bears a 17p chromosomal deletion	CLL is the most frequently diagnosed leukemia among adults in the U.S., and about 4,600 patients die of the disease each year. Dinaciclib is a small-molecule inhibitor of multiple cyclin-dependent kinases, enzymes responsible for regulating cell division and other essential cellular processes. Inhibiting cyclin-dependent kinases purportedly preferentially leads to cell death in neoplastic cells. In clinical trials, dinaciclib (14 mg/m^2) is administered intravenously on days 1, 8, and 15 of a 28-day cycle. Merck & Co., Inc., Whitehouse Station, NJ Phase III trial ongoing	Alemtuzumab, bendamustine, chlorambucil, or lenalidomide with or without rituximab Ibrutinib Ofatumumab	Increased overall survival Increased progression-free survival Improved quality of life
EGEN-001 gene therapy 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 treatment with a platinum-based regimen	Patients with platinum-resistant ovarian cancer have a poor prognosis and few treatment options. EGEN-001 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. EGEN-001 is formulated with the TheraPlas™ delivery system that forms active nanoparticles that transfect cells with IL-12; this formulation is optimized for delivery into the tumor microenvironment. This agent is currently being tested in platinum-refractory ovarian cancer. In clinical trials, EGEN-001 is administered by intraperitoneal catheter at a dosage of 24 mg/m^2, weekly. EGEN, Inc., Huntsville, AL Phase II trial ongoing; with favorable initial results; FDA granted orphan drug status; early stage trials ongoing in other treatment settings and disease indications	Docetaxel Etoposide Gemcitabine Paclitaxel Pegylated 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
eIF5A1 modulator (SNS01-T) for treatment-refractory B-cell malignancies	Patients in whom a treatment-refractory B-cell malignancy (i.e., diffuse large B-cell lymphoma, mantle cell lymphoma, or multiple myeloma) has been diagnosed	SNS01-T is a novel therapeutic intended to sensitize cancer cells to apoptotic signals by targeting eukaryotic translation initiation factor 5A1 (eIF5A1). EIF5A1 functions as a shuttle protein, selectively translocating mRNAs from the nucleus to cytosolic ribosomes for translation. It exists in pro-apoptotic and antiapoptotic forms; the antiapoptotic form is generated by posttranslational modification. SNS01-T consists of 2 nucleic acid–based molecules: (1) a plasmid that drives expression of a pro-apoptotic form of eIF5A1 that has been modified to prevent its post-translational modification to the antiapoptotic form, and (2) an antisense molecule that inhibits expression of endogenous eIF5A1, which normally serves as the precursor to antiapoptotic eIF5A1. By altering the balance of pro-apoptotic and antiapoptotic eIF5A1, SNS01-T purportedly promotes cell death over cell growth and survival. In clinical trials, it is administered by intravenous infusion, twice weekly. Senesco Technologies, Inc., Bridgewater, NJ Phase I/II trial ongoing; FDA granted orphan drug status for treating diffuse large B-cell lymphoma, mantle cell lymphoma, and multiple myeloma	Various chemotherapeutic regimens	Increased overall survival Increased progression-free survival Improved quality of life
Elotuzumab for treatment of multiple myeloma	Patients in whom multiple myeloma or relapsed/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. CS1 has been identified as a glycoprotein expressed preferentially on multiple myeloma cells, and elotuzumab is a humanized, monoclonal antibody specific for CS1. 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. Bristol-Myers Squibb, New York, NY Phase III trials ongoing; FDA granted orphan drug and breakthrough therapy status	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
Enobosarm (Ostarine) for treatment of cancer-related cachexia	Patients in whom cancer-related cachexia has been diagnosed	Many patients with cancer experience a wasting syndrome known as cachexia, which is characterized by weight loss, muscle atrophy, fatigue, weakness, and anorexia. Cachexia may involve a tumor-related inflammatory immune response that triggers catabolism. No effective therapies exist to prevent or slow its progression. Enobosarm (Ostarine®) is a selective androgen receptor modulator that is under investigation for lung cancer–related cachexia. In phase III trials, it is being administered in a once-daily, oral dose of 3 mg. GTx, Inc., Memphis, TN Phase III trials completed; FDA granted fast-track status; manufacturer announced phase III trial failed to meet primary endpoint; plans to meet with FDA to discuss future development path	Cannabinoids Corticosteroids Dietary modifications Hormonal therapy (in development; i.e., insulin, ghrelin) Progestogens	Improved physical function Increased lean body mass Improved quality of life
Entinostat for treatment of breast cancer	Patients with locally advanced/unresectable or metastatic estrogen receptor–positive breast cancer whose disease has progressed after 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 II and III trials ongoing; FDA granted breakthrough therapy status Sept 2013	Everolimus plus exemestane Targeted therapies (in development; e.g., bevacizumab) Various single-agent or combination 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
Enzalutamide (Xtandi) for treatment of castration-resistant prostate cancer	Patients in whom metastatic castration-resistant prostate cancer (CRPC) has been diagnosed	Median overall survival for patients with CRPC is only about 18 months. Most prostate cancer tumors depend on androgen signaling for growth and survival. Multiple androgen signaling inhibitors are available (e.g., bicalutamide, abiraterone); however, many metastatic prostate cancers do not respond to these therapies or they develop resistance. Enzalutamide (Xtandi) is an androgen receptor antagonist that purportedly inhibits androgen signaling at 3 levels by blocking testosterone binding to the androgen receptor, inhibiting nuclear translocation of the activated androgen receptor, and inhibiting DNA binding of activated androgen receptor. By more completely inhibiting androgen signaling, enzalutamide may overcome limitations of current antiandrogen therapies. Enzalutamide is being tested in both chemotherapy-naïve patients and patients who have previously been treated with docetaxel. Enzalutamide is administered orally at a dose of 160 mg (four 40 mg capsules) orally, once daily. Medivation, Inc., San Francisco, CA Astellas Pharma, Inc., Tokyo, Japan FDA approved Aug 2012 for patients with metastatic CRPC who have previously been treated with docetaxel; Oct 2013, companies announced that a phase III trial in chemotherapy-naive patients had met primary endpoints of improving overall and progression-free survival; Mar 2014, companies announced they had submitted a supplemental new drug application to FDA for treatment of chemotherapy-naive patients; FDA has granted the application a priority review status with a decision deadline under the Prescription Drug User Fee Act of Sept 18, 2014	Abiraterone Cabazitaxel Docetaxel Radium-223 Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
Erismodegib for treatment of medulloblastoma	Patients in whom hedgehog pathway–activated, progressive or recurrent medulloblastoma has been diagnosed	Patients with recurrent medulloblastoma have a 2-year survival rate of less than 10%. The hedgehog signaling pathway, which is involved in cellular growth, differentiation, and repair, is constitutively activated in about 30% of medulloblastomas. Blocking this pathway may inhibit tumor growth. Erismodegib selectively binds and antagonizes Smoothened, a G protein–coupled receptor in the hedgehog signaling pathway. In clinical trials, erismodegib is being compared with temozolomide for treating recurrent or progressive medulloblastoma in groups of patients stratified according to pretreatment with radiation therapy and/or temozolomide. Erismodegib is given at an unspecified dose as a once-daily oral medication. Novartis International AG, Basel, Switzerland Phase III trial ongoing	Combination chemotherapy Radiation 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
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 regimens 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 the slow release of the drug as the linkages are metabolized in the patient. Slow release extends the time during which the patient's disease is exposed to therapeutic levels of the drug, thus limiting exposure to high levels of the drug at the time of 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. NKTR-102 is approved for treating colorectal cancer and it is also being investigated for treating ovarian, colorectal, and other cancers. Nektar Therapeutics, San Francisco, CA Phase III trial ongoing; FDA granted fast-track status	Eribulin Gemcitabine Ixabepilone Nab-paclitaxel Pemetrexed Vinorelbine	Increased overall survival Increased progression-free survival Improved quality of life
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 at a daily, oral dose of 5 mg, in combination with vinorelbine and trastuzumab. Novartis International AG, Basel, Switzerland Phase III trial ongoing, positive data published Apr 2014; FDA approved everolimus Jul 2012 for postmenopausal women with advanced hormone receptor–positive, HER2-negative breast cancer in combination with exemestane after treatment failure with letrozole or anastrozole	Cytotoxic chemotherapy HER2-targeted antibody therapies: Pertuzumab Trastuzumab HER2-targeted tyrosine kinase inhibitors: Afatinib Lapatinib	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
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 relapsed/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
Ex vivo expanded cord blood (StemEx) for allogeneic bone marrow transplant for treatment of hematologic malignancies	Patients with hematologic malignancies who need a bone marrow transplant and for whom no suitable matched donor is available	Suitably-matched bone marrow donors are not available for all patients with hematologic malignancies who could benefit from a transplant because of the difficulty in identifying suitably matched donors. An exact match is needed for adult marrow transplants to avoid complications from graft-versus-host disease (GVHD), and cord blood is associated with a lower risk of GVHD. However, the number of stem cells in cord blood is not sufficient 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. 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 relapsed or refractory hematologic malignancies who are receiving high-dose therapy, 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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ex vivo expanded cord blood as allogeneic bone marrow transplant for treatment of hematologic malignancies	Patients with a hematologic malignancy who need a bone marrow transplant and for whom no suitable matched donor is available	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 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. 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
Exemestane (Aromasin) for prevention of breast cancer in postmenopausal women at elevated risk of breast cancer	Postmenopausal women at risk of developing invasive breast cancer	The available therapies for preventing breast cancer in patients who have not developed the disease but are at elevated risk, tamoxifen and raloxifene, have limited patient acceptance because of persistent, undesirable side effects. More tolerable therapies are needed to prevent breast cancer in women at higher risk of developing the disease. Exemestane (Aromasin®) is an aromatase inhibitor that blocks estrogen production. Exemestane is approved for treating advanced breast cancer that has progressed after tamoxifen therapy and as an adjuvant therapy after 2–3 years of tamoxifen treatment in women with estrogen receptor–positive breast cancer. A large (n=4,560), phase III trial reported that women who took exemestane as a primary preventive therapy were 65% less likely to develop breast cancer. At 3-year followup, no toxicities were observed and the drug had minimal impact on quality of life. However, further analyses revealed increased loss of bone density in women taking exemestane, which is the focus of ongoing studies. In ongoing trials, the drug is administered 25 mg, orally, once daily in the morning. Pfizer, Inc., New York, NY Phase III trial ongoing; approved for other breast cancer indications; could be prescribed off label; phase III trial on bone density effects ongoing	Raloxifene Tamoxifen	Decreased risk of developing breast cancer Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Farletuzumab for treatment of 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 in platinum-sensitive disease failed to meet primary endpoint of progression-free survival in Jan 2013; company reported trend towards improved progression-free survival in subset of patients and that it would "determine a new development strategy based on discussion with external experts and the relevant health authorities;" received orphan drug status from FDA	Platinum-sensitive ovarian cancer: combination chemotherapy including 1 or more of the following: Carboplatin Docetaxel Gemcitabine Paclitaxel Pegylated liposomal doxorubicin Topotecan Platinum-refractory ovarian cancer: Docetaxel Etoposide Gemcitabine Paclitaxel Pegylated 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
Ganetespib (STA-9090) for treatment of nonsmall cell lung cancer	Patients with advanced or metastatic nonsmall cell lung cancer (NSCLC) who have undergone 1 prior systemic therapy for advanced or metastatic disease	Patients with advanced NSCLC that has progressed after prior chemotherapy have a poor prognosis and few treatment options. Ganetespib (STA-9090) is a novel anticancer agent that acts as an inhibitor of 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 III ongoing; FDA granted fast-track status	Crizotinib (if ALK+) Erlotinib Single-agent chemotherapy (e.g., docetaxel, pemetrexed)	Increased overall survival Increased progression-free survival Improved quality of life
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-mediated cytotoxic immunotherapy (ProstAtak) for prostate cancer	Patients in whom intermediate- to high-risk, localized prostate cancer has been diagnosed	Prostate cancer recurrence rates after first-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 injection of the virus 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 first RT, at the time of first RT, and 2–3 weeks after first RT. Advantagene, Inc., Auburndale, MA Phase III trial ongoing under FDA special protocol assessment	Androgen-deprivation therapy Radiation therapy Surgical resection	Increased overall survival Increased disease-free survival Improved quality of life
Glembatumumab vedotin for treatment-refractory 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, 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 to capecitabine in patients previously treated with anthracycline and taxane chemotherapy. Glembatumumab vedotin is an intravenous medication given at a dose of 1.88 mg/kg, once every 3 weeks. Celldex Therapeutics, Inc., Needham, MA Phase II trial (METRIC) ongoing and intended to support accelerated approval; FDA granted fast-track status for treatment-resistant or refractory breast cancer	Albumin-bound paclitaxel Capecitabine Docetaxel Doxorubicin Eribulin Gemcitabine Ixabepilone Liposomal doxorubicin Paclitaxel 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 trials ongoing; 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
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 previous prostate cancer treatment. EDAP TMS S.A., Lyon, France Phase II/III trial met primary endpoint; FDA accepted premarket approval application in Mar 2013; FDA advisory committee meeting is scheduled for Jul 30, 2014; available in Europe since 2000	Brachytherapy External beam radiation Observation Other HIFU systems (in development) Radical prostatectomy	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
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 with 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; system FDA cleared for the laparoscopic or intraoperative ablation of soft tissue	Brachytherapy External beam radiation Observation Radical prostatectomy Other HIFU systems (in development)	Increased overall survival Increased progression-free survival Improved patient quality of life
Hypoxia-activated DNA alkylating agent (TH-302) 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. TH-302 is a novel cytotoxic agent purported to be preferentially activated in hypoxic conditions. In its activated form, TH-302 is said to be a potent DNA alkylating agent (dibromo isophoramide mustard). Selective activation of TH-302 in hypoxic conditions might target alkylating activity to tumors. TH-302 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, in partnership with Merck KGaA, Darmstadt, Germany Phase III trial ongoing; FDA granted orphan drug status	Various chemotherapies including 1 or more of the following: 5-Fluorouracil Capecitabine Erlotinib Gemcitabine Leucovorin Oxaliplatin Nab-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 (TH-302) 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 option for soft tissue sarcomas (excluding GIST 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 the tissues' inaccessibility to standard drugs and/or slow rate of cell division. TH-302 is a novel cytotoxic agent that purportedly is preferentially activated in hypoxic conditions. In its activated form, TH-302 is a potent DNA alkylating agent (dibromo isophoramide mustard). Selective activation of TH-302 in hypoxic conditions might target alkylating activity to tumors. In clinical trials for soft tissue sarcoma, TH-302 is being used as 1st-line therapy in combination with doxorubicin to try to target both the hypoxic and normoxic regions of the tumor. TH-302 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 ongoing; companies signed agreement in Feb 2012 to codevelop and commercialize TH-302; FDA granted orphan drug status	Doxorubicin 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
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, Inc., Sunnyvale, CA, in partnership with the Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ Phase III trials ongoing; FDA granted orphan drug and breakthrough therapy statuses; FDA granted accelerated approval Feb 2014 for treating patients with "chronic lymphocytic leukemia (CLL) who have received at least 1 prior therapy"; supplemental new drug application for full approval submitted and granted priority review by FDA with a decision date of Oct 7, 2014	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 with newly diagnosed the nongerminal-center B-cell (GCB) subtype of diffuse large B-cell lymphoma (DLBCL)	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. 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, Inc., Sunnyvale, CA, in partnership with the Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ Phase III trial ongoing	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 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, Inc., Sunnyvale, CA, in partnership 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
Ibrutinib (Imbruvica) for treatment of Waldenström's macroglobulinemia	Patients in whom Waldenström's macroglobulinemia has been diagnosed	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 patients with Waldenström's macroglobulinemia. In clinical trials, ibrutinib has been orally administered at a once-daily dose of 560 mg. Pharmacyclics, Inc., Sunnyvale, CA, in partnership with the Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ Phase II trial ongoing; FDA granted breakthrough therapy status Feb 2013	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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Idelalisib for treatment of chronic or small lymphocytic leukemia	Patients in whom chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia has been diagnosed	Idelalisib 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 or small lymphocytic leukemia. In ongoing trials, the drug is administered orally, 150 mg, twice daily. Gilead Sciences, Inc., Foster City, CA Phase III trials ongoing; FDA granted breakthrough therapy status for treating relapsed CLL; Dec 2013, Gilead submitted a new drug application to FDA for treating CLL; FDA has granted the application priority review with a decision date under the Prescription Drug User Fee Act of Aug 6, 2014	Various chemotherapy regimens including 1 or more of the following: Cyclophosphamide Doxorubicin Fludarabine Ibrutinib Obinutuzumab Prednisolone Rituximab Vincristine	Increased overall survival Increased progression-free survival Improved quality of life
Idelalisib 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 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; company submitted new drug application to FDA Sept 2013; accepted by FDA for review with a decision date in Sept 2014	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

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 therapies for OM, 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 over 4 minutes. Soligenix, Inc., Princeton, NJ Phase II trial ongoing; FDA granted fast-track status Jun 2013	Lidocaine Narcotics	Decreased pain and oral side effects Improved ability to eat and drink Improved treatment adherence Improved quality of life
Injected hydrogel (SpaceOAR) to protect healthy tissue during radiation therapy	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 Phase III pivotal trial ongoing in prostate cancer; Conformité Européene (CE) marked; in May 2011, Varian Medical Systems, Inc., Palo Alto, CA, invested in Augmenix with option to buy company	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 previous 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. 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 trial ongoing	Combination chemotherapy (e.g., pemetrexed plus cisplatin) Targeted immunotherapy (e.g., bevacizumab, cetuximab) Targeted therapy (e.g., crizotinib/ceritinib [if ALK+], afatinib/erlotinib [if EGFR mutation+])	Increased overall survival Increased progression-free survival Improved quality of life
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 at a dose of 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 Phase III trial in chemotherapy-naïve patients ongoing; Sept 2013, company announced phase III trial did not meet primary endpoint of improving overall survival in patients who had previously undergone docetaxel therapy; next steps being considered	Abiraterone Docetaxel Enzalutamide Radium-223 Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
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 at a dose 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 trial ongoing	Etoposide and platinum therapy (cisplatin or carboplatin) Radiation 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
Irreversible electroporation (NanoKnife) for treatment of hepatocellular carcinoma	Patients with early-stage hepatocellular carcinoma (HCC) that is not surgically resectable	Surgical resection and/or ablation of locally advanced tumors is the only potentially curative treatment option for patients with HCC. However, many patients are not eligible for surgical resection because the location of their tumors is in close proximity to essential structures (e.g., major blood vessels). The NanoKnife® system uses a novel treatment modality known as irreversible electroporation in which pulses of high-voltage direct current are applied to the target tissue using needle-like electrodes, a process that induces the irreversible formation of nanopores in cellular membranes. The presence of these nanopores is highly toxic to cells, leading to cell death via an apoptosis-like process. Unlike other local ablation technologies (e.g., radiofrequency [RF] ablation, cryotherapy), irreversible electroporation does not induce heat sink effects and can leave the extracellular structure of large blood vessels intact, potentially allowing local ablation of tumors in close proximity to vessels while retaining vessel patency. In treating HCC, irreversible electroporation is performed in a minimally invasive laparoscopic procedure. AngioDynamics, Latham, NY Unphased trial ongoing; FDA cleared for surgical ablation of soft tissue but not for any cancer indication; some cancer centers using off label	Cryotherapy RF ablation	Increased overall survival Increased clinical downstaging to surgically resectable tumor Improved adverse event profile Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Irreversible electroporation (NanoKnife) for treatment of pancreatic cancer	Patients with locally advanced pancreatic cancer that is not resectable by surgery	Surgical resection and/or ablation of locally advanced tumors is the only potentially curative treatment option for patients with pancreatic cancer. However, many patients are not eligible for surgical resection because the location of their tumors is in close proximity to essential structures (e.g., major blood vessels). The NanoKnife® system uses a novel treatment modality known as irreversible electroporation in which pulses of high-voltage direct current are applied to the target tissue using needle-like electrodes, a process that induces the irreversible formation of nanopores in cellular membranes. The presence of these nanopores is highly toxic to cells, leading to cell death via an apoptosis-like process. Unlike other local ablation technologies (e.g., radiofrequency [RF] ablation, cryotherapy), irreversible electroporation does not induce heat sink effects and can leave the extracellular structure of large blood vessels intact, potentially allowing local ablation of tumors in close proximity to vessels while retaining vessel patency. In treating pancreatic cancer, irreversible electroporation may be performed in an open surgical or minimally invasive laparoscopic procedure. AngioDynamics, Latham, NY Various phase trials ongoing; FDA cleared for surgical ablation of soft tissue but not for any cancer indication; some cancer centers using off label	Cryotherapy RF ablation External beam radiation therapy	Increased overall survival Increased rate of clinical downstaging to surgically resectable tumor Improved adverse event profile Improved quality of life
Lenvatinib 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 diagnosed 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 (E7080) 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 dose of 24 mg. Eisai Co., Ltd., Tokyo, Japan Phase III trial ongoing; Eisai announced trial met its primary endpoint of improving progression-free survival; FDA granted orphan drug status Feb 2013	Pazopanib (off label) Sorafenib Sunitinib (off label)	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
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
Leukocyte interleukin (Multikine) immune therapy 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 intended to be delivered before conventional treatment (surgery, radiotherapy, chemotherapy). In a clinical trial, Multikine is administered before standard of care therapy in treatment-naive 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	Surgical resection and chemoradiation 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
Liposome encapsulated irinotecan for treatment of pancreatic cancer	Patients with metastatic pancreatic cancer previously treated with gemcitabine	Only about 25% of patients with metastatic pancreatic cancer have disease that responds to 1st-line therapy with gemcitabine; patients have a poor prognosis with current 2nd-line treatment options. Irinotecan (MM-398) is a novel formulation of the topoisomerase 1 inhibitor irinotecan that encapsulates the drug in liposomal particles and is intended to be used as a 2nd-line treatment. Liposomal encapsulation of irinotecan has 3 potential benefits: (1) liposomal particles may preferentially accumulate in tumor tissues because of increased porosity of tumor vasculature; (2) liposomes may provide slow release of the active drug, potentially increasing duration of exposure to therapeutic dose; and (3) irinotecan is hydrolyzed to a relatively inert form in aqueous solutions and liposomal encapsulation might protect the drug from this hydrolysis. Combination therapy with 5-fluorouracil (5-FU) and leucovorin is being investigated, as well as monotherapy, in the 2nd-line setting. In clinical trials, irinotecan is being administered by intravenous infusion at a dose of 120 mg/m^2, every 3 weeks. Merrimack Pharmaceuticals, Inc., Cambridge, MA Phase III trial ongoing; company announced trial met its primary endpoint of improved overall survival; FDA granted orphan drug status	Capecitabine Capecitabine plus oxaliplatin FOLFOX (i.e., folinic acid [leucovorin], 5-FU, oxaliplatin) Nab-paclitaxel	Increased overall survival Increased progression-free survival Improved quality of life
Liposome-encapsulated vincristine (Marqibo) for treatment of acute lymphoblastic leukemia	Adult patients with recurrent Philadelphia chromosome–negative acute lymphoblastic leukemia (ALL)	Adult patients with recurrent ALL have a poor prognosis and few treatment options. The microtubule-assembly inhibitor vincristine is a mainstay of ALL treatment both in the frontline and salvage settings. However, the effectiveness of vincristine is limited by the inability to maintain therapeutic levels of the drug for long periods of time and the inability to further escalate the dose because of toxicity. Marqibo® is a novel liposomal formulation of vincristine that purportedly allows the slow release of vincristine, potentially maintaining therapeutic levels of the agent and improving efficacy. It is administered as a once-weekly injection. The labeling includes a boxed warning that it must be administered intravenously because other injection methods, such as injection into spinal fluid, could result in death. Spectrum Pharmaceuticals, Henderson, NV (Spectrum acquired the former developer Talon Therapeutics, Inc., San Mateo, CA) FDA granted Marqibo orphan drug status for treating ALL in the salvage setting; FDA approved Aug 2012 for patients whose leukemia has recurred 2 or more times, or whose leukemia has progressed after 2 or more therapy regimens; 1st commercial shipments made in Sept 2013; phase III confirmatory study ongoing	Combination chemotherapy including 1 or more of the following: Anthracyclines Asparaginase High-dose cytarabine Methotrexate Steroids Vincristine	Increased overall 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
MABp1 (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 current treatment options. Cancer-related cachexia may limit the ability of patients 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. MABp1 (Xilonix™) 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 trial 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
Magnetic resonance image–guided focused ultrasound (ExAblate system) for treatment of pain from bone metastases	Patients experiencing pain from bone metastases	Bone metastases occur in late stages of the majority of solid tumors and are associated with significant morbidity and mortality; however, few treatments targeting bone metastases are available. Pain is a common symptom of bone metastases and significantly hinders quality of life. Nonnarcotic treatments for the pain from bone metastases are needed, particularly in those ineligible to receive radiation therapy. The ExAblate system is a noninvasive, magnetic resonance image–guided focused ultrasound device that provides targeted treatment to sites of bone metastases. High-intensity ultrasound waves are used to try to ablate the pain-causing nerves with the intention of providing rapid, extended relief. InSightec Ltd., Tirat Carmel, Israel FDA approved Oct 2012 for “pain palliation of metastatic bone cancer in patients 18 years of age or older who are suffering from bone pain due to metastatic disease and who are failures of standard radiation therapy, or not candidates for, or refused radiation therapy”; phase IV postapproval trial required by FDA is ongoing	Opiates and other analgesics Palliative radiation therapy Radiopharmaceuticals	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
MarginProbe System for intraoperative identification of positive margins during breast cancer lumpectomy	Patients undergoing breast lumpectomy	Successful breast lumpectomy requires that the margins of a resected tumor be free of cancerous tissue; however, with current standard of care, up to 30% of patients undergo a 2nd lumpectomy because cancer-positive margins are identified by pathology results several days after the initial operation. The MarginProbe® System purportedly enables intraoperative identification of cancer-positive margins in excised tissues, allowing the surgeon to resect additional tissue during the same surgical procedure; the system uses radiofrequency spectroscopy to discern differences in the electromagnetic signature of cancerous cells relative to normal tissue. Dune Medical Devices, Inc., Framingham, MA FDA approved Jan 2013 for intra-operative tissue assessment of surgical margins during surgery for early-stage breast cancer; system has been available in Europe since 2008	No marketed comparator in the U.S.	Reduced number of reexcision surgeries performed Improved rate of complete surgical resection (e.g., no positive margins)
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 ongoing	Dacarbazine Interleukin-2 Ipilimumab Nilotinib (in development)	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 pancreatic cancer	Patients in whom advanced/metastatic pancreatic cancer has been diagnosed	Only about 5% of patients with pancreatic cancers respond to the current standard of care (gemcitabine chemotherapy), and the prognosis for these patients is very poor. Masitinib is an orally administered multikinase inhibitor under study for treating patients who have pancreatic cancer. Masitinib inhibits several tyrosine kinases that have been shown to be overexpressed in pancreatic cancers (e.g., platelet-derived growth factor receptors, fibroblast growth factor receptor-3) or whose expression is associated with chemotherapy resistance (e.g., focal adhesion kinase). Additionally, masitinib inhibits mast cell differentiation, proliferation, and granulation through its activity on stem cell growth factor receptor (KIT) and Lyn kinase. Tumor infiltration by mast cells has been associated with increased tumor growth and spread. In clinical trials, masitinib (at a dosage of 9 mg/kg/day) has been used in combination with gemcitabine. AB Science S.A., Paris, France Phase III trial enrollment complete; positive data reported for 2 specific patient populations with poor prognoses; FDA granted orphan drug status for treating pancreatic cancer; regulatory submission made to European Medicines Agency; companion diagnostic test intended to identify likely responders to masitinib on the basis of an RNA-based blood test in development in conjunction with Skuldtech (Montpellier, France)	Various chemotherapies including 1 or more of the following: 5-Fluorouracil Capecitabine Erlotinib Gemcitabine Leucovorin Oxaliplatin Nab-paclitaxel	Increased overall survival Increased progression-free survival Improved quality of life
MEK inhibitor (MEK162) 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 NRAS 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. MEK162 is a MEK1/2 inhibitor that effectively treated about 20% of BRAF- and NRAS-mutated melanomas in phase II trials. In a phase III trial on patients with NRAS-mutated melanoma, MEK162 is administered as a once-daily, oral dose of 45 mg (three 15 mg tablets). Novartis International AG, Basel, Switzerland; licensed by Array BioPharma, Inc., Boulder, CO Phase II and III trials ongoing; also under investigation in combination with RAF inhibitors for treating BRAF-mutated melanoma	Dabrafenib Dacarbazine Interleukin-2 Ipilimumab Temozolomide Trametinib Vemurafenib	Increased overall survival Increased progression-free survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
MEK inhibitor (MEK162) for treatment of serous ovarian, fallopian tube, and peritoneal cancers	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 following at least 1 prior platinum-based chemotherapy regimen and no more than 3 lines of prior chemotherapy regimens. MEK162 is administered as a once-daily, oral dose of 45 mg (three 15 mg tablets). Novartis International AG, Basel, Switzerland; licensed by Array BioPharma, Inc., Boulder, CO Phase II and III trials ongoing	Bevacizumab (Avastin) Chemotherapy (monotherapy or combination therapy) Radiation Surgery (debulking)	Increased overall survival Increased progression-free survival Improved quality of life
Melapuldencel-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%. Melapuldencel-T 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. California Stem Cell, Inc., Irvine, CA Phase III trial registered, not yet recruiting; FDA granted fast-track status	Dabrafenib (if BRAF-positive) Dacarbazine Interleukin-2 Ipilimumab Temozolomide Trametinib (if BRAF-positive) Vemurafenib (if BRAF-positive)	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 various 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; company has entered a commercialization agreement with Polymedco, Inc., Cortlandt Manor, NY, for distribution of test in North American markets Epigenomics submitted premarket approval application Jan 2013 for the test kit for Epi proColon 2.0; FDA granted it priority review status. In 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; available in Europe as Epi proColon 2.0 since 2011	Colonoscopy Computed tomographic colonography Fecal DNA tests 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). Addition of 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 of age 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, 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 conversion of 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; initial phase I AML trial results were promising	Various chemotherapy regimens	Increased overall survival Increased progression-free survival Improved quality of life
Moxetumomab pasudotox for treatment of advanced hairy cell leukemia	Patients with hairy cell leukemia who have undergone at least 2 prior systemic therapies or are intolerant of purine analog 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 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
MUC1 therapeutic vaccine (CVac) for ovarian cancer	Patients with ovarian cancer who are in 1st or 2nd remission after cytoreduction and chemotherapy	No maintenance therapies are approved to preserve remission in ovarian cancer treatment. CVac™ is an autologous dendritic cell–based vaccine that is primed with mucin-1 (a tumor antigen) coupled to mannan (a sugar derivative that acts as an immune stimulant). The vaccine is intended to induce an immune response to ovarian cancer cells, preventing or slowing recurrence. CVac is administered via intradermal injection, every 4 weeks for 3 cycles, then every 12 weeks for 3 cycles. Prima BioMed, Ltd., Melbourne, Australia Phase II trial ongoing; FDA granted orphan drug status and fast-track status; in Oct 2013, enrollment in phase II trial was suspended after top-line analysis of results from a 2nd phase II trial did not demonstrate improved progression-free survival; following amendments to the clinical trial protocol, patient recruitment has commenced again in some countries	Other ovarian cancer vaccines (in development)	Decreased recurrence rates Increased overall survival Increased progression-free survival Improved quality of life
MUC1 therapeutic vaccine (TG4010) for nonsmall cell lung cancer	Patients with metastatic, chemotherapy-naïve nonsmall cell lung cancer (NSCLC) that is mucin-1 (MUC-1)-positive	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 current 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 SA, Cedex, France Phase IIb/III trial ongoing; FDA granted fast-track status	Combination chemotherapy (e.g., pemetrexed plus cisplatin) Targeted therapy (e.g., afatinib, bevacizumab, cetuximab, crizotinib, erlotinib)	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 ongoing, enrollment completed Nov 2012; FDA granted orphan drug status	Sunitinib	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
Nab-paclitaxel (Abraxane) for treatment of pancreatic cancer	Patients in whom advanced/metastatic pancreatic cancer has been diagnosed; patients with nonmetastatic pancreatic cancer who have recently undergone surgical resection of tumor	Only about 5% of patients with pancreatic cancers respond to the current standard of care (gemcitabine chemotherapy), and the prognosis for these patients is very poor. Nab-paclitaxel (Abraxane®) is an albumin-bound nanoparticle form of the microtubule stabilizing agent paclitaxel. In clinical trials for patients with pancreatic cancer, nab-paclitaxel (125 mg/m^2) is being administered in combination with gemcitabine. Besides the direct antitumor activity of paclitaxel, preliminary studies have indicated that it may lead to increased intratumoral concentrations of gemcitabine. Celgene Corp., Summit, NJ Phase III trial ongoing; FDA approved Sept 2013 for treating metastatic pancreatic cancer; also being tested in the adjuvant setting after surgical resection of pancreatic cancer to promote disease-free survival	Various chemotherapies including 1 or more of the following: 5-Fluorouracil Capecitabine Erlotinib Gemcitabine Leucovorin Oxaliplatin	Increased overall survival Increased progression-free survival Improved quality of life
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, resulting in inhibition of cell growth and induction of apoptosis. It 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 dose 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 ongoing in squamous and nonsquamous NSCLC; Lilly announced May 2014 that SQUIRE phase III trial treating squamous NSCLC met primary increased overall survival endpoint	Combination chemotherapy (e.g., pemetrexed plus cisplatin) Targeted immunotherapy (e.g., bevacizumab, cetuximab)	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 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. RXi Pharmaceuticals Corp. subsidiary of Galena Biopharma, Lake Oswego, OR Phase III ongoing under FDA special protocol assessment; phase II trial ongoing for combination therapy with trastuzumab	Aromatase inhibitors Tamoxifen	Increased overall survival Increased progression-free survival Improved quality of life
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 first-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 ongoing	Combination chemotherapy including 1 or more of the following: Carboplatin Docetaxel Gemcitabine Paclitaxel Pegylated 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
Nintedanib (Vargatef) for treatment-resistant 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 ongoing	Various combination therapies including 1 or more of the following: Bevacizumab Carboplatin Crizotinib Docetaxel Erlotinib Pemetrexed	Increased overall survival Increased progression-free survival Improved quality of life
Niraparib for treatment of BRCA-positive breast cancer	Patients in whom BRCA mutation–positive, HER2-negative, platinum-sensitive, locally advanced or metastatic breast cancer has been diagnosed; patients with 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 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. 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 ongoing	Combination or single agent chemotherapy with 1 of the following: Alkylating agents (e.g., cyclophosphamide) Anthracyclines (e.g., doxorubicin) Antimetabolites (e.g., fluorouracil, gemcitabine) 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
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 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 ongoing	Bevacizumab	Increased overall survival Increased progression-free survival Improved quality of life
Nivolumab 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 (BMS-936558) 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 at a dose of 3 mg/kg, once every 2 weeks. Bristol-Myers Squibb, New York, NY Phase III trials ongoing in several treatment settings as monotherapy and combination therapy with ipilimumab; FDA granted fast-track status	Dabrafenib (if BRAF-positive) Dacarbazine Ipilimumab Trametinib (if BRAF-positive) Vemurafenib (if BRAF-positive)	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 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 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 ongoing; FDA granted fast-track status; company expects to file new drug application by the end of 2014	Docetaxel Erlotinib Pemetrexed Platinum doublet (plus or minus bevacizumab)	Increased overall survival Increased progression-free survival Improved quality of life
Nivolumab for treatment of advanced renal cell carcinoma	Patients with advanced or metastatic clear cell renal cell carcinoma (ccRCC) who have undergone prior 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 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. Nivolumab is administered as a 3 mg/kg intravenous infusion, once every 2 weeks. Bristol-Myers Squibb, New York, NY Phase III trial ongoing; FDA granted fast-track status	Axitinib Bevacizumab Everolimus Interferon Interleukin-2 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
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
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 through activation of 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 multiple other academic institutions Phase II trials ongoing in neoadjuvant setting; phase III trial ongoing in adjuvant setting to prevent recurrence; phase I/II trials ongoing in metastatic disease	Various chemotherapy regimens Various hormone therapies	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 rosuvastatin (Crestor) to prevent colon cancer recurrence	Patients who have had a stage I or II colon cancer surgically resected	Patients who undergo curative resection of stage I or II colon cancers have a 50% recurrence rate in the 1st 3 years after surgery, making a chemopreventive agent for this patient population highly sought. Retrospective studies of clinical trials assessing the use of statins for cardiovascular applications suggested that patients treated with statins had a reduced incidence of precancerous colon polyps; therefore, rosuvastatin (Crestor) is believed to have potential as a chemopreventive agent for colon cancer. National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA (investigator) National Cancer Institute, Bethesda, MD (investigator) Phase III trial ongoing	No commonly used chemopreventive agent exists for treating colorectal cancer Compounds under investigation include: Aspirin Calcium supplements Curcumin Nonsteroidal anti-inflammatory drugs Omega-3 fatty acids	Reduced recurrence rate of adenomatous polyps Increased overall survival
Olaparib for treatment of ovarian cancer	Patients in whom BRCA-mutated ovarian cancer has been diagnosed 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 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, olaparib is administered at a dosage of 300 mg, orally, twice daily. AstraZeneca, London, UK Phase III trials ongoing; FDA granted orphan drug status and priority review; Jun 2014, FDA advisory committee voted against accelerated approval	Bevacizumab 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
Omacetaxine mepesuccinate (Synribo) for treatment of tyrosine kinase inhibitor–resistant chronic myelogenous leukemia	Patients with tyrosine kinase inhibitor–resistant chronic myelogenous leukemia (CML)	CML often responds to treatment with tyrosine kinase inhibitors targeting the *BCR-ABL* fusion gene; however, patients whose disease progresses after 1st- and 2nd-line tyrosine kinase inhibitor treatment have few treatment options and a poor prognosis. Omacetaxine mepesuccinate (Synribo®) is a cytotoxic alkaloid derived from the evergreen tree *Cephalotaxus harringtonia*. Omacetaxine mepesuccinate purportedly acts as a reversible, transient inhibitor of protein elongation. This inhibition leads to cell death through multiple mechanisms of action, including inhibition of HSP90, which leads to destabilization of BCR-ABL and downregulation of the antiapoptotic protein MCL-1. In clinical trials, omacetaxine mepesuccinate was administered twice daily, by subcutaneous injection. Cephalon unit of Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, (developed by ChemGenex Pharmaceuticals, Ltd., which was acquired by Cephalon) FDA granted accelerated approval Oct 2012 for treating adults with CML whose disease is resistant to or who cannot tolerate other FDA-approved drugs for CML; Feb 2014, FDA granted full approval; May 2014, FDA modified approval to allow home administration	Allogeneic stem cell transplantation Ponatinib	Increased overall survival Increased progression-free survival Improved quality of life
Onartuzumab (MetMAb) for treatment of advanced nonsmall cell lung cancer	Patients with MET-positive advanced (stage IIIb/IV) nonsmall cell lung cancer (NSCLC); patients may have newly diagnosed NSCLC harboring an activating mutation in *EGFR* or have disease that has progressed following 1st-lilne cytotoxic therapy	Patients with advanced/metastatic NSCLC that has progressed after 1st-line therapy have a poor prognosis and few treatment options. MET (also known as hepatocyte growth factor receptor) is a receptor tyrosine kinase that regulates cell growth and survival. MET has been implicated in the development of tumor resistance to epidermal growth factor receptor (EGFR) inhibition. Onartuzumab (MetMAb) is a single-armed monoclonal antibody that blocks ligand-mediated activation of the MET receptor tyrosine kinase. In late-stage trials, it is being studied in combination with the EGFR inhibitor erlotinib. Onartuzumab is administered at 1 mg/kg, intravenously, on day 1 of each 3-week cycle. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials ongoing in combination with erlotinib in multiple treatment settings; In Mar 2014, the independent data monitoring committee for the phase III METLung study recommended that the trial be stopped due to a lack of clinically meaningful efficacy	Afatinib Docetaxel Erlotinib monotherapy 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
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 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. Onartuzumab (MetMAb) is administered intravenously. In clinical trials, it is being used in combination with a chemotherapy regimen consisting of oxaliplatin, folinic acid, and 5-fluorouracil (5-FU). F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trial ongoing	Various chemotherapy regimens, including 1 or more of the following: 5-docetaxel 5-FU Capecitabine Carboplatin Cisplatin, Epirubicin Fluoropyrimidine Irinotecan Oxaliplatin Paclitaxel	Increased overall survival Increased progression-free survival Improved quality of life
Oncolytic reovirus (Reolysin) for 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 completed May 2014; company stated intentions to seek FDA approval for randomized, follow-on phase III trial for recurrent head and neck cancers	Various combination or monotherapy regimens including: 5-fluorouracil Bleomycin Cetuximab Cisplatin Docetaxel Gemcitabine Ifosfamide Methotrexate Paclitaxel 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
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 ongoing; the Imagio™ breast imaging system received the European Union CE Mark	Diagnostic breast ultrasound Diagnostic breast MRI Breast biopsy	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. Various research institutions, including Weill Medical College of Cornell University, New York, NY, and Boston IVF, Boston, MA Several unphased trials ongoing; case series 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 for treatment of breast cancer	Patients in whom locally advanced/unresectable or metastatic, estrogen receptor–positive, HER2-negative 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 (PD-0332991) 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 first-line treatment setting 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 ongoing; FDA granted breakthrough therapy status	Anastrozole Fluoxymesterone Fulvestrant High-dose estrogen Letrozole Progestin Tamoxifen Toremifene	Increased overall survival Increased progression-free survival Improved quality of life
Panobinostat for treatment of recurrent multiple myeloma	Patients in whom recurrent multiple myeloma has been diagnosed	Although treatments for multiple myeloma have improved, the median life expectancy for patients with multiple myeloma 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. Histone deacetylase (HDAC) inhibitors are a class of anticancer drugs whose exact mechanism of action is unclear but might be related to inhibition of DNA-damage repair or modification of cell-cycle proteins. Although 2 HDAC inhibitors (i.e., vorinostat and romidepsin) have been approved for treating cutaneous T-cell lymphoma, no HDAC inhibitor is approved for treating multiple myeloma. In an ongoing registration-phase clinical trial, panobinostat is being tested in combination with the proteasome inhibitor bortezomib and the glucocorticosteroid dexamethasone in patients whose disease requires retreatment after at least 1 round of chemotherapy. Panobinostat is orally administered at a dose of 20 mg. Patients receive panobinostat 3 times weekly during weeks 1 and 2 of a 3-week cycle. Novartis International AG, Basel, Switzerland Phase III trial ongoing; FDA granted orphan drug status; new drug application submitted to FDA in Mar 2014; May 2014, FDA granted application priority review	Chemotherapy at standard or high doses including 1 or more of the following: Bendamustine Bortezomib Carfilzomib Cisplatin Cyclophosphamide Dexamethasone Doxorubicin Etoposide Lenalidomide 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
PARP inhibitor (BMN 673) 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. 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. BMN-673 binds PARP and prevents PARP-mediated DNA repair. Accumulation of DNA strand breaks in the cell promotes genomic instability and eventually leads to apoptosis, potentially underlying BMN-673's antineoplastic potential. This agent is being tested for treating advanced breast cancers in patients with BRCA 1 or 2 mutations. In clinical trials, BMN-673 is administered daily, 1 mg, orally, for 21 consecutive days and is being compared to a physician's choice comparator (e.g., capecitabine, eribulin, gemcitabine, vinorelbine). BioMarin Pharmaceutical, Inc., Novato, CA Phase III trial ongoing	Combination or single-agent chemotherapy may include 1 of the following: Cyclophosphamide Docetaxel Doxorubicin Fluorouracil Gemcitabine Paclitaxel	Increased overall survival Increased progression-free survival Improved quality of life
Pegylated arginine deiminase (ADI-PEG 20) for treatment of hepatocellular carcinoma	Patients with advanced hepatocellular carcinoma (HCC) whose disease has failed to respond to 1 prior 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. ADI-PEG 20 is a pegylated preparation of arginine deiminase, which 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 at 18 mg/m^2, by intramuscular injection, weekly. Polaris Pharmaceuticals, Inc., San Diego, CA Phase III trial initiated under FDA special protocol assessment; FDA granted orphan drug status; also under investigation for hematological malignancies, mesothelioma, melanoma, lung cancer, and prostate cancer	Locoregional therapy Sorafenib (if not used in 1st-line setting)	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 for treatment of advanced melanoma	Patients in whom advanced (unresectable stage III or stage 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 (MK-3475) 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 at a dose of 10 mg, once every 2 weeks. Merck & Co., Inc., Whitehouse Station, NJ Phase III trial ongoing; FDA granted breakthrough therapy status Apr 2013; rolling biologic license application initiated Jan 2014; FDA granted priority review in May 2014	Dabrafenib Dacarbazine Ipilimumab Trametinib Vemurafenib	Increased progression-free survival Increased overall survival Improved quality of life
Pembrolizumab 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	According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, the 5-year survival rate for patients with advanced NSCLC (stage IIIA, IIIB, or IV) is less than 15% with current treatments. A hallmark of cancer is its ability to evade an immune response. Pembrolizumab (MK-3475) is a monoclonal antibody that targets a novel immune-checkpoint pathway. 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 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 ongoing; FDA granted breakthrough therapy status Apr 2013 for treating melanoma	Erlotinib MEDI4736 (in development) MPDL3280A (in development) Nivolumab (in development) Single-agent chemotherapy (e.g., docetaxel, 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
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 first- and second-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	1st-line: Pemetrexed plus cisplatin 2nd-line: Single-agent chemotherapy (e.g., doxorubicin, gemcitabine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life
Phosphoinositide-3-kinase (PI3K)-delta and PI3K-gamma inhibitor (IPI-145) for treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma	Patients with relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)	IPI-145 is a small-molecule kinase inhibitor with activity against the delta and gamma isoforms of phosphoinositide 3-kinase (PI3K). PI3Ks regulate multiple aspects of cell proliferation and cell survival and, therefore, their inhibition may have be of therapeutic benefit in various cancers. The delta and gamma isoforms of PI3K are expressed predominately in cells of the hematopoietic lineages and, therefore, inhibition of these isoforms (as opposed to all PI3Ks) may be effective in treating blood cancers such as CLL and SLL while limiting side effects on normal tissues. IPI-145 is orally administered at a dosage of 25 mg twice daily. Infinity Pharmaceuticals, Inc., Cambridge, MA Phase III trial ongoing	Chemoimmunotherapy Ibrutinib Lenalidomide with or without rituximab Ofatumumab Other PI3K inhibitors in development Rituximab	Increased progression-free survival Increased overall survival Improved quality of life
Photodynamic therapy with Tookad photosensitive agent 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	Increased overall survival Increased progression-free survival Fewer therapy-related side effects 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 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
Pomalidomide (Pomalyst) for treatment-refractory multiple myeloma	Patients with treatment-resistant (i.e., lenalidomide and bortezomib) multiple myeloma	Treatments for multiple myeloma have improved, but the median life expectancy for patients in whom it is diagnosed is only 5–7 years. Additionally, as several newer treatments for multiple myeloma have moved to the 1st-line setting as combination therapies, additional salvage treatments are needed in cases in which the disease no longer responds to treatment. Pomalidomide (Pomalyst®) is a novel thalidomide derivative that has modulatory effects on angiogenesis, inflammation, and immune cell costimulation. In clinical trials for treating multiple myeloma, pomalidomide is administered orally, at a daily dose of 4 mg, in combination with low-dose dexamethasone. Celgene Corp., Summit, NJ Phase III trials ongoing; in Feb 2013, FDA granted accelerated approval based on phase II data and required a boxed warning and risk evaluation and mitigation strategy certification for prescribers	Combination chemotherapy including 1 or more of the following: Bendamustine Bortezomib Cisplatin Cyclophosphamide (including high dose) Dexamethasone Doxorubicin Etoposide 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
Ponatinib (Iclusig) for treatment of chronic myelogenous leukemia or Philadelphia chromosome–positive acute lymphoblastic leukemia	Adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) and adult patients with these diseases for whom no other tyrosine kinase inhibitor therapy is indicated	Patients with treatment-refractory CML or ALL generally have a poor prognosis, rapidly progressing disease, and few treatment options. New therapies are needed. The translocation leading to the Philadelphia-chromosome mutation is a hallmark of CML and activates several proteins and enzymes that accelerate cell division and destabilize the genome; some ALL cells also carry this mutation (more frequently in adults, whose disease is harder to treat). Ponatinib (Iclusig™) is a next-generation BCR-ABL tyrosine kinase inhibitor rationally designed to be effective against common mutations conferring resistance to current BCR-ABL tyrosine kinase inhibitors. Administered orally, 45 mg, once daily. Ariad Pharmaceuticals, Inc., Cambridge, MA FDA granted accelerated approval in Dec 2012 for patients with CML or Ph+ ALL that is resistant or intolerant to available tyrosine kinase inhibitors. Ariad's phase III trial in the 1st-line setting was terminated Oct 2013 after reports of arterial thrombotic events in patients treated with ponatinib; in Oct 2013, U.S. marketing of ponatinib was suspended pending further investigation of vascular adverse events. In Dec 2013, distribution resumed under a risk evaluation and mitigation strategy informing health care providers of revised indications, new safety information about serious risk of vascular occlusion, and new dosing considerations	Bosutinib Dasatinib Imatinib Nilotinib	Increased overall survival Increased progression-free survival Improved quality of life
Primary care physician–administered colonoscopy (Endoscopy Training in Primary Care) for prevention of colorectal cancer	Patients eligible to receive colonoscopy	Research suggests that disparities exist in colorectal cancer (CRC) incidence and mortality for individuals who live in rural areas or otherwise medically underserved areas. This disparity may be attributable to the limited access that rural residents have to CRC prevention tools. To address this unmet need, researchers have begun investigating the feasibility and efficacy of training primary care physicians in rural areas to perform colonoscopies. According to its developers, the Endoscopy Training in Primary Care (ETPC) program involves the following: (1) an online didactic seminar, (2) an endoscopy simulator to provide the opportunity for basic and advanced skill acquisition, and (3) proctored endoscopy with an endoscopist. Colorado Area Health Education Center, Department of Family Medicine, University of Colorado, Denver Trials completed	Colonoscopy performed by gastrointestinal specialists	Earlier diagnosis of CRC Increased screening rates

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Prophage G-series therapeutic vaccine (HSPPC-96) for treatment of glioma	Patients with primary or recurrent gliomas, including glioblastoma multiforme (GBM)	Gliomas, which include GBM, can be difficult to treat and are often associated with a poor patient prognosis. 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 is under investigation in newly diagnosed gliomas and Prophage G-200 is being studied 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 trials ongoing; phase II trial ongoing; FDA granted orphan drug status	Adjuvant: Radiation therapy Temozolomide Recurrence: Bevacizumab Bevacizumab plus chemotherapy Combination PVC Cyclophosphamide Nitrosourea Platinum-based regimens Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life
ProstVac for treatment of 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 options. About 30% of AML cases bear an activating mutation in the gene encoding the receptor tyrosine kinase FLT3, which causes constitutive activation of 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 Phase III trial ongoing; FDA granted orphan drug status in 2009 and fast-track status in 2010	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 of 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., New York, NY A second FDA-approved phase III trial is recruiting; failure of first phase III trial was reported in Jan 2013; manufacturer reported potential benefit for patient subgroup receiving optimized RF ablation procedure time and designed the second phase III trial to incorporate standardized RF ablation	RF tumor ablation Systemic chemotherapy Targeted immunotherapy (e.g., sorafenib) Transcatheter arterial chemoembolization	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
Radium-223 dichloride (Xofigo) for treatment of bone metastases associated with solid tumors	Patients in whom bone metastases associated with advanced hormone-refractory metastatic prostate cancer have been diagnosed	Bone metastases occur in late stages of the majority of solid tumors and are associated with significant morbidity and mortality; however, few treatments targeting bone metastases are available. Pain is a common symptom of bone metastases and significantly hinders quality of life. Nonnarcotic treatments for the pain from bone metastases are needed. Radium-223 dichloride is a preparation of radium-223, an alpha particle–emitting isotope that has a natural affinity for bone. It purportedly accumulates in the bone where it preferentially attacks tumors rather than bone marrow because of the short distance over which alpha particles are cytotoxic. Radium-223 dichloride is administered at 50 kBq (1.35 microcurie)/kg, at 4-week intervals for 6 total injections. Algeta ASA, Oslo, Norway, in collaboration with Bayer AG, Leverkusen, Germany (Bayer acquired Algeta in Dec 2013) May 2013, FDA granted approval for treating bone metastases associated with advanced hormone-refractory metastatic prostate cancer; investigations ongoing in osteosarcoma and breast cancer with bone metastases	Cabozantinib (in development) Denosumab	Increased overall survival Increased progression-free survival Increased rate of alkaline phosphatase normalization Reduced pain from bone metastases Improved quality of life
Ramucirumab (Cyramza) for the treatment of gastric cancer	Patients with metastatic gastric cancer whose disease has progressed following 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 Apr 2014, FDA approved ramucirumab (after granting fast-track status) for completion of phase III REGARD trial; Phase III RAINBOW trial completed and met its primary endpoint; Company indicates that a 2nd regulatory submission for use of ramucirumab in combination with paclitaxel is forthcoming	Taxane (e.g., docetaxel, paclitaxel) monotherapy Various irinotecan-based single and combination therapies	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 prior therapy with sorafenib	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 following 1st-line sorafenib therapy. In clinical trials for HCC, ramucirumab is administered intravenously, 8 mg/kg, once every 2 weeks. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trial ongoing; Jun 2014, company announced ramucirumab failed to meet its primary endpoint of overall survival as 2nd-line treatment; next steps under consideration	No consensus exists on treatment for this patient population	Increased overall survival Increased progression-free survival Improved quality of life
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 ongoing, enrollment complete	Various FOLFIRI-based therapies with or without cetuximab or panitumumab	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 metastatic nonsmall cell lung cancer	Patients in whom metastatic nonsmall cell lung cancer (NSCLC) has been diagnosed	Patients with metastatic NSCLC whose disease has progressed after 1st-line chemotherapy have few treatment options and a median overall survival of 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 1 round of platinum-based chemotherapy. In clinical trials for NSCLC, ramucirumab is intravenously administered at a dose of 10 mg/kg, once every 3 weeks, as an adjunct to standard 2nd-line chemotherapy with docetaxel. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trial ongoing; Feb 2014, Lilly announced trial met its primary endpoint of improving overall survival	Ceritinib (if ALK-positive) Crizotinib (if ALK-positive) Erlotinib Single-agent chemotherapy: docetaxel pemetrexed	Increased overall survival Increased progression-free survival Improved quality of life
Regorafenib (Stivarga) for treatment of gastrointestinal stromal tumors	Patients with advanced gastrointestinal stromal tumors (GISTs) that have progressed after treatment with imatinib and sunitinib	Patients with GIST whose disease progresses after imatinib and sunitinib therapy have few treatment options and a poor prognosis with approximate progression-free survival of 100 days and overall survival of 300 days. Regorafenib (Stivarga®) inhibits multiple tyrosine kinases, including the pro-angiogenic kinases vascular endothelial growth factor receptor 2 and TIE-2 (as well as RAF, RET, and KIT); inhibition of both primary angiogenic kinase pathways is a novel combination in multikinase-inhibitor drugs (e.g., regorafenib, imatinib, sunitinib). For treating GIST, regorafenib is administered at a dose of 160 mg, orally, once daily for 3 weeks of each 4-week cycle. Bayer AG, Leverkusen, Germany Phase III trials ongoing; FDA approved Feb 2013 for treating “locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate”	Sorafenib	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). Regorafenib's Inhibition of both primary angiogenic kinase pathways puts it in a class of novel multikinase-inhibitor drugs including imatinib and 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 trial ongoing; FDA approved for treating gastrointestinal stromal tumors and metastatic colorectal cancer	Locoregional treatment	Increased overall survival Increased progression-free survival Improved quality of life
Regorafenib (Stivarga) for treatment of metastatic colorectal cancer	Patients with metastatic colorectal cancer (mCRC) who have undergone prior treatment	Many treatment options are available for mCRC; however, 5-year survival rates are only about 25%. No multikinase inhibitors have been approved for use in mCRC. Regorafenib (Stivarga®) inhibits multiple tyrosine kinases, including the pro-angiogenic kinases vascular endothelial growth factor receptor 2 and TIE-2 (as well as RAF, RET, and KIT); inhibiting both primary angiogenic kinase pathways is a novel combination in multikinase inhibitor drugs (e.g., regorafenib, imatinib, sunitinib). Regorafenib is indicated for 3rd-line treatment of colorectal cancer in patients who have had prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and (in the case of KRAS wild-type patients) an anti-EGFR therapy. Regorafenib is administered at a dose of 160 mg, orally, once daily for 3 weeks of each 4-week cycle. Bayer AG, Leverkusen, Germany FDA approved for treating mCRC in Sept 2012; phase III trial ongoing in patients who have undergone resection of CRC liver metastases; in Jan 2013, Bayer announced regorafenib improved overall survival as second-line treatment	No standard salvage therapies in this setting	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 trials complete; FDA granted orphan drug and fast-track status; 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
Rigosertib (Estybon) for treatment of myelodysplastic syndrome	Patients with azacitidine- or decitabine-refractory myelodysplastic syndrome with excess blasts	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 the phosphoinositide 3 kinase (PI3K) and pololike kinase 1 (PLK1). Inhibition of PI3K may disrupt cell signaling that promotes cell growth and survival, and inhibition of 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; in Feb 2014, Onconova announced that the phase III trial failed to meet its primary endpoint of extending overall survival	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
Rilotumumab for treatment of gastric cancer	Patients with previously untreated, unresectable, locally advanced, or metastatic gastric cancer that expresses high levels of MET	Patients with locally advanced or metastatic gastric cancer have a poor prognosis with available 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. Rilotumumab (AMG 102) is a monoclonal antibody that binds to the MET ligand hepatocyte growth factor (HGF). By neutralizing HGF, rilotumumab may inhibit MET activity, potentially having an antineoplastic effect. In clinical trials it is being used in combination with a chemotherapy regimen consisting of epirubicin, cisplatin, and capecitabine. Rilotumumab is administered intravenously at a dose of 15 mg/kg, once every 21 days. Amgen, Inc., Thousand Oaks, CA Phase III trial ongoing	Various chemotherapy regimens, including 1 or more of the following: 5-Flurouracil Capecitabine Carboplatin Cisplatin Docetaxel Epirubicin Fluoropyrimidine Irinotecan Oxaliplatin Paclitaxel	Increased overall survival Increased progression-free survival Improved quality of life
Rindopepimut 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 patient prognosis. New therapies that improve survival and slow disease progression are needed. Rindopepimut is a peptide-based vaccine designed to stimulate an immune response to cells expressing the EGFRvIII variant. EGFRvIII is an oncogenic splice variant of EGFR, and this variant 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 first-line treatment in newly-diagnosed (phase III) and recurrent (phase II) GBM and is administered at a dose of 500 mcg rindopepimut/150 mcg of GM-CSF, via intradermal injection, biweekly during month 1, then monthly thereafter. Celldex Therapeutics, Inc., Needham, MA Phase III trial ongoing; phase IIb trial with expansion cohort ongoing in recurrent GBM; FDA granted orphan drug and fast-track statuses	Bevacizumab Temozolomide 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
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 special protocol assessment being discussed with FDA; 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
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 treatment regimens.	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 completing successful platinum-based chemotherapy. Rucaparib is a tablet orally administered twice daily (dose not specified in trial description). Clovis Oncology, Boulder, CO Phase III trial ongoing	Bevacizumab Paclitaxel	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 prior round of therapy for advanced/metastatic disease	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. 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. However, no MEK inhibitor is available. Selumetinib is an orally administered 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 ongoing	Crizotinib (if ALK mutation–positive) Ceritinib (if ALK mutation–positive) Erlotinib Cytotoxic chemotherapy (e.g., docetaxel, pemetrexed)	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 breast cancer	Patients in whom metastatic or locally advanced/unresectable HER2-negative breast cancer has been diagnosed; patients must have received up to 2 prior chemotherapy regimens 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 chemotherapy regimens. Sorafenib is a multiple kinase inhibitor (VEGFR, PDGFR, 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. In a trial of patients with advanced breast cancer, sorafenib is administered at a dose of 600 mg, daily, in combination with capecitabine. Bayer AG, Leverkusen, Germany, and Onyx Pharmaceuticals (now a subsidiary of Amgen, Inc., Thousand Oaks, CA) Phase III trial ongoing	Single-agent or combined chemotherapy regimens (e.g., capecitabine, cyclophosphamide, gemcitabine, nab-paclitaxel, platinum agents, vinorelbine) Various targeted therapies (under development; e.g., bevacizumab)	Increased overall survival Increased progression-free survival Improved quality of life
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 Chemotherapy Lenvatinib Off-label sunitinib (trials ongoing) Radiation therapy Surgical intervention	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
Specialized care model for adolescents and young adults with cancer	Adolescents and young adults (AYAs) with cancer	AYAs undergoing treatment for cancer have unique care needs that often go unmet in traditional pediatric or adult cancer units. Treatment adherence and psychological issues are of particular concern in this patient population. The Teenage Cancer Trust and Teen Cancer America work with hospitals to develop specialized cancer units and care programs that address the needs of this patient population. Program features include redesigned inpatient and outpatient facilities, provider training, clinical trial counseling/enrollment, and psychosocial support. Teen Cancer America and Ronald Reagan UCLA Medical Center, Los Angeles, CA 25 specialized teen cancer units are open in the United Kingdom; several U.S. centers established, with additional sites in development	Adult cancer units Pediatric cancer units	Improved physical and emotional health outcomes Improved treatment adherence Improved quality of life
Spicamycin-derived, nonopioid, nonnarcotic (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 KRN500 for pain have been undertaken. DARA BioSciences, Inc., Raleigh, NC Phase IIa trial completed; FDA granted fast-track status in 2011; FDA granted 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 CRCs: 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 10,000-patient DeeP-C trial complete; premarket approval application submitted to FDA Jun 2013; on Mar 27, 2014, FDA's Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee unanimously voted (10-0) that Cologuard trials had demonstrated safety, effectiveness, and a favorable risk-benefit profile; final decision date not yet announced	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 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 following 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
Tabalumab for treatment of multiple myeloma	Patients in whom recurrent or refractory multiple myeloma has been diagnosed	Although treatments for multiple myeloma have improved, the median life expectancy for these patients is only 5–7 years after diagnosis. Tabalumab is a monoclonal antibody specific for the cytokine B-cell activating factor (BAFF). Researchers have observed elevated serum levels of BAFF in patients with multiple myeloma, and BAFF is thought to stimulate multiple myeloma cell growth and promote multiple myeloma cell survival. Tabalumab is administered intravenously. In clinical trials, it is being administered 100 mg, intravenously over 30 minutes, on day 1 of every 21-day cycle for 8 cycles, in combination with dexamethasone and bortezomib. Eli Lilly and Co., Indianapolis, IN Phase II trial ongoing; FDA granted orphan drug status for treating multiple myeloma	Carfilzomib Pomalidomide	Increased overall survival Increased progression-free survival Improved quality of life
Talimogene laherparepvec 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 (TVEC) granulocyte macrophage colony-stimulating factor (GM-CSF) is an oncolytic virus; the virus purportedly replicates only in tumor cells. OncoVex 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 ongoing; manufacturer announced trial demonstrated improved durable response rate in Mar 2013 and a trend towards improved overall survival signal at an interim analysis in Nov 2013; Amgen plans to submit a new drug application for TVEC to FDA	Dacarbazine Dabrafenib (if BRAF positive) Interleukin-2 Ipilimumab Temozolomide Trametinib (if BRAF positive) Vemurafenib (if BRAF positive)	Increased overall survival Increased progression-free survival Improved quality of life
Tasquinimod for treatment of castration-resistant prostate cancer	Patients in whom asymptomatic or mildly symptomatic castration-resistant prostate cancer (CRPC) has been diagnosed	Median overall survival for patients with CRPC is only about 18 months. Advanced prostate tumors can become resistant to androgen-deprivation therapy; new treatments with novel mechanisms of action are needed. Tasquinimod is a novel oral antiangiogenic compound that is intended to restrict blood flow to prostate tumors, thus inhibiting growth; tasquinimod may also exert antitumor effects. Administered at doses of 0.25, 0.5, or 1.0 mg/day. Active Biotech, AB, Lund, Sweden 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
Tecemotide (Stimuvax) for treatment of advanced nonsmall cell lung cancer	Patients with unresectable, stage III nonsmall cell lung cancer (NSCLC) who have undergone prior treatment with concurrent chemoradiotherapy and had a response to treatment or stabilized disease	Advanced NSCLC has a poor prognosis and often responds poorly to chemotherapeutic regimens; new treatment strategies with novel mechanisms of action are needed. Tecemotide (formerly Stimuvax®) is a therapeutic vaccine composed of a 25-amino acid sequence of the MUC-1 protein, which is frequently expressed in NSCLC cells, encapsulated in a liposomal formulation; the vaccine is thought to work by stimulating anti-MUC-1 T-cell responses. The first step in treatment is administration of a single intravenous infusion of 300 mg/m^2 of cyclophosphamide 3 days before the 1st immunization. The vaccine is administered first in 8 consecutive weekly subcutaneous injections (1,000 mcg tecemotide) and then at 6-week intervals beginning at week 14 until antitumor responses are observed. Merck KGaA, Darmstadt, Germany Oncothyreon, Inc., Seattle, WA Dec 2012, initial phase III START trial missed primary endpoint of improving overall survival; new phase III START2 trial ongoing in patients who received prior concurrent chemoradiotherapy	No approved maintenance therapy in this setting	Increased overall survival Increased progression-free survival Improved quality of life
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 patients 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 trial ongoing; FDA granted orphan drug and fast-track statuses	Chemotherapy (e.g., capecitabine, dacarbazine, 5-fluorouracil, temozolomide) Interferon alfa Octreotide	Decreased rate of bowel movements Decreased 5-HIAA levels Decreased rate of flushing episodes Improved quality of life (e.g., less pain, discomfort)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tergenpumatucel-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 current 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	Various combination therapies including: Bevacizumab Carboplatin Crizotinib Docetaxel Erlotinib Pemetrexed Various immunotherapies (in development)	Improved overall survival Improved progression-free survival
Therapeutic melanoma antigen vaccine (POL-103A) 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. 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, POL-103A 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 ongoing	High-dose interferon	Increased overall survival Increased progression-free survival Improved quality of life
Tivantinib for treatment of hepatocellular carcinoma	Patients with unresectable hepatocellular carcinoma (HCC) that has failed to respond to 1 prior 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 trial ongoing	Locoregional 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
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 intended 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 completed, total progression-free survival was significantly improved; phase III trial is registered, not yet recruiting	Bevacizumab Chemotherapy-free interval Leucovorin plus 5-fluorouracil	Increased overall survival Increased progression-free survival Improved quality of life
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	Immunotherapeutics (in development, e.g., HSPPC-95, ICT107) Radiation therapy Surgical resection (with or without carmustine wafer) 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
Trebananib for treatment of 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 following 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 ongoing in 1st and 2nd-line treatment settings; Jun 2013, manufacturer announced positive top-line data for TRINOVA-1 (2nd-line setting in combination with paclitaxel); FDA granted orphan drug status for treating ovarian cancer	Docetaxel Etoposide Gemcitabine Liposomal doxorubicin Paclitaxel Topotecan	Increased overall survival Increased progression-free survival Improved quality of life
Urocidin for treatment of non–muscle-invasive bladder cancer	Patients in whom non–muscle-invasive bladder cancer (cancer on the surface of the bladder) has been diagnosed	Treatments that can provide better outcomes and reduced rates of recurrence are needed for patients with bladder cancer. Urocidin™ is a mycobacterial cell wall/DNA preparation proposed to create a localized immune response. The mechanism of action is unclear. In clinical trials, urocidin in 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. Bioniche Life Sciences, Inc., Belleville, Ontario, Canada Phase II/III trial complete; a 2nd phase III trial was discontinued Nov 2012; company reported in Mar 2014 that it is in discussions with FDA "concerning the most appropriate and efficient regulatory pathway for Urocidin" and is reapplying for orphan drug status; FDA granted fast-track status in 2006	BCG treatment Cystectomy Intravesical chemotherapy Radiation therapy	Avoided cystectomy 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 triple-negative breast cancer	Patients with early stage, triple-negative 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 BRCA1 (a breast cancer predisposition gene that is also involved in DNA repair), and triple-negative breast cancers frequently harbor such mutations. Veliparib is an orally administered medication. In a phase III trial in the neoadjuvant setting, 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. AbbVie, North Chicago, IL Phase III trial ongoing	Various combination chemotherapy regimens: Docetaxel plus cyclophosphamide Doxorubicin plus cyclophosphamide followed by or proceeded by paclitaxel	Increased overall survival Increased complete response rate Improved quality of life
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. Inhibition of 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; FDA granted breakthrough therapy status in Sept 2013 and orphan drug status in Apr 2014	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
Vosaroxin for treatment of relapsed or refractory acute myeloid leukemia	Patients in whom acute myeloid leukemia (AML) has been diagnosed	For patients with relapsed 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 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	Cladribine, cytarabine, and granulocyte colony-stimulating factor (GM-CSF) plus or minus mitoxantrone or idarubicin Clofarabine, cytarabine, and GM-CSF Etoposide and cytarabine plus or minus mitoxantrone Fludarabine, cytarabine, and GM-CSF plus or minus idarubicin High-dose cytarabine and GM-CSF plus or minus anthracycline	Increased overall survival Increased progression-free survival Improved quality of life
Web-based intervention to reduce barriers to clinical trial enrollment in oncology	Patients in whom cancer has been diagnosed who may be eligible to enroll in clinical trials	Numerous barriers have been identified that limit patient enrollment in important oncology trials. Novel programs are needed to improve patients' knowledge and preparedness to consider clinical trial enrollment as a treatment option. To address this unmet need, investigators have developed a tailored, interactive, Web-based intervention called PRE-ACT (Preparatory Education About Clinical Trials). Patients complete an initial assessment to determine personal barriers to clinical trial participation. Afterwards, the intervention provides patients with customized educational video clips designed to address individual barriers that may prevent clinical trial consideration and improve preparedness to consider clinical trial programs as a treatment option. Patients assigned to the comparator group receive general text about clinical trials excerpted from National Cancer Institute materials. PRE-ACT is intended for use before a patient's initial consultation with an oncologist. Case Comprehensive Cancer Center of Case Western Reserve University, Cleveland, OH Phase III trial completed; initial results reported at ASCO 2013	Physician counseling Patient research	Increased consideration of clinical trial enrollment Improved preparedness to discuss clinical trial opportunities Increased rates of clinical trial enrollment

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 analog 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 in dosage of 267 mg/m^2, every 3 weeks, up to 9 treatment cycles. AEterna Zentaris, Inc., Quebec, Quebec, Canada, in partnership with Ergomed Ltd., Frankfurt, Germany Phase III trial ongoing; additional trials are testing zoptarelin doxorubicin for treating prostate and breast cancer	Doxorubicin	Increased overall survival Increased progression-free survival Improved quality of life

Table 3. AHRQ Priority Condition: 03 Cardiovascular Disease: 47 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Left atrial appendage occlusion device (WaveCrest) for prevention of atrial fibrillation–associated stroke	Patients with atrial fibrillation who are not good surgical candidates	Atrial fibrillation (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 may 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 the delivery catheter. 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 Medical, Inc., Salt Lake City, UT Pilot trial completed; Sept 2013, Conformité Européene (CE) marked	Amplatzer Cardiac Plus AtriClip LAA Exclusion System AtriClip Gillinov-Cosgrove LAA Clip Cryoablation Lariat Suture Delivery Device (in development) Long-term anticoagulation therapy Radiofrequency ablation Watchman LAA device (in development)	Reduced AF-associated stroke risk

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Abdominal stent graft system (Ovation Prime) for treatment of abdominal aortic aneurysms with small vessel anatomy	Patients with abdominal aortic aneurysms (AAAs) who have small vessel anatomy	Surgical therapy options to treat AAAs include open abdominal and endovascular surgeries. Endovascular repair of AAAs is a minimally invasive way to repair an aneurysm with lower perioperative risks and faster recovery than open surgery. But the relatively large size of available stent systems for endovascular repair has made patients with small vessel anatomy ineligible for endovascular repair of AAAs. The Ovation Prime™ abdominal stent graft system is intended to provide a minimally invasive alternative to open surgery for patients with AAAs and small vessel anatomy. TriVascular, Inc., Santa Rosa, CA FDA granted humanitarian device exemption Nov 2011; FDA granted premarket approval Oct 2012; postmarket trials ongoing; Apr 2014, FDA approved expanded indication eliminating the minimum aortic neck length requirement and including clarification on appropriate vascular access techniques	Open surgical repair	Decreased perioperative risks Decreased mortality Faster recovery

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 treatment of chronic 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 (Generx®) is a DNA-based angiogenic growth factor that purportedly increases myocardial blood 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 occlude a coronary artery and produce transient ischemia while also infusing 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 Reduced 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 for treatment of hypercholesterolemia	Patients in whom hypercholesterolemia has been diagnosed	In the U.S., more than 34 million people have hypercholesterolemia. Current 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 Regeneron Pharmaceuticals, Inc., Tarrytown, NY ODYSSEY worldwide phase III clinical trials program announced in Jul 2012 comprising 10 trials enrolling 22,000 patients	Lifestyle changes 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. Merck & Co., Inc., Whitehouse Station, NJ Phase III trials (DEFINE, REVEAL) ongoing for indications including dyslipidemia, hypercholesterolemia, homozygous 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
Angiotensin receptor neprilysin inhibitor (LCZ696) 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, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers are used to treat stage A (i.e. early stage) disease, but are sometimes ineffective or suboptimally effective. LCZ696 is a 1st-in-class angiotensin receptor neprilysin inhibitor (ARNI) 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, LCZ696 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 Pivotal phase III PARADIGM-HF trial closed early on basis of Data Monitoring Committee in Mar 2014 because of strength of interim results; company is preparing regulatory submissions globally.	ACE inhibitors Angiotensin II receptor blockers Beta blockers Diuretics Inotropes Nesiritide Vasodilators	Decreased morbidity Decreased mortality Improved heart failure symptoms Improved quality of life
Autologous bone marrow–derived 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). Aastrom Biosciences, Inc., Ann Arbor, MI Phase III trial ongoing, FDA granted fast-track status for CLI	Percutaneous angioplasty and stenting Pharmacotherapy (e.g., cilostazol and pentoxifylline) Surgery	Tissue regeneration Improved circulation Reduced need for amputation Reduced morbidity and mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous bone marrow–derived stem cell therapy (C-Cure) for 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. 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. Cardio3 BioSciences, S.A., Mont-Saint-Guibert, Belgium Phase III trial (CHART-1) began Jun 2013; Jan 2014, the company announced FDA approved start of 2nd phase III trial (CHART-2)	Cardiac rhythm therapy devices Heart transplant Implanted cardioverter defibrillator Pharmacotherapy Total artificial heart implantation Ventricular assist device	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	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 25-45%. 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 usually 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 2 are used to sense ventricular activity. The device purportedly delivers nonexcitatory electrical signals during the absolute refractory period (between beats) to purportedly 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; Conformité Européene (CE) marked	Implanted pacemakers and/or defibrillators Optimal pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics)	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 renal denervation (Symplicity System) for treatment-resistant hypertension	Patients in whom uncontrolled hypertension has been diagnosed	Many pharmacotherapies are available for treating hypertension, and typically 3 types of pharmacotherapy 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. 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 Symplicity® catheter system is intended to accomplish renal denervation through a minimally invasive procedure. The device affects the output of the sympathetic nerves outside the renal artery walls. The system consists of a proprietary generator and flexible catheter that is inserted through the femoral artery and threaded into the renal artery near each kidney. Once in place, the catheter tip delivers low-power radiofrequency energy to deactivate surrounding sympathetic nerves. Renal denervation does not involve a permanent implant. Medtronic, Inc., Minneapolis, MN Phase III trial SYMPLICITY HTN-3 ongoing; completed enrollment May 2013; FDA and the Centers for Medicare & Medicaid Services (CMS) accepted Symplicity renal denervation system for consideration in their parallel review program, which allows CMS to begin its national coverage determination process while FDA completes its review of safety and efficacy; Dec 2013, the company announced start of phase III trial SYMPLICITY HTN-4; Jan 2014, the company announced that the SYMPLICITY HTN-3 trial did not meet primary efficacy endpoint, but did meet primary safety endpoint; enrollment suspended in SYMPLICITY HTN-4 trial; Mar 2014, the company announced that it will continue to develop the Symplicity device	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 attacks, kidney failure, and stroke

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 device purportedly has the potential to be the 1st minimally invasive, catheter-based treatment for ischemic HF. According to its manufacturer, the Parachute™ Ventricular Partitioning Device 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. The procedure is performed with the patient under conscious sedation in a catheterization lab and takes about 75 minutes, according to the company. CardioKinetix, Inc., Menlo Park, CA Phase III trials ongoing (PARACHUTE IV pivotal trial in U.S.; other trials ongoing in Europe and Asia); received the Conformité Européene (CE) mark in Oct 2012	Heart transplant Pharmacotherapy (e.g., beta blockers) Surgical ventricular revision 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
Darapladib for treatment of atherosclerosis	Patients with atherosclerosis who are at high risk of myocardial infarction	Despite available pharmacotherapy, coronary artery disease remains the leading cause of death in the U.S. Current treatment options include lifestyle changes, pharmacotherapy, and surgery. This intervention represents a novel mechanism of action for treating atherosclerosis. Darapladib is a lipoprotein-associated phospholipase A2 (LP-PLA2) inhibitor being investigated for treating atherosclerosis. LP-PLA2 plays a role in atherosclerosis development and progression. Its levels predict cardiovascular risk, and it has been suggested that it is involved in determining plaque stability. By inhibiting LP-PLA2, this agent may help improve atherosclerosis, stabilize unstable plaques, and reduce cardiovascular risk. In clinical trials, darapladib is being administered orally as a 160 mg enteric coated tablet, daily. GlaxoSmithKline, Middlesex, UK Phase III trials ongoing; Nov 2013, the company announced that the STABILITY trial did not meet its primary endpoint; Jun 2014, the company announced that the SOLID-TIMI 52 did not meet its primary endpoint; company is analyzing data to consider next steps	Angioplasty with or without stenting Lifestyle modification Pharmacotherapy (e.g., statins)	Improved plaque stability Reduced atherosclerosis Reduced morbidity and mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Desmoteplase for treatment of ischemic stroke	Patients in whom acute 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 FDA 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 ischemic stroke receive tPA because most do not present for treatment within the necessary time frame. Desmoteplase, a fibrin-specific plasminogen activator, is a chemical derived from the saliva of vampire bats that catalyzes the conversion of plasminogen to plasmin, the enzyme responsible for breaking down fibrin blood clots. Structurally, the chemical is similar to tPA, but has much higher fibrin selectivity and, therefore, does not cause systemic plasminogen activation and fibrinogen depletion. H. Lundbeck a/s, Valby, Denmark 2 phase III trials completed; other phase III trial ongoing (DIAS 4); FDA granted fast-track status; Jun 2014, company announced that 2 phase III trials did not meet primary efficacy endpoints but met safety endpoints; company reported "efficacy signals" in per protocol group and further development is under consideration pending discussions with FDA and others	Anticoagulant therapy (e.g., tPA [alteplase], aspirin) as indicated by patient history and time of presentation for care	Increased blood flow to the brain Reversed damage Improved stroke-related outcomes

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%. Treatments depend on the stage of disease. 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 equal to or less than 35%. CVRx, Inc., Minneapolis, MN 3 pivotal trials ongoing	Angiotensin-converting enzyme inhibitors Angiotensin II receptor blockers Beta blockers Digoxin Diuretics Minimally invasive heart surgery Ventricular assist devices	Improved left ventricular ejection fraction Reduced 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
Electrical stimulation of carotid baroreceptors (Barostim neo System) for treatment-resistant hypertension	Patients in whom severe, drug-resistant hypertension has been diagnosed	Available pharmacotherapies for treating hypertension do not result in desired blood pressure control in many cases. Uncontrolled and treatment-resistant hypertension is associated with high morbidity and mortality; novel interventions are needed to meet the needs of these patients. 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. Researchers are investigating baroreceptor stimulation for treatment-resistant hypertension. The Neo-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 2 pivotal trials ongoing; Apr 2013, FDA granted investigational device exemption status for U.S. trials; received Conformité Européene (CE) mark in 2011; also in separate HOPE4HF IDE trial for treatment of heart failure	Catheter-based renal denervation (in development) Optimal medical management	Reduced cardiovascular events Reduced hypertension Reduced mortality Reduced stoke incidence Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Endovascular aneurysm sealing system (Nellix) for treatment of infrarenal abdominal aortic aneurysms	Patients in whom an infrarenal abdominal aortic aneurysm (AAA) has been diagnosed	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 vessel anatomy ineligible for endovascular repair of AAAs. The Nellix device is an endovascular aneurysm sealing system intended to treat infrarenal AAAs, and was originally developed as an alternative to endovascular stent grafts. The device purportedly seals the aneurysm sac, thus reducing the risk for aneurysm rupture or leakage. The device consists of bilateral stents that maintain blood flow from infrarenal segments to the legs, and endobags, which are inflated with a biostable polymer to seal the aneurysm. The Nellix device is inserted via a catheter through the femoral artery. Endologix, Irvine, CA Pilot trials completed; EVAS FORWARD-IDE and EVAS-Global trials recruiting; Conformité Européene (CE) marked	Endovascular stent grafts Open surgical repair	Decreased mortality Reduced leakage Reduced rupture
Evacetrapib for prevention of cardiovascular events	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. Administered orally as a 130 mg tablet once daily for up to 4 years, in addition to standard of care. Eli Lilly and Co., Indianapolis, IN Phase III (ACCELERATE) trial ongoing and no longer recruiting; completion anticipated in 2016	Pharmacotherapy Sclerotherapy	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 for treatment of hyperlipidemia and familial hypercholesterolemia	Patients in whom hyperlipidemia has been diagnosed	Despite available therapies, cholesterol levels of some patients with 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. AMG 145 is a monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9), and purportedly decreases LDL-C levels by increasing the number of LDL receptors at the hepatocellular surface. In clinical trials, AMG 145 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 14 phase III trials ongoing for hyperlipidemia as monotherapy, as combination therapy with statins, and as therapy for familial-related hypercholesterolemia: LAPLACE-2, YUKAWA-2, GAUSS-2, GAUSS-3, MENDEL-2, RUTHERFORD-2, TAUSSIG, TESLA, TAUSSIG, THOMAS-1, and THOMAS-2; Mar 2014, the company announced that multiple phase III trials have met primary endpoints	Mipomersen (in development) MTP-I inhibitors (in development) 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 stroke and blood clots. 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™) initiated Nov 2012; received the Conformité Européene (CE) mark in Jul 2012	Implanted pacemakers and/or defibrillators Optimal pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics) Ventricular assist devices	Decreased morbidity Increased cardiac output Increased survival Reduced cardiac workload Reduced risk of stroke or thrombi

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 prior 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 investigational device exemption trial enrolled 86 patients with 62 discharged home; Feb 2013, company filed premarket approval application (FDA approved TAH-t in 2004); Conformité Européene (CE) marked Mar 2010; Health Canada approved May 2011; worldwide, more than 100 patients have received system for out-of-hospital use	TAH-t used with in-hospital driver	Extended survival for patients awaiting heart transplantation Reduced hospitalization costs Restored mobility
Imatinib (Gleevec) 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. Imatinib (Gleevec®) is a small-molecule, ABL kinase inhibitor that purportedly inhibits cellular processes that are responsible for uncontrolled growth of arterial smooth muscle cells. In clinical trials, imatinib has been administered orally, 200–400 mg, once daily. Novartis International AG, Basel, Switzerland Phase III trials completed and ongoing	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Fewer hospitalizations

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 heart attack previously. 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; expected completion mid-2014; Conformité Européene (CE) marked Sept 2010	Conventional, external MI detection technologies Patient report Routine physician followup	Earlier detection of impending heart attack Prevention of heart damage Increased overall survival
Injectable biopolymer (Algisyl-LVR) for prevention or reversal of advanced heart failure	Patients with advanced heart failure 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 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 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 and 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)	Implanted pacemakers and/or defibrillators Heart transplant Minimally invasive mitral valve surgery Mitral valve surgery Optimal pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics) Ventricular assist devices	Increased left ejection fraction Reduced progression of HF Reduced 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
Leadless pacemaker (Micra Transcatheter Pacing System) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	Data from the National Health and Nutrition Examination Survey (2007 to 2010)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. The competing Nanostim device (St. Jude Medical) also is purportedly 10% the size of a standard pacemaker (41.4 mm). Medtronic, Inc., Minneapolis, MN Phase III trial ongoing	Nanostim leadless pacemaker (in development) Ventricular pacing with leads	Reduced adverse events Reduced 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 the National Health and Nutrition Examination Survey (2007 to 2010) 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	Micra TPS leadless pacemaker (in development) 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. Oxygen Biotherapeutics, 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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia	Patients in whom homozygous familial hyper-cholesterolemia (HoFH) has been diagnosed	Outcomes with current medications for HoFH are suboptimal. Lomitapide represents a novel class of medication, a microsomal triglyceride transfer protein inhibitor (MTP-I) that is intended to lower both cholesterol and triglycerides. MTP is a lipid transfer protein that is required for moving lipid molecules from their site of synthesis, so inhibiting MTP prevents both hepatic very-low-density lipoproteins and intestinal chylomicron secretion (from food/diet) that, in turn, lowers plasma lipids. Lomitapide is intended to replace statins. It is given orally. Labeling states “initiate treatment at 5 mg once daily. Titrate dose based on acceptable safety/tolerability: increase to 10 mg daily after at least 2 weeks; and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and up to the maximum recommended dose of 60 mg daily." Aegerion Pharmaceuticals, Inc., Cambridge, MA FDA approved Dec 2012 as “an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH)”; labeling includes boxed warning about risk of hepatotoxicity	Extracorporeal apheresis Liver transplant Pharmacotherapy (e.g., statins)	Reduced low-density lipoprotein levels Improved cardiovascular outcomes Improved quality of life Improved long-term health outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Noninvasive fractional flow reserve estimation using coronary computed tomographic angiography for diagnosis of coronary artery stenosis and virtual treatment planning	Patients in whom coronary artery stenosis is suspected	Despite available pharmacotherapy, coronary artery disease remains the leading cause of death in the U.S. Current treatment options include lifestyle changes, pharmacotherapy, and surgery. Fractional flow reserve (FFR) measurement during invasive coronary angiography is used to identify coronary lesions that cause ischemia and aids in clinical decisionmaking for coronary revascularization. No noninvasive methods exist that can determine the clinical significance of both a coronary lesion and stent placement at that lesion. FFR estimation using coronary computed tomography (CT) angiography is a noninvasive method that purportedly improves accuracy of diagnosing coronary lesions. Computer modeling associated with the FFR estimation technology aids in clinical decisionmaking for revascularization by predicting changes in FFR if a stent is placed across the diagnosed obstruction. HeartFlow, Inc., Redwood City, CA Phase IV clinical trial completed; DISCOVER-FLOW study complete; PLATFORM study ongoing	FFR-guided coronary angiography	Improved coronary revascularization Decreased morbidity associated with invasive angiography

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 various 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 first 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®) 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 at a dosage of 15–20 mg weekly plus 1.0 mg folic acid 6 days/week. National Heart, Lung, and Blood Institute, Bethesda, MD Brigham and Women's Hospital, Boston, MA 188 other institutions 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
Percutaneous left atrial appendage ligation (Lariat Suture delivery device) for prevention of atrial fibrillation–associated stroke	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. Surgical ligation of the left atrial appendage (LAA) is performed in patients intolerant to anticoagulant therapy, but because of its invasive nature, many risks are associated with this procedure. The new percutaneous approach to ligating the LAA using the Lariat Suture delivery device may provide a minimally invasive option for stroke prevention in patients with AF. SentreHEART, Inc., Redwood City, CA FDA approved in 2009 for soft tissue ligation and subsequently adapted for use for LAA; invitational observational study ongoing; PLACE II trial ongoing; phase IV PLACE III trial at University of California, San Francisco withdrawn prior to enrollment	Amplatzer Cardiac Plus AtriClip LAA Exclusion System AtriClip Gillinov-Cosgrove LAA Clip Cryoablation Long-term anticoagulation therapy Radiofrequency ablation Watchman LAA device (in development) WaveCrest LAA device (in development)	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 (Watchman) for prevention of atrial fibrillation–associated stroke	Patients with atrial fibrillation who are not good surgical candidates	Atrial fibrillation 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 atrial fibrillation; 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 atrial fibrillation. 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., Natick, MA Phase III trials completed and ongoing; Dec 2013, FDA Circulatory System Devices advisory panel voted 13-1 that the device is safe and effective and that its benefits outweigh its risks; Jun 2014, FDA notified the company that a 3rd advisory panel would need to be convened before gaining approval; no date was announced for the meeting.	Amplatzer Cardiac Plus AtriClip LAA Exclusion System AtriClip Gillinov-Cosgrove LAA Clip Cryoablation Lariat Suture Delivery LAA device (in development) Long-term anticoagulation therapy Radiofrequency ablation WaveCrest LAA device (in development)	Improved quality of life Reduced morbidity Reduced stroke risk

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Riociguat (Adempas) 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. Riociguat purportedly stimulates the soluble guanylate cyclase pathway that is involved in nitric oxide signaling and vasodilation, which may relieve symptoms of PAH. Riociguat (Adempas) is administered orally, 1.0, 1.5, 2.0, or 2.5 mg, 3 times daily. Bayer AG, Leverkusen, Germany 2 phase III trials completed; Feb 2013, manufacturer submitted for regulatory approval in the U.S. and EU; Oct 2013, FDA approved riociguat (Adempas) for marketing; received marketing authorization from European Commission in Mar 2014	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalizations
Selexipag 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 (ACT-293987) is a 1st-in-class, selective prostacyclin (PGI2) receptor agonist; prostacyclin counteracts the vasoconstrictor and prothrombotic activity of endothelin. Selexipag is an orally available, long-acting, nonprostanoid prostacyclin receptor agonist that mimics the actions of endogenous prostacyclin and exerts vasodilating effects. Selexipag is administered as an oral tablet twice daily. Actelion Pharmaceuticals, Ltd., Allschwil, Switzerland Phase III trials ongoing; Jun 2014, the company announced completion of the pivotal phase III GRIPHON study	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
Serelaxin 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 (RLX030) 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 RELAX-AHF trial completed; FDA granted breakthrough therapy status Jun 2013; Mar 2014, FDA Cardiovascular and Renal Drugs advisory panel voted 11-0 against approval because the evidence was insufficient to support the indication; May 2014, FDA rejected approval of serelaxin due to insufficient evidence of efficacy and issued a complete response letter. The company met with FDA and stated it "will continue to expedite [its] clinical trial program to build the supporting body of evidence." Results from the company's ongoing phase III trial are expected by 2016.	Diuretics Vasodilators	Relief of dyspnea Decreased mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Silk Road System for prevention of stroke during carotid artery stenting	Patients undergoing placement of carotid artery stents	Carotid artery stenting (CAS), as it is currently performed, is associated with risk of embolic debris releasing during the procedure and causing a stroke or death. Available embolic protection devices include baskets, and filters, all of which have purportedly limited efficacy and significant risks to patients. The Silk Road System device is intended to provide safer and more effective cerebral embolic protection during CAS. The system enables the interventional cardiologist to deliver a stent directly from the neck rather than from the femoral artery to avoid complications associated with catheterization that starts from the femoral artery in the groin, as is typical. Starting from the groin can purportedly increase the risk of releasing plaque debris, which can travel to the brain and cause stroke. To protect the patient's brain during the procedure, the Silk Road system purportedly temporarily reverses blood flow to move any debris away from the brain. It does not use a catchment device as other embolic protection technologies do. The clinician can purportedly regulate the speed of carotid blood flow and even stop it momentarily if needed. The device consists of a circuit of arterial and venous sheaths that are connected by surgical tubing and an in-line flow controller for clinician manipulation. Silk Road Medical, Sunnyvale, CA Pivotal ROADSTER trial ongoing	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
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 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, 5 mcg/kg/day, for 10 days. Sponsored by Washington University School of Medicine, St. Louis, MO Phase III clinical trial completed	Angioplasty with stent or drug-eluting balloon placement Bypass surgery Percutaneous transluminal angioplasty	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
Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy	Patients with cardiomyopathy who are at risk of sudden cardiac arrest	Cardiomyopathy is a disease that affects the heart muscle, and is known to be a cause of sudden cardiac arrest. Current treatments are aimed at managing conditions that may cause or contribute to the disease. The S-ICD® System is an entirely subcutaneous ICD that does not require electrode lead placement in or on the heart; the leads are placed subcutaneously. The system is designed to be implanted during a minimally invasive procedure, during which the S-ICD components are placed using anatomic landmarks, obviating the need for fluoroscopic imaging during the procedure. The system consists of a pulse generator, subcutaneous electrode, and programmer. The subcutaneous electrode is electrically connected to the pulse generator, and the programmer communicates with the pulse generator wirelessly via radiofrequency telemetry. The partially coated electrode is designed to sense the patient's heartbeat, and the battery-powered pulse generator is intended to detect patterns of cardiac activity and provide defibrillation during an episode of ventricular tachycardia. The external programmer allows clinicians to set parameters for the pulse generator and to retrieve data. According to the manufacturer, the subcutaneous ICD implant procedure can be performed with the patient under general or local anesthesia. Boston Scientific Corp., Natick, MA (acquired developer Cameron Health Jun 2012) FDA approved Sept 2012 to provide defibrillation therapy for life-threatening ventricular tachyarrhythmias in patients who have no symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that can be terminated with antitachycardia pacing; Conformité Européene (CE) marked in 2009	Other implantable defibrillators	Faster recovery after implantation Reduced risk of unnecessary shocks Reduced risk of failures to shock 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 needing hospital readmission. Thus, new treatment options are needed. Ularitide is a synthetic form of urodilatin, the natriuretic peptide that is formed in the kidney. This peptide has natriuretic, diuretic, and vasodilatory properties and is being investigated for treating ADHF. 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 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 heart failure and serious cardiac arrhythmias. Some patients are not candidates for open surgery and could benefit from a minimally invasive option. The VenTouch system is a minimally invasive device intended to repair the root cause of MR. It consists of an impermeable bladder that is positioned over a targeted area of the posterior and septal lateral left ventricle. The bladder is then injected with a saline solution until the desired level of regurgitation is achieved. The system applies a light amount of pressure that forces valve leaflets closer together, thus reducing regurgitation. The device is implanted without open surgery or cardiopulmonary bypass. After implantation, the device can be adjusted in the office setting via a permanently accessible, subcutaneous port. Mardil Medical, Inc., Plymouth, MN Pilot trial completed	MitraClip Clip Delivery System (percutaneous minimally invasive) 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 aortic valve (CoreValve) implantation for treatment of severe aortic stenosis	Patients in whom severe aortic stenosis has been diagnosed	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 all patients with symptomatic, severe aortic stenosis are not suitable candidates for valve implantation performed as an open-heart surgery procedure. The transcatheter aortic valve (CoreValve® and CoreValve Evolut) implantation procedure uses fluoroscopic guidance in a minimally invasive procedure to replace the native aortic heart valve without open heart surgery; an 18-French diameter catheter is used for delivery of a self-expanding nitinol frame stent with a porcine pericardial tissue valve. According to Medtronic, the valve's self-expanding nitinol frame "enables physicians to deliver the device to the diseased valve in a controlled manner, allowing for accurate placement. The CoreValve Evolut™ is 23 mm, and CoreValve comes in 26 mm, 29 mm and 31 mm sizes. All valve sizes are delivered via the smallest (18Fr, or 6mm) TAVR [transcatheter aortic valve replacement] delivery system" to purportedly enable treatment of patients with difficult or small vasculature. Medtronic, Inc., Minneapolis, MN FDA approved Jan 17, 2014, for treating "severe aortic stenosis in patients who are too ill or frail to have their aortic valves replaced through traditional open-heart surgery." Approval was granted without convening an advisory panel meeting because results from "Extreme Risk Study" significantly exceeded anticipated goal required by FDA. Medicare covers the valve under “cover with evidence development” rules; Conformité Européene (CE) marked in 2007. May 2014, Medtronic settled global patent litigation with Edwards Lifesciences, another manufacturer of transcatheter heart valves. Jun 2014, FDA approved CoreValve for treatment of "patients with severe aortic stenosis who are at high risk for surgery."	Open surgery Optimal medical management Other transcatheter aortic valves	Improved cardiac 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
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
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 administration of transcranial ultrasound, and sonographers capable of detecting occluded cerebral artery segments are available only in specialized stroke centers or emergency departments. ClotBust™-ER is an 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 sonographer to administer therapeutic ultrasound in the principal regions in which 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 ongoing	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

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	Despite available pharmacotherapies for treating hypertension, many cases of are not well controlled. Treatment-resistant hypertension is associated with high morbidity (e.g., end-organ damage) and mortality, and novel interventions are needed for this population. 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 that can be performed in any hospital exam room and does not require the use of a catheterization laboratory. Kona Medical, Inc., Bellevue, WA Phase I trial completed; 4 clinical trials ongoing (phase not specified)	Catheter-based renal denervation systems (in development) Optimal medical therapy with 3 anti-hypertensive 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 company states that 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 May 2013 in final phase of pivotal trial; trial is ongoing	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 Improved 6-minute walk test Reduced need for medication Improved quality of life

Table 4. AHRQ Priority Condition: 04 Dementia (including Alzheimer's): 16 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
[18F] FDDNP positron emission tomography imaging agent 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). FDDNP 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 an unphased trial of PET imaging with FDDNP, results showed that compared with tau protein deposits in control patients, increased tau protein deposits were present in these regions in the 5 retired National Football League players who participated. University of California, Los Angeles Phase II trial ongoing; unphased trial completed	Posthumous diagnosis through brain tissue examination	Improved treatment protocol Reduced mild cognitive impairment and other CTE symptoms Improved quality of life
Beta-amyloid precursor protein site–cleaving enzyme inhibitor (MK-8931) for treatment of Alzheimer's disease	Patients in whom prodromal or mild to moderate Alzheimer's disease (AD) has been diagnosed	No approved disease-modifying agents are available for treating AD; therapy is limited to managing symptoms. MK-8931 is a beta-amyloid precursor protein site–cleaving enzyme (BACE) inhibitor that is being investigated for treating AD and prodromal AD. The company states that the drug is intended to exert its effects by inhibiting 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 the company states that this agent may have the potential to improve outcomes in this condition. In clinical trials, MK-8931 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 Nutrition therapy Pharmacotherapy: Donepezil Galantamine Memantine Rivastigmine	Reduced amyloid beta load in brain Regressed or slowed disease progression 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
Brexpiprazole for treatment of agitation associated with Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	Worldwide, more than 35 million people have AD; in the U.S, an estimated 5 million people have symptoms of AD, and it is the 6th-leading cause of death. 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 effective 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 proposed clinical trials, brexpiprazole is administered in tablet form, daily. Otsuka Holdings Co., Ltd., Tokyo, Japan, in collaboration with H. Lundbeck a/s, Valby, Denmark Phase III trials ongoing; positive top-line results from phase III trial reported at European Psychiatry Association Congress Mar 2014	Caregiver intervention and environmental modification (removed or alleviated stressors) Nonantipsychotic pharmaceutical combinations (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
Combined brain imaging analysis (MRI) with 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	A diagnosis of probable AD 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. Dr. Sylvie Belleville at Institut Universitaire de Gériatrie de Montréal / Université de Montréal, Montreal, Quebec, Canada No ongoing clinical trials	Cognitive assessment of probable AD Noninvasive retinal imaging of probable AD (in development) Structural neuroimaging evaluation (PET imaging) of probable AD	New diagnostic models Contribution to comprehensive early intervention programs Improved patient quality of life
Deep brain stimulation for treatment of Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	No approved disease-modifying agents are available for treating AD; therapy is limited to managing symptoms. Available therapeutic options have limited efficacy. 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 have suggested 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. Various study sponsors: Functional Neuromodulation, Ltd., Toronto, Ontario, Canada (ADvance study using Medtronic DBS system) Ohio State University, Columbus (appears to be an independent study) 1 trial completed, 1 phase I/II study ongoing; 1 unphased trial ongoing. Case studies of DBS targeting nucleus basalis of Meynert and fornix have been reported	Behavior therapy Nutrition therapy Pharmacotherapy: Donepezil Galantamine Memantine Rivastigmine	Delayed progression to AD 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
EVP-6124 for treatment of Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	AD is a progressive, degenerative, neurologic condition characterized by cognitive impairment and memory loss. It is the most common cause of dementia among older people. 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. EVP-6124 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, EVP-6124 purportedly allows smaller amounts of ACh to activate the receptor. In clinical trials, patients received daily capsules of EVP-6124 at doses of 0.1, 0.3, or 1.0 mg, alone or with previously prescribed dosages of donepezil or rivastigmine. FORUM Pharmaceuticals (formerly EnVivo Pharmaceuticals), Watertown, MA 3 phase III trials ongoing; results of phase II and IIb studies reported	Behavior therapy Nutrition therapy Pharmacotherapy: Donepezil Galantamine Memantine Rivastigmine	Reduced caregiver burden Reduced cost of care Improved patient quality of life
Gantenerumab for treatment of prodromal Alzheimer’s disease	Patients in whom prodromal Alzheimer’s disease (AD) has been diagnosed, aged 50–85 years	No approved disease-modifying agents are available for treating AD; therapy is limited to managing symptoms. Gantenerumab is a fully human anti–beta-amyloid antibody. It has been shown to pass the blood-brain barrier purportedly with a high capacity to bind to beta-amyloid plaques in the brain. This binding purportedly clears amyloid plaques by a process called phagocytosis. In clinical trials, gantenerumab is given as a subcutaneous dose of 105 or 225 mg, every 4 weeks for 104 weeks. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials ongoing	Behavior therapy Nutrition therapy Pharmacotherapy: Donepezil Galantamine Memantine Rivastigmine	Slowed disease progression, or regression 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
Handheld event-related potential/ quantitative electroencephalography system (Cognision) for diagnosis of Alzheimer's disease	Patients in whom a diagnosis of probable Alzheimer's disease (AD) is suspected	A diagnosis of probable AD 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. An unmet need exists for diagnostic and screening tools that can detect the condition before significant loss of memory, cognition, and activities of daily living occur so that patients and families can plan for care. Cognision™ System is a device intended to provide objective assessment of cognitive function using electrodes attached to a hat-like frame, which is placed on the head. The noninvasive system measures auditory event-related potentials (ERPs); according to the manufacturer, ERPs are generated in response to auditory stimuli and can accurately measure the cognitive performance of a patient's brain before overt AD symptoms are present. Patient data are located in a central data bank, which is used to analyze data and classify the patient's brainwaves based on similarities to known neurologic risk profiles. Neuronetrix, Inc., Louisville, KY 2 unphased trials completed	Blood or cerebrospinal-fluid tests for biomarkers Neuropsychological test battery PET scans with beta amyloid–binding contrast agents	Improved ability to diagnose, rule out, and/or screen for AD Earlier intervention Improved outcomes Improved quality of life
Leuco-methylthioninium (LMTX) for treatment of Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	No approved disease-modifying agents are available for treating AD; therapy is limited to managing symptoms. Leuco-methylthioninium (LMTX™) inhibits tau aggregation, purportedly dissolving tau protein tangles and oligomers, which are hypothesized to be precursors of tau tangles in the brain. Tau proteins, found mostly in neuronal cells, are hypothesized to stabilize microtubules; when defective, they no longer perform this function. Some researchers suggest that this defective state leads to AD and dementia. In clinical trials, leuco-methylthioninium is administered at an oral dose of 75–125 mg, twice daily. TauRx Pharmaceuticals Ltd., Singapore, Republic of Singapore Phase III trials ongoing outside the U.S.	Behavior therapy Nutrition therapy Pharmacotherapy: Donepezil Galantamine Memantine Rivastigmine	Increased survival Slowed progression of AD 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 Alzheimer's disease (AD). No disease-modifying agents are available for treating AD; therapy is limited to managing symptoms. 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 increase brain levels of norepinephrine, which controls behavior. Researchers hypothesize that these properties may have some use in treating MCI. This drug class has been studied in patients with dementia, but not yet in patients with MCI. It is taken orally, at a dose of up to 100 mg, daily. Eli Lilly and Co., Indianapolis, IN (manufacturer) Emory University, Atlanta, GA, with the National Institute on Aging, Bethesda, MD (investigators) 2 phase II trials ongoing; manufacturer does not appear to be seeking a labeled indication change	Behavior therapy Nutrition therapy Pharmacotherapy: 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	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 in 3.125, 6.25, 12.5, and 25.0 mg tablets, given at a maximum dose of 50 mg per day. A controlled-release formulation is also available at 10, 20, 40, and 80 mg oral doses, given daily. A daily, oral dose of 25 mg is being tested in patients with mild AD. GlaxoSmithKline, Middlesex, UK (manufacturer) Johns Hopkins University, Baltimore, MD, in collaboration with Mount Sinai School of Medicine, New York, NY (study sponsors) Phase IV trial is recruiting participants	Behavior therapy Nutrition therapy Pharmacotherapy: Donepezil Galantamine Memantine Rivastigmine Other off-label beta blockers	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 citalopram for treatment of agitation associated with Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	Worldwide, more than 35 million people have AD; in the U.S, an estimated 5 million people have AD symptoms, and it is the 6th-leading cause of death. Besides the neurocognitive declines associated with the disease, 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 for patients. Effective pharmaceutical interventions are needed. Neurobiologic data suggest that agitation may result from reduced serotonin levels and increased noradrenaline and dopamine levels. Citalopram is a selective serotonin reuptake inhibitor purported to reduce agitation in patients with AD by increasing extracellular serotonin levels. In clinical trials, citalopram is being administered in tablet form, daily, at titrated dosages ranging from 10 to 30 mg, depending on patient tolerance and response. Clinical trials initiated and supported by collaborators as part of the CitAD Research Group, including: Johns Hopkins University School of Public Health, Baltimore, MD (listed sponsor) National Institute on Aging, Bethesda, MD National Institute of Mental Health, Rockville, MD Other U.S. and Canadian universities in the CitAD group Phase III trial ongoing; results of phase III CitAD study reported in 2014. In 1998, FDA granted marketing approval for citalopram for treating major depressive disorder	Brexpiprazole (under development) Caregiver intervention and environmental modification (removed or alleviated stressors) Nonantipsychotic pharmaceutical combinations: Analgesics Antiepileptics Anxiolytics Beta-adrenoceptor antagonists Cannabinoid receptor agonists Lithium Hormonal agents Physician-selected typical and atypical antipsychotics Prazosin	Reduced cost of care Reduced agitation (on 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
Off-label intranasal insulin for treatment of Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	No approved disease-modifying agents are available for treating AD; therapy is limited to managing symptoms. Intranasal insulin represents a new mechanism of action for treating AD. Insulin is known to play a role in normal brain function, modulating glucose metabolism in the hippocampus, facilitating memory at optimal levels, modulating levels of beta amyloid, and providing neuroprotection for synapses against beta amyloid. Patients with AD have reduced levels of insulin and insulin activity. Insulin cannot be delivered peripherally because of the risk of hypoglycemia or induction or exacerbation of peripheral insulin resistance. Therefore, researchers have investigated delivering insulin intranasally (branded insulin, delivered via a nasal drug delivery device), administered at 20 or 40 IU total dose, twice daily. HealthPartners Research Foundation, Minneapolis, MN University of Kansas, Lawrence University of Washington, Seattle Wake Forest University, Winston-Salem, NC, in collaboration with Alzheimer's Disease Cooperative Study, a service of the National Institute on Aging and University of California, San Diego Phase II and II/III trials ongoing; insulin manufacturers do not appear to be pursuing expanded labeling	Behavior therapy Nutrition therapy Pharmacotherapy: Donepezil Galantamine Memantine Rivastigmine	Slowed disease progression, or regression Improved memory Improved long-term outcomes Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pioglitazone (AD-4833) 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)	AD is a progressive, degenerative, neurologic condition characterized by cognitive impairment and memory loss. It is the most common cause of dementia among older people. In patients with AD, cells in the medial temporal lobe begin to die, interrupting memory storage and recall. Patients with early-onset forms of AD exhibit MCI, a neuropsychological status characterized by small but significant declines in working memory, short- and long-term memory, and general executive functioning. Pioglitazone is a glitazone approved for treating diabetes mellitus. This off-label indication purportedly delays the onset of MCI in patients who have a genetic predisposition to developing AD. In clinical studies, pioglitazone is prescribed once daily at low dosage, orally, for up to 5 years. Takeda Pharmaceutical Co., Ltd., Osaka, Japan Phase III trials ongoing; in 2014, clinicians published a case report of 4-year sustained cognitive response in early AD treated with pioglitazone	Behavior therapy Nutrition therapy Pharmacotherapy: Donepezil Galantamine Memantine Rivastigmine	Delayed onset of MCI symptomatic of early AD Reduced long-term cost of care Improved quality of life
Selective serotonin receptor-6 antagonist (Lu AE58054) plus donepezil for treatment of Alzheimer's disease	Patients in whom probable Alzheimer's disease (AD) has been diagnosed	AD is a progressive, degenerative, neurologic condition characterized by cognitive impairment and memory loss. It is the most common cause of dementia among older people. In patients with AD, cells in the medial temporal lobe begin to die, interrupting memory storage and recall. Lu AE58054 is a serotonin $5HT_6$ antagonist intended to treat cognitive impairments symptomatic of AD and other neurocognitive disorders, as a complement to donepezil. Clinical trials are under way to investigate an optimal dosage, with patients receiving oral doses of 30 or 60 mg Lu AE58054 paired with 10 mg donepezil, once daily. H. Lundbeck a/s, Valby, Denmark, and Otsuka Holdings Co., Tokyo, Japan Phase III trials ongoing	Behavior therapy Nutrition therapy Pharmacotherapy: Donepezil alone Galantamine Memantine Rivastigmine	Reduced symptoms of cognitive impairment 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 prevention or treatment of Alzheimer's disease	Patients in whom mild probable Alzheimer's disease (AD) has been diagnosed	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. It is intended for mild-to-moderate AD and in clinical trials, is administered 400 mg, intravenously, every 4 weeks for 80 weeks. Eli Lilly and Co., Indianapolis, IN Phase III trial in mild AD ongoing despite prior trials, EXPEDITION 1 and 2, not meeting endpoints; 2 phase III trials to prevent AD in at-risk patients ongoing	Behavior therapy Nutrition therapy Pharmacotherapy: Donepezil Galantamine Memantine Rivastigmine	Decreased brain beta-amyloid load Slowed or halted disease progression Improved memory and cognition Improved survival Improved quality of life

Table 5. AHRQ Priority Condition: 05 Depression and Other Mental Health Disorders: 16 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Amitifadine 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. Amitifadine (EB-1010) is a novel, unbalanced, triple serotonin-norepinephrine-dopamine reuptake inhibitor antidepressant that acts simultaneously as a reuptake inhibitor for the 3 monoamines. It demonstrates greatest affinity for transporters that inhibit serotonin reuptake, 1/2 as much against norepinephrine reuptake, and 1/8 as much against dopamine reuptake. In clinical trials, EB-1010 is administered as an oral dose of 25–50 mg, twice daily. Euthymics Biosciences, Inc., Cambridge, MA Phase II/III trial completed; top-line results failed to meet primary endpoint	Serotonin-norepinephrine reuptake inhibitors Tricyclic antidepressants	Increased serotonin, norepinephrine, and dopamine neurotransmission Improved symptoms, as measured by standard depression rating scales Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 these of patient's 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 with 16 patients completed, with results published in 2013	Cognitive behavior therapy Cognitive remediation Computerized cognitive training	Fewer symptoms Improved functioning Improved quality of life
Bright-light adjunctive therapy for nonseasonal major depressive disorder and bipolar major depression	Patients in whom nonseasonal major depressive disorder (MDD) or bipolar depression (BPD) has been diagnosed	Many pharmacologic and psychotherapeutic options are available patients in whom MDD or BPD has been diagnosed, yet fewer than half of these patients achieve remission. Additionally, many available treatments have undesired side effects. 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 bright light therapy as a stand-alone or adjunctive treatment, with varied dosing protocols, for patients with MDD or BPD with and 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 1 phase III trial and earlier phase and unphased 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 Improved sleep patterns Improved quality of life Reduced rates of suicide attempts and completed suicides

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Deep brain stimulation for treatment-resistant Tourette's syndrome	Patients in whom Tourette's syndrome (TS) has been diagnosed	In some patients with TS, symptoms can become severe and unresponsive to adequate management with pharmacotherapy. 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, Inc. (Minneapolis MN), 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. Johns Hopkins University, Baltimore, MD University Hospitals, Cleveland, OH University of Florida Center for Movement Disorders and Neurorestoration, Gainesville Various other universities worldwide Phase II and III trials ongoing; multiple case studies, including 2- and 3-year patient followup data, have been reported	Botulinum toxin type A injections Pharmacotherapy: Antidepressants Central adrenergic inhibitors Fluphenazine Pimozide Stimulant medications	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
Deep brain stimulation of Brodmann area 25 (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 multiple medications, psychotherapy, and electroconvulsive therapy have failed, no treatment options are available for MDD. The Libra™ Deep Brain Stimulation (DBS) System is an implant intended to send mild pulses of current from an implanted device to stimulate the brain. 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 trials ongoing; preliminary trial and case study data have been reported. In 2014, investigators published data indicating a potential biomarker for treatment response to this intervention.	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 Improved sleep patterns Reduced rates of suicide attempts and completed suicides Improved quality of life
Glycine transporter type 1 inhibitor (bitopertin) for treatment of negative symptoms of schizophrenia	Patients in whom schizophrenia has been diagnosed	Existing pharmacotherapies for schizophrenia may 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. Bitopertin is a glycine transporter type 1 inhibitor. Elevation of extracellular synaptic glycine concentration by blockade of glycine transporter type 1 has been hypothesized to potentiate N-methyl-D-aspartate receptor function. It is intended to mediate negative symptoms, which include blank stares, monotone and monosyllabic speech, lack of animation, seeming lack of interest in the world and other people, and inability to feel pleasure. Available treatment focuses on positive symptoms. In trials, the drug is being given orally, once daily, at several unspecified dose levels. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials ongoing; phase II and II/III trial results reported in 2014. Jan 2014, Roche reported that 2 phase III trials did not meet primary endpoints of significantly reducing social withdrawal or lack of motivation at 24 weeks compared with placebo; Roche is continuing several other trials of the drug while considering next steps	Pharmacotherapy (e.g., atypical antipsychotics)	Decreased 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
Mobile apps to aid in treatment of major depressive disorder	Patients in whom major depressive disorder has been diagnosed	Psychotherapy for major depression traditionally involves in-person meetings between a therapist and patient or client. This method has limitations, including issues of access by all those in need, lack of intervention at critical moments, and an inability to reach individuals who lack the means or willingness to enter a traditional therapeutic relationship. To address these unmet needs, researchers have created mobile applications ("apps") that purportedly provide psychotherapeutic benefit to patients with depression. These apps range in their capabilities and intended benefits. Features include medication adherence monitoring, real-time information feedback to health professionals, tools for patient self-assessment of emotional state, cognitive behavioral modification guides, and tools or resources intended to develop or support coping and other emotional skills. Various research institutions, including Northwestern University, Evanston, IL; University of California, San Francisco; National Institute of Mental Health, Bethesda, MD Clinical trials ongoing; pilot data and systematic review of small trials published in 2013	Cognitive behavior therapy In-person psychotherapy Internet-delivered psychotherapy (not on a mobile device) Video-game based cognitive behavior therapy	Improved performance on mental health rating scales Reduced 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
Nicotinic alpha-7 agonist (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	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 cognitive symptoms of schizophrenia. EVP-6124 is a selective, potent compound intended to enhance synaptic transmission in the brain and act as a co-agonist with acetylcholine (ACh) to enhance cognition. According to the manufacturer, the agent sensitizes the alpha-7 receptor, allowing smaller amounts of naturally occurring ACh to be effective in activating the alpha-7 receptor. The company purports that this mechanism could alleviate the undesirable side effects caused by other systemic compounds (e.g., acetylcholinesterase inhibitors), which are associated with toxic side effects at certain doses. In ongoing clinical trials, 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; proof-of-concept trial data published in 2014	Atypical antipsychotics	Improved cognitive symptoms Improved social functioning Improved quality of life
NMDA receptor modulator (GLYX-13) for treatment – resistant major depressive disorder	Patients in whom major depressive disorder (MDD) has been diagnosed Patients in whom 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. GLYX-13, a functional partial agonist selective modulator of the NMDA receptor (NMDAR), is an experimental oral medication purported to treat MDD using a novel mechanism, targeting glycine-site regions of the NMDAR. In clinical trials, GLYX-13 is administered at dosages of 5 or 10 mg/kg, as an adjunct therapy to a patient's current antidepressant prescription. Naurex, Inc., Evanston, IL Phase II trials ongoing; Feb 2014, results of phase I and IIa trials reported in review paper. In Mar 2014, FDA granted fast-track status to GLYX-13 as an adjunct therapy for treatment-resistant MDD.	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 scores on standardized depression measures Reduced MDD 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 has been diagnosed	No pharmacotherapies are approved by FDA for binge-eating disorder, and off-label pharmacotherapies are associated with limited efficacy, undesirable side effects, and low patient adherence to treatment recommendations. Armodafinil (Nuvigil®) is a wakefulness-promoting drug with an unknown mechanism of action; it was approved in 2007 for treating excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work disorder. Some investigators have suggested that binge-eating disorder may mediate a known relationship between narcolepsy and obesity, so researchers are investigating its off-label use in patients with binge-eating disorder. In a clinical trial, the drug is administered orally, at a variable dosage of 150–250 mg/day. Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel (manufacturer) Lindner Center of Hope, Mason, OH (investigator) Phase III trial recruiting participants	Cognitive behavior therapy Off-label pharmacotherapies (e.g., antiepileptics, norepinephrine reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors)	Improved symptoms of binge eating Reduced morbidity Reduced mortality
Off-label intranasal oxytocin for treatment of schizophrenia	Patients in whom schizophrenia has been diagnosed	Existing pharmacotherapies for schizophrenia may 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 schizophrenia. Psychotherapeutic interventions are limited by suboptimal efficacy and availability. Release of oxytocin is associated with social bonding, empathy, and trust. Given oxytocin's importance in social behavior, researchers purport it may have utility in improving the negative symptoms of schizophrenia and their social cognition deficits. The drug is under study in varying doses (e.g., 0.6 mL) that are self administered intranasally at varying intervals (e.g., twice daily). Several institutions, including National Institute of Mental Health, Bethesda, MD; University of California, Los Angeles; University of Maryland, College Park; and University of North Carolina, Chapel Hill Phase IV trial completed; phase II and III trials ongoing; pilot data published	Behavior therapy Other medications for negative symptoms	Improved social cognition 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 and 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 formal 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 formulations have also been reported for this indication. Ketamine is being studied as both a monotherapy and as an augmentative therapy to electroconvulsive therapy. Various institutions conducting trials sponsored by the National Institute of Mental Health, Bethesda, MD Phase II–IV trials ongoing; data reported from multiple phase II trials and case studies	Cognitive behavior therapy Deep brain stimulation Electroconvulsive therapy Off-label scopolamine Psychotherapy Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors Transcranial magnetic stimulation Tricyclic antidepressants Vagal nerve stimulation	Rapid improvement in depression symptoms Improved treatment adherence 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 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 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 as an oral dose of 50–100 mg, daily, and is being investigated as both an individual and adjunctive intervention. Sanofi, Paris, France (manufacturer) Investigators include: Brigham and Women's Hospital, Boston, MA National Institute of Mental Health, Bethesda, MD Yale University, New Haven, CT Phase II trials ongoing; several phase II trials completed; FDA approved for treating amyotrophic lateral sclerosis	Cognitive behavior therapy Deep brain stimulation Electroconvulsive therapy Off-label scopolamine Psychotherapy Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors Transcranial magnetic stimulation Tricyclic antidepressants Vagal nerve stimulation	Glutamatergic modulation Improved MDD 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 scopolamine (intravenous, transdermal, oral) 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. 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 National Institutes of Health, Bethesda, MD Clinical trials ongoing; positive findings published from several studies	Cognitive behavior therapy Deep brain stimulation Electroconvulsive therapy Off-label ketamine Psychotherapy Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors Transcranial magnetic stimulation Tricyclic antidepressants Vagal nerve stimulation	Improvement in symptoms on standard depression rating scales Reduced remission rates 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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Video game-based cognitive behavior therapy for adolescents with major depressive disorder	Adolescent and young adult (AYA) patients in whom mild- to moderate-severity major depressive disorder (MDD) has been diagnosed or early-onset major depressive disorder (eoMDD) is suspected	Many AYA patients with MDD or eoMDD do not have the condition diagnosed or do not respond favorably to conventional therapy, leading to potentially serious consequences. Engaging, well-received therapy options are needed for this patient population. SPARX is a fantasy-based, 3-dimensional, interactive, role-playing computer game designed to provide cognitive behavior therapy (CBT) to AYAs experiencing clinically significant symptoms of depression. SPARX guides the user through modules that feature CBT-based challenges. The user interacts in the 1st person with a guide that provides education, gauges mood, and monitors progress on the challenges. The program purports to promote the development of coping and life skills that reduce depression symptoms. University of Auckland in partnership with Metia International, both of Auckland, New Zealand; published by LinkedWellness, Baltimore, MD Unphased trials completed with data published in 2012; data for customized software version (Rainbow SPARX) designed for sexual minority youth published in 2014	Cognitive behavior therapy Internet-delivered psychotherapy Mobile app-delivered cognitive behavior therapy or psychotherapy therapy Psychotherapy (in person) Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors Tricyclic antidepressants	Reduced severity of depression symptoms Increased remission rates Improved quality of life

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cyclocreatine (LUM-001) for treatment of creatine transporter deficiency	Patients in whom creatine transporter deficiency (CTD) has been diagnosed	CTD (also called *SLC6A8* Deficiency or CRTR) is a rare x-linked, recessive, inherited inborn error of creatine metabolism. CTD is classified as an autism spectrum disorder and a form of x-linked mental retardation; it is also 1 of 3 general cerebral creatine deficiency syndromes. CTD is caused by a defect in the *SLC6A8* gene that encodes the transporter protein necessary for transporting creatine across cell membranes and the blood-brain barrier. This defect results in deficient creatine levels in the brain. Male patients with CTD exhibit autistic behavior, epilepsy, and severe developmental delays, including speech delays and intellectual disability. Female CTD patients may be asymptomatic, or exhibit mild behavioral problems and learning problems. CTD also represents the 2nd-largest cause of autism, after fragile X syndrome. No approved treatments exist for CTD. LUM-001, a repurposed small-molecule analogue of creatine, purportedly treats CTD by providing a source of biofunctional creatine capable of crossing the blood-brain barrier. The drug was previously studied under an investigational new drug application for intravenous use in a solid tumor indication. Lumos Pharma is required to repeat some preclinical studies in an oral formulation. LUM-001 will be administered orally to patients with CTD. Lumos Pharma, Austin, TX FDA granted orphan drug status Jul 2012; company has not registered clinical trials yet	No approved or investigational treatments have been demonstrated effective in treating patients with CTD	Increased cerebral creatine levels Reduced autistic behaviors Reduced intellectual and speech disabilities Improved patient 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 (MG01CI), a nonstimulant, extended-release, ion-pair salt of pyridoxine and 2-pyrrolidone-5-carboxylate, 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, patients receive the drug orally, 1,400 mg, once daily, for 6 weeks. Patients receiving other medication for ADHD complete a washout period before MG01CI administration. Alcobra, Ltd., Tel Aviv, Israel Phase II/III trial ongoing; results reported from completed phase II trials	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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label intranasal oxytocin (Syntocinon) for treatment of autism spectrum disorders	Patients in whom autism spectrum disorder (ASD) has been diagnosed	According to the U.S. Centers for Disease Control and Prevention, ASDs are diagnosed in about 9 of 1,000 people in the U.S. Available therapies include behavior and communication therapies (including applied behavior analysis) and dietary, medical, and complementary interventions. Pharmacologic therapies address symptoms of hyperactivity and depression, but pharmacologic treatments for social deficits in individuals with ASD are lacking. A pharmacologic treatment targeted at the core social deficits of ASD in early childhood could affect developmental pathways to make other psychosocial interventions possible. Oxytocin acts on smooth muscle cells (causes uterine contractions and milk ejection); it also can influence activity in the brain's amygdala, an area involved in social and emotional processing. Oxytocin may increase visual contact to the eye region of human faces, increase memory for faces, and improve the ability of people to infer the mental states of others, which are challenges associated with autism. In ongoing studies of children and adults with ASDs, this treatment is administered intranasally (e.g., 12-unit puff per nostril, twice daily, totaling 48 IU daily). Children's Hospital of Philadelphia, Philadelphia, PA Massachusetts General Hospital, Boston Mount Sinai School of Medicine, New York, NY Montefiore Medical Center, Bronx, NY Stanford University School of Medicine, Stanford, CA University of Illinois at Chicago University of Minnesota - Clinical and Translational Science Institute, Minneapolis Phase II/III and II trials ongoing	Behavior and physical interventions addressing speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Central nervous system pharmacology Melatonin Selective gamma aminobutyric acid type B receptor agonist (in development)	Improved Diagnostic Analysis of Nonverbal Accuracy results Improved Social Responsiveness Scale™ scores Improved Clinical Global Impressions Scale–Improvement scores

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label N-acetylcysteine for treatment of autism spectrum disorders	Adolescent patients in whom autism spectrum disorder (ASD) has been diagnosed	According to the U.S. Centers for Disease Control and Prevention, ASDs are diagnosed in about 9 of 1,000 people in the U.S. Available therapies include behavior and communication therapies (including applied behavior analysis) and dietary, medical, and complementary interventions. N-acetylcysteine (NAC) is a glutamate modulator and antioxidant known to increase glutathione in children who have autism. NAC has been administered orally or intravenously at various doses and regimens (e.g., weekly intravenous administration of 20 mg/kg mixed with glutathione 600 mg IV and vitamin C 2,000 mg; oral 60 mg/kg/day thrice daily to a maximum dose of 4,200 mg/day). Stanford University School of Medicine, Stanford, CA Indiana University School of Medicine, Indianapolis National Alliance for Autism Research, Princeton, NJ Phase II trials completed and met primary endpoints	Behavior and physical interventions addressing speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Central nervous system pharmacology Melatonin Selective gamma aminobutyric acid type B receptor agonist (in development)	Improved Clinical Global Impressions Rating Scale results Improved Repetitive Behavioral Scale score Improved social responsiveness Improved speech and language Improved metabolic measures Improved quality of life
Video game software for treatment of 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 treatment. 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 to be 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) Pilot 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
XBox 360 musical program (Kinect audio project) for improving social skills in childhood autism	Children in whom autism spectrum disorder (ASD) has been diagnosed	According to the U.S. Centers for Disease Control and Prevention, ASDs are diagnosed in about 9 of 1,000 people in the U.S. Available therapies include behavior and communication therapies (including applied behavior analysis) and dietary, medical, and complementary interventions. Interactive therapy using XBox 360's Kinect system has been targeted by researchers attempting to improve social skills in patients with autism. The Kinect Audio Project is an XBox 360 program/system that uses the Kinect camera and motion sensor with PC software to allow children to participate in virtual music lessons by providing them with virtual gloves that allow "touching" of music notes when they place the gloves over the symbol on the screen. This allows inclusion of children with autism in student music activities that might have otherwise been difficult with normal instruments. This program is intended to increase mobility skills, improve understanding of movement and association, enhance unsolicited participation, and improve overall social interaction. South Downs Community Special School, Eastbourne, UK Various testing projects ongoing	Educational and behavior programs	Improved social skills and human interaction Improved activities of daily living Improved quality of life

Table 7. AHRQ Priority Condition: 07 Diabetes Mellitus: 13 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Alpha-1 antitrypsin 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) 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; FDA granted orphan drug status Aug 2011	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 system 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 T2DM, 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 first low-glucose suspend system, a 1st step to a total APDS, is commercially available. Various manufacturers in collaboration with the Juvenile Diabetes Research Foundation, 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 9, 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. In Sept 2013, FDA approved the Medtronic MiniMed 530G® threshold system with Enlite®, a combined insulin pump and sensor that is considered to be the 1st step toward fully artificial pancreas	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
C-peptide replacement therapy (Ersatta) for treatment of diabetic peripheral neuropathy	Patients in whom diabetic peripheral neuropathy has been diagnosed	According to diabetes researchers, an estimated 15% of people with diabetes develop at least 1 foot ulcer during their lifetime, and 60–70% of these ulcers are primarily neuropathic in origin. Available treatments for diabetic peripheral neuropathy involve control of secondary symptoms (i.e., pain management). In the body, c-peptide is generated during insulin processing and is secreted along with insulin. Until recently, c-peptide was not thought to possess biological activity and was used as a biomarker; however, recent studies suggest that a lack of c-peptide (which is not provided by exogenous insulin administration) may contribute to various secondary complications of diabetes. Ersatta™ is an extended-release formulation of c-peptide under study for treating various secondary complications of diabetes, including neuropathy. In trials, it is given as an injection at high dose (2.4 mg) or low dose (0.8 mg), once weekly, for up to 52 weeks. Cebix, Inc., La Jolla, CA Phase II trial ongoing; FDA granted fast-track status for diabetic peripheral neuropathy	Analgesics Duloxetine (antidepressant) Lidocaine patches Pregabalin (anticonvulsant) Selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, antiepileptics	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
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; approved Sept 2012 in Japan; submitted for approval in Europe; FDA issued complete response letter in Feb 2013 for both drugs requesting additional cardiovascular data from a dedicated cardiovascular outcomes trial	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
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 Phase III trials completed; new drug application (NDA) submitted Jun 2010; FDA issued complete response letter in Dec 2010 asking for additional safety data; NDA resubmitted May 2011; Nov 2011, FDA issued complete response letter; company submitted response; company announced that a Prescription Drug User Fee Act date of Oct 17, 2013, had been set; FDA issued complete response letter in Oct 2013 asking for additional safety data and to notify the manufacturer that an advisory committee meeting would be convened Jan 27, 2014; Dec 2013, FDA determined that an advisory committee was no longer necessary but that manufacturer is still required to respond to safety issues presented in complete response letter; Mar 2014, company resubmitted NDA. Iluvien has received marketing approval in several European nations; FDA assigned decision date of Sept 26, 2014	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
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 T2DM, taking insulin. Patients who require daily insulin may someday benefit from a closed-loop system, termed an artificial pancreas device system (APDS). An APDS is a 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, Inc., Minneapolis, MN 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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interactive text messaging program (Care4Life) to improve management of type 2 diabetes mellitus	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. Despite available treatments and blood glucose monitoring devices for T2DM, achieving adequate glycemic control remains a prominent issue for patients. Care4Life is an interactive text-messaging program intended to help improve treatment adherence and achieve better glycemic control in patients with T2DM. The text messaging and online health record system is intended to deliver customized educational content based on the user's own medication plan and health goals. The system delivers messages intended to motivate a patient to keep track of blood glucose levels and his or her fitness and weight goals and improve medication adherence. Patients can enter health data via text that will be captured on a Web portal that can be made accessible to the patient's health care team. Text messages can be delivered in English and Spanish. This intervention could be especially useful for reaching underserved communities with limited access to health care providers. Vovixa, Inc., Washington, DC (manufacturer) HealthInsight, Salt Lake City, UT (investigator) Pilot trial ongoing; program launched Oct 2012	Diabetes behavior and lifestyle support groups Hardcopy patient education Internet-based patient education	Improved glycated hemoglobin (HbA_{1c}) levels Reduced secondary complications Reduced health disparities and improved access to diabetes program Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
ITCA 650 (exenatide continuous subcutaneous delivery) 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 [GLP1] mimetic) delivered subcutaneously and continuously through a tiny implanted stick-shaped pump and is purported to remain 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; in 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 Improved quality of life Reduced glycemic excursions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Metabolic (bariatric) surgery for resolution of type 2 diabetes in obese and nonobese patients	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 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 skin measurement screening test (Diab-spot) for type 2 diabetes	Patients at risk of developing type 2 diabetes mellitus (T2DM)	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. Late detection typically leads to secondary complications (e.g., cardiovascular disease, nephropathy, neuropathy) that could be prevented or delayed with earlier diagnosis. Late diagnosis may occur for many reasons, including patient nonadherence with recommended screening (blood draw). 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 Conformité Européene (CE) mark and Health Canada License approval	Noninvasive glucose screening test in development (i.e., SCOUT DS) 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
Peptide immune modulator (DiaPep277) for treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus (T1DM) has recently 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. DiaPep277® has a novel mechanism of action and is an immune-modulating therapy intended to dampen the immune system's activity against beta-islet cells, thereby promoting their survival and preserving function of the pancreas. Therapy consists of a peptide derived from heat shock protein 60, which is 1 of the main antigens on beta-islet cells recognized by cytotoxic T cells. DiaPep277 is designed to interact with both the T-cell receptor and TLR2, which has the effect of downregulating the inflammatory response induced by T helper cells. If approved, the therapy would be delivered as a vaccine in a physician's office rather than as a self-administered drug (or self-administered insulin). Hyperion Therapeutics, Inc., Brisbane, CA Phase III trials ongoing (open label extension DIA-AID1 and international multicenter DIA-AID 2); phase I/II trial ongoing in Israel; FDA granted orphan drug status	Insulin modifications Islet cell transplantation Pancreas transplantation	Improved beta-cell function (measured as change from baseline in stimulated C-peptide secretion during a mixed-meal tolerance test) Increased glycemic control

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Topical pexiganan acetate antimicrobial 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; thus, treatment is becoming 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 in treating DFI. Pexiganan acetate cream 1% is a novel, topical, broad-spectrum antimicrobial peptide that is being investigated as a topical anti-infective agent for treating mild DFIs. Pexiganan 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)	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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ultra-rapid-acting inhaled insulin (Technosphere Insulin Inhalation System with Afrezza) for treating diabetes that requires insulin	Patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (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 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: 84 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Alemtuzumab (Lemtrada) for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	Alemtuzumab (Lemtrada™) represents a new mechanism of action for RRMS. It is a humanized monoclonal antibody targeted to the CD52 antigen (expressed on T and B lymphocytes, monocytes, macrophages, and eosinophils); intended to target antigen-carrying cells, thereby rapidly removing T cells from blood, bone marrow, and organs. T-cell depletion is said to last for more than 1 year. The drug is given as a once-yearly treatment regimen (once a day for 5 days) via intravenous administration. Genzyme subsidiary of Sanofi, Paris, France Phase III and IV trials ongoing. Dec 2013, FDA rejected Lemtrada for marketing approval, but accepted Sanofi's resubmitted supplemental biologics license application in May 2014, with an official review expected in late 2014. In 2013, Lemtrada received European marketing approval (for RRMS) and Canadian marketing approval (for treating patients with treatment-refractory RRMS).	Dimethyl fumarate (Tecfidera®) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Reduced frequency of relapse Slowed disease progression Improved quality of life
Alipogene tiparvovec gene therapy (Glybera) 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, in which the development of chylomicronemia leads to hypertriglyceridemia and acute pancreatitis. Currently 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 1×10^{12} genome copies per kg, in a single series of intramuscular injections. uniQure, Amsterdam, the Netherlands Phase III trial completed; granted orphan drug status in the U.S. and EU; in Nov 2012, it became the 1st approved gene-therapy drug in 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
Amitriptyline/ketamine analgesic cream (AmiKet) for treatment of peripheral neuropathy	Patients in whom chemotherapy-induced peripheral neuropathy (PN) has been diagnosed	PN results from damage to the peripheral nerves caused by drug-related toxicity (e.g., chemotherapeutics) or mechanical trauma (e.g., surgery, injury) and can cause significant pain and reduce quality of life. This condition often responds poorly to standard pain treatments. AmiKet (4% amitriptyline/2% ketamine topical cream) is a novel approach to treating neuropathic pain, combining the tricyclic antidepressant amitriptyline and the NMDA receptor antagonist ketamine into a topical analgesic. In clinical trials, this agent is applied to the affected areas twice daily. Immune Pharmaceuticals, Inc. (formerly EpiCept Corp.), New York, NY (manufacturer) University of Rochester, Rochester, NY, in collaboration with National Cancer Institute, Bethesda, MD (investigators) British Columbia Cancer Agency, Canada (investigator) 1 phase III trial ongoing, another completed; FDA granted fast-track status; also under study for post-herpetic neuralgia	Antiepileptic agents Interventions for treating the primary cause of nerve damage Opioid analgesics Oral tricyclic antidepressants Over-the-counter analgesics	Decreased pain frequency and intensity Improved quality of life
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 disease in which muscles atrophy and weaken and 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. Current SMA treatments address disease symptoms only. Treatments are needed that address the underlying cause of disease. ISIS-SMNRx is an antisense molecule that is purported to boost levels of survival motor neuron 1 protein by addressing an RNA splicing irregularity. Low levels of survival motor neuron 1 protein are purported to lead to the development of SMA. The ongoing trial is enrolling children age 2 to 14 who are medically stable; the drug is administered during a single injection of 1 of 4 dosage levels of into the spinal cord fluid. Isis Pharmaceuticals, Inc., Carlsbad, CA Biogen Idec, Weston, MA Phase I and II trials ongoing, with results from 2 completed phase I trial reported; FDA granted fast-track and orphan drug status	Supportive therapy	Reduced SMA symptoms Improved motor function Improved patient quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Apical sodium-dependent bile acid transporter (LUM001) 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. Current treatment options have limited efficacy and many patients eventually require surgical intervention or transplantation. LUM001 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. Lumos Pharma, Austin, TX 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 Reduced serum bile acid levels Reduced symptoms (e.g., pruritus) Improved quality of life
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 II trial completed; FDA granted orphan drug status; approved for treating psoriatic arthritis	Corticosteroids	Improved visual symptoms Reduced pain and frequency of oral/genital ulcers 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
Asfotase alfa 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 regulation of bone mineralization. Alterations in the *TNSALP* gene result in extracellular accumulation of inorganic pyrophosphate, leading to inhibition of bone mineralization and resultant rickets or osteomalacia or both. Incidence has been estimated at 1 per 100,000 births. Asfotase alfa (ENB-0040) 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. This 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/III trials ongoing; 2 phase II trials completed; FDA granted fast-track status, orphan drug status, and breakthrough therapy status	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
Autologous bone marrow–derived mesenchymal stem cell therapy (NurOwn) for amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	The average life expectancy of a patient with ALS is 3–5 years, 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 for ALS 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 (manufacturer) Massachusetts General Hospital, Boston, MA (US clinical trial collaborator) Phase II U.S. trial registered; phase IIa trial ongoing in Israel, with preliminary results reported in 2013; FDA granted orphan drug status Feb 2011; U.S.-based phase II multicenter trial planned to begin by end of 2013	Riluzole Physical therapy and assistive technology (e.g., speaking tubes, motored chairs)	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
Balloon angioplasty and/or stenting of azygos and internal jugular vein for treatment of multiple sclerosis	Patients with multiple sclerosis (MS) who exhibit evidence of chronic cerebrospinal venous insufficiency (CCSVI)	Current treatments for MS may slow disease progression, but they are not effective in all patients, and the disease has no cure. CCSVI, in particular stenotic and occlusive lesions in the azygos and internal jugular veins, is hypothesized to play a role in the cause, disease progression, and pathogenesis of MS. Image-guided interventional endovascular management is a procedure in which an interventional radiologist performs percutaneous transluminal angioplasty using an angioplasty balloon and/or stent to improve circulation and reduce hypoperfusion of brain parenchyma to relieve MS symptoms. 1st reported by University of Ferrara, Italy University of British Columbia, Canada Procedure uses existing technologies; in early diffusion in Europe and U.S.; 1 phase II Canadian and 1 phase III Italian trial recruiting; other trials ongoing; FDA issued safety warning in May 2012 about performing procedure outside of clinical trial setting	Dimethyl fumarate (Tecfidera®) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Improved cognitive and motor function Reduced relapse Reduced lesions on imaging Improved quality of life
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 trial recruiting; FDA granted breakthrough therapy status Aug 2013; 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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 2 phase III trials ongoing: VTI-208 randomized, controlled trial for alcohol induced liver decompensation expected to complete 1H 2015; VTI-210 randomized controlled trial for acute alcoholic hepatitis;1 phase 2 trial (VTI-212) ongoing on fulminant hepatic failure or surgery-induced liver failure; FDA granted orphan status for acute liver failure	Antibiotics Lactulose Liver transplant	Improved rate of 30-day transplant-free survival Increased time to progression of end-stage liver disease
BioErodible MucoAdhesive delivery of buprenorphine for treatment of moderate to severe chronic pain	Patients experiencing moderate to severe chronic pain	For patients whose chronic pain is resistant to standard medications, more effective treatment options are needed. Buprenorphine is an opioid that is used in current formulations for opioid maintenance therapy or management of moderate pain. BEMA™ (BioErodible MucoAdhesive) is a drug-delivery technology used to deliver opioids and other drugs by encapsulating the drug in a dissolvable polymer film used on the inside of the cheek for buccal delivery. In clinical trials, BEMA buprenorphine, also called EN3409, is applied to the buccal mucosa, twice daily. BioDelivery Sciences International, Raleigh, NC, in collaboration with Endo Health Solutions, Inc., Malvern, PA Phase III trials completed and ongoing; BEMA delivery system has FDA approval for use with fentanyl; under development for delivery of buprenorphine and buprenorphine/naloxone combinations; new drug application submission planned for late 2014	Alternative long-acting opioid formulations COX-2 inhibitors Nonsteroidal anti-inflammatory drugs	Reduced pain (average pain numerical rating scale) Reduced risk of addiction

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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, about 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 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 first treatment intended to halt IgA nephropathy. Blisibimod is administered by subcutaneous injection. Anthera Pharmaceuticals, Hayward, CA Phase III trials 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
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. Banyan Biomarkers, Inc., Alachua, FL, with support from the U.S. Department of Defense Unphased trial completed	Clinical neurologic evaluation Computed tomography Magnetic resonance imaging	Improved sensitivity Improved specificity

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
COR-003 (NormoCort) 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. COR-003 (NormoCort) is being developed as single 2S, 4R enantiomer of ketoconazole for treating endogenous Cushing's syndrome. It purportedly affects the down-regulation of cortisol synthesis by targeting multiple points in the synthetic pathway. Cortendo AB, Partille, Sweden Phase III trial ongoing; FDA granted orphan drug status Mar 2012	Mifepristone (Korlym) Off-label pharmacotherapy agents (ketoconazole, metyrapone, mitotane) Radiotherapy Surgery	Improved symptoms Reduced ACTH levels Reduced morbidity from excess cortisol Improved quality of life
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 patient 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 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 (manufacturer) Cornea and Laser Eye Institute, Teaneck, NJ (trial sponsor) Phase III trials completed and ongoing; FDA granted orphan drug status and priority review; FDA sent complete response letter to application requiring additional information Mar 2014; Conformité Européene (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 therapy (ALXN1101) for treatment of molybdenum cofactor deficiency (MoCD) 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 accumulation of toxic levels of sulphite and neurologic damage, 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 of ALXN1101, with dosages increased monthly as tolerated. Alexion Pharmaceuticals, Cheshire, CT Phase II trial ongoing; ongoing separate unphased observational follow-up study of patients who have received treatment; Oct 2013, FDA granted breakthrough therapy status	No comparators or approved treatments are available	Decreased mortality Increased molybdenum cofactor activity Improved quality of life Reduced MoCD type A symptomology

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Daclizumab (Zenapax) 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, at a dose of 150 mg, once every 4 weeks. Biogen Idec International GmbH, Zug, Switzerland AbbVie, North Chicago, IL Phase III trials ongoing; FDA granted fast-track status	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
Deferiprone (Ferriprox) for treatment of pantothenate kinase–associated neurodegeneration	Patients in whom pantothenate kinase–associated neurodegeneration (PKAN) has been diagnosed	PKAN is a form of neurodegeneration in which the brain accumulates iron In affected persons, it usually manifests in early childhood (before age 10 years) and is characterized by progressive dystonia and basal ganglia iron deposition. Characteristics of the disorder include dysarthria, rigidity, and pigmentary retinopathy, and about 25% of affected persons have onset later than 10 years showing prominent speech defects, psychiatric disturbances, and more gradual disease progression. Investigators have not found a cure. Deferiprone (Ferriprox®) is purportedly an iron chelator intended to reduce the accumulation of iron in patients' brains. In a clinical trial, deferiprone is being administered as an oral solution, twice daily, for 18 months at a dosage of 5–15 mg/kg. ApoPharma, Inc., Toronto, Ontario, Canada Phase II and III trials ongoing	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
Delayed-release cystine-depleting capsule (RP 103) for treatment of Leigh syndrome and non-Friedreich's ataxia inherited mitochondrial diseases	Patients in whom Leigh syndrome (SNEM) has been diagnosed 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, non-Friedreich's–ataxia, inherited mitochondrial diseases. RP 103 (Procysbi®) is a delayed-release, 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 RP 103, daily, dependent on tolerance. Raptor Pharmaceutical Corp., Novato, CA Phase II/III trial ongoing; FDA approved RP 103 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 patient lifespan Improved quality of life Reduced disease symptoms
Dimethyl fumarate (Tecfidera) for treatment of relapsing multiple sclerosis	Patients in whom relapsing forms of multiple sclerosis (MS) have been diagnosed	Current treatments for MS may slow disease progression, but they are not effective in all patients, and the disease has no cure. Dimethyl fumarate (BG-12, Tecfidera®) is a fumaric acid ester (FAE) that purportedly reduces peripheral CD4+ and CD8+ T lymphocytes because FAE can induce apoptosis. Dimethyl fumarate purportedly represents a novel mechanism of action through modulating the Nrf-2 pathway and mediating neuroprotective and anti-inflammatory effects. Reported results suggest that that the safety profile of dimethyl fumarate may allow combination dosing. In clinical trials, dimethyl fumarate is administered orally, 120 mg, twice daily for 7 days followed by a maintenance dosage of 240 mg, twice daily. Biogen Idec International GmbH, Zug, Switzerland FDA approved Mar 2013 for treating relapsing forms of MS; phase IV trials ongoing	Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Reduced frequency of relapse Reduced symptom severity 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
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, and 49–50)	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; technology uses small pieces of DNA called antisense oligonucleotides to skip a defective exon (small gene-code sequences that code for sections of protein) to correct the reading frame and allow a normal protein to be produced. This RNA therapeutic is given by injection. Prosensa Therapeutics, Leiden, the Netherlands Phase III trials ongoing; manufacturer announced accelerated regulatory pathway, with plans to submit a new drug application by the end of 2014; Jan 2013, FDA granted orphan drug status	Orthotic devices Pharmacotherapy (e.g., corticosteroids, beta-2 agonists) Physical therapy Respiratory support (respirator/ ventilators)	Decreased muscle degeneration Improved symptoms Decreased need for supportive devices Increased survival Improved quality of life
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. Prior treatment options have included pharmacotherapy, which often do not achieve an adequate response in many patients. Droxidopa (Northera™) is a norepinephrine precursor that allows for reuptake of norepinephrine into peripheral nervous system neurons, stimulating receptors for vasoconstriction and providing physiologic improvement in symptomatic nOH. Administered orally, up to 3 times daily. H. Lundbeck A/S, Deerfield, IL (acquired Northera developer Chelsea Therapeutics International, Charlotte, NC, Jun 23, 2014), Phase III trials completed and ongoing; FDA approved Feb 2014 for "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." The drug is not yet available in pharmacies; Lundbeck announced availability is expected in fall 2014 through specialty pharmacies.	Diet and lifestyle modifications Pharmacotherapy (e.g., midodrine hydrochloride)	Decreased confusion from reduced cerebral circulation Decreased nOH Decreased risk of falling

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 prevalence in the U.S. 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 is purported to directly affect 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 trial is ongoing, with phase II trial results reported in 2013; approved 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
Electrode-embedded garment (Mollii) for treatment of muscle spasms and pain from traumatic brain injury	Patients with painful muscle spasms 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 garments estimated cost is $7,600. Royal Institute of Technology (KTH), Stockholm, Sweden Conformité Européene (CE) marked; expanded launch to include U.S. and other countries anticipated in 2014	Muscle relaxants Surgery	Decreased pain and muscle spasms Increased mobility Improved quality of life
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. In clinical trials, eliglustat tartrate has been administered twice daily; however, the manufacturer intends to ultimately market the drug as a once-daily treatment. If approved for marketing, eliglustat tartrate would be the 1st available 1st-line oral treatment option for patients with Gaucher's disease type 1. Trials are testing doses of 50, 100, and 150 mg, once or twice daily, orally. Genzyme Corp. subsidiary of Sanofi, Paris, France 3 phase III trials ongoing; ENGAGE and ENCORE trials met primary endpoints; FDA granted priority review with a decision date of Jun 11, 2014	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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Elosulfase alfa (Vimizim) for treatment of Morquio A syndrome	Patients in whom the genetic disorder 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., Novato, CA Pivotal phase III trial preliminary data completed; additional trials ongoing; FDA approved Feb 2014; manufacturer began commercial sales in 1st quarter of 2014	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
Eltrombopag (Promacta) for treatment of severe aplastic anemia	Patients with severe aplastic anemia (SAA) whose disease has not responded to immunosuppressive therapy	SAA is a bone marrow disease in which bone marrow cells are damaged, resulting in deficiencies in white and red blood cells and platelets. SAA 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. In ongoing trials, eltrombopag is administered at 150 mg/day, orally. GlaxoSmithKline, Middlesex, UK (manufacturer) in collaboration with University of Utah, Salt Lake City; National Institutes of Health Clinical Center, Bethesda, MD; National Heart, Lung, and Blood Institute, Bethesda, MD; European Group for Blood and Marrow Transplantation, Leiden, The Netherlands (investigators) Phase II and III trials ongoing; FDA granted breakthrough therapy status	Blood transfusion for symptom relief Bone marrow transplant Immunosuppressive therapy	Blood transfusion independence Improved hemoglobin levels Increased neutrophil, eosinophil, or platelet counts

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 which purportedly binds and modulates the activity of CD22, an antigen found on B cells purported to prevent autoreactive responses. Autoreactive B cells are believed to play a major role in SLE pathogenesis. In clinical trials, the drug is administered as a subcutaneous injection, once monthly. UCB, S.A., Brussels, Belgium Immunomedics, Inc., Morris Plains, NJ Phase III trials ongoing; FDA granted fast-track status	Belimumab Rituximab Rontalizumab	Delayed disease progression Reduced symptoms Reduced flares Improved quality of life
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. Within the U.S., the prevalence of AA amyloidosis is unknown, but it has been determined that the disorder 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. Bellus Health, Inc. (formerly Neurochem), Laval, Quebec, Canada Celtic Therapeutics Management LLP, St. Thomas, U.S. Virgin Islands 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; in spring 2014, company announced phase III study completion expected in 2016	Biologics Immunosuppressants Supportive care Surgical excision of infected tissue and antibiotics for chronic infection Kidney transplantation for kidney failure Colchicine for familial Mediterranean fever	Reduced risk of organ failure (especially kidneys, liver, spleen) Reduced mortality

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	Current 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; 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, thereby restoring the gene's ability to make a shorter (i.e., not perfect, but functional) form of dystrophin. It is delivered once weekly in intravenous infusion. Sarepta Therapeutics, Inc. (formerly AVI BioPharma, Inc.), Cambridge, MA Phase IIb trial completed 2013; manufacturer plans to file for early FDA approval by end of 2014; FDA granted orphan drug status	Beta-2 agonists Corticosteroids Orthotic devices Physical therapy Respiratory support devices	Delayed or halted muscle degeneration Reduced symptoms Increased survival Improved quality of life
Extended-release cysteamine bitartrate (Procysbi) for treatment of nephropathic cystinosis	Patients in whom nephropathic cystinosis has been diagnosed	Nephropathic cystinosis disease is characterized by the abnormal transport of cystine out of lysosomes, which leads to renal failure, growth failure, rickets and fractures, photophobia, and blindness. Poor patient adherence with conventional treatment because of dosing frequency (4 times a day) and side effects has led to complications for patients. Procysbi is an enteric-coated, delayed-release, microbead formulation of cysteamine bitartrate that is intended to reduce gastrointestinal adverse events associated with immediate-release cysteamine bitartrate. It requires 1/2 the number of daily doses as existing medical treatment. Cysteamine bitartrate converts cystine to cysteine and cysteamine-mixed disulfide, preventing resultant organ damage. The drug is administered orally, 75 mg, twice daily. Raptor Pharmaceutical Corp., Novato, CA FDA approved Apr 2013 for managing nephropathic cystinosis in adults and children older than 6 years; phase III trials ongoing	Cystagon® Growth hormone therapy Indomethacin Renal transplant Replacement of urinary losses	Improved glomerular function 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
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, Boston Scientific Corp, and Epilepsy Foundation (investigators) Phase II study completed, unphased study recruiting; FDA approved start of phase III trial Jul 2013	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. CIDP 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 purported to be 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; new phase III trials planned; FDA approved 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) Phase III trial recruiting; Conformité Européene (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
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, that causes progressive vision loss. 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. Advanced Cell Technology, Inc., Santa Monica, CA Phase I/II trial recruiting; FDA and EU granted orphan drug status	No treatment is available	Improved vision Improved functional status Reversed loss of central vision 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	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. 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 II and III trials completed; FDA granted orphan drug status; manufacturer plans to discuss accelerated approval with FDA and the European Medicines Agency	Eteplirsen, AVI-4658 (in development) Orthotic devices Physical therapy Respiratory support (respirator/ ventilators) Symptom control using corticosteroids and beta-2 agonists	Delayed or halted muscle degeneration Reduced 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
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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
L-glutamine for treatment of 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, red blood cells are more susceptible to oxidative damage, which alters their properties leading to vaso-occlusion. A vaso-occlusion crisis (VOC) can cause severe pain and require hospitalization. Patients may progress to organ failure and early death. Despite advancements in managing complications of SCD (i.e., pain crises), the only drug FDA approved for treatment is hydroxyurea. 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, pharmaceutical grade L-glutamine is mixed in with food or beverage at 0.3 g/kg body weight in 5 g increments, up to 30 g, daily. Emmaus Medical, Inc., Torrance, CA (manufacturer) Los Angeles Biomedical Research Institute, CA (investigator) Phase III trial completed successfully to support new drug application (NDA); FDA granted orphan drug and fast- track status; manufacturer intends to submit NDA mid-2014	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
Macrophage regulator (NP001) for treatment of amyotrophic lateral sclerosis	Patients in whom 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 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. Administered intravenously, 1 or 2 mg/kg for 6 months. Neuraltus Pharmaceuticals, Inc., Palo Alto, CA Phase II trial completed; phase III trial planned; FDA granted fast-track and orphan drug statuses Aug 2011	Riluzole 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 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 being administered orally, 6 mg/kg, daily. AB Science S.A., Paris, France Phase IIb/III trial ongoing; pilot clinical trial data reported in 2012	Dimethyl fumarate (Tecfidera®) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Delayed disease progression Reduced symptoms Improved quality of life
Mepolizumab (Bosatria) 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 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, 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; 2 completed feasibility studies in 8 patients reported positive results	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
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 the physician's office. 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) 2 phase III trials completed; trial ongoing; FDA granted humanitarian use device exemption (HUD) for monitoring hepatic metabolism in acute liver failure patients; HUD is intended for use for a condition that affects fewer than 4,000 people in the U.S. each year; Exalenz obtained a patent for BreathID use in detecting liver function Aug 2013	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 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. Current enzyme replacement therapies for the disease are expensive and have been subject to recent shortages. Migalastat hydrochloride (AT1001) is a small-molecule drug that molecularly 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, orally. Amicus Therapeutics, Inc., Cranbury, NJ, in collaboration with GlaxoSmithKline, Middlesex, UK Phase III trials ongoing; FDA submission on hold until late 2015 because phase III trial failed to meet primary endpoint; FDA granted orphan drug status	Enzyme replacement therapy Palliative treatment	Decreased globotriaosylceramide (GL-3) levels Improved renal function (e.g., glomerular filtration rate) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mobile phone monitoring application (MyVisionTrack) for age-related macular degeneration	Patients in whom age-related macular degeneration (AMD) has been diagnosed	According to the National Eye Institute, an estimated 1.75 million people in the U.S. have received a diagnosis of AMD. The standard for monitoring AMD consists of a complete eye exam including the Amsler grid test. MyVisionTrack has the potential to fulfill an unmet need brought about by a lack of self-monitoring diagnostics for AMD. It is a mobile application provided via hand-held digital devices such as smartphones and tracks changes in the ability to distinguish shapes. The prescription-only application purportedly enables patients with retinal eye diseases to self-monitor their vision status at home, helping them notice changes or a decline in vision that could indicate a need for medical attention. Test results are stored and automatically compared with earlier results. Results may be sent to a physician's office or a central monitoring service when a statistically significant change occurs. Vital Art and Science, Inc., Richardson, TX (manufacturer) National Eye Institute, Bethesda, MD; Retina Foundation of the Southwest, Dallas, TX; University of Texas Southwestern Medical Center, Dallas; Texas Retina Associates, Dallas (investigators in collaboration with Vital Art and Science) Pilot study completed; unphased study recruiting; FDA cleared device for marketing Mar 2013; device not yet commercially available; also under study for diabetic retinopathy and diabetic macular edema	Complete eye exam with Amsler grid test Optical coherence tomography	Earlier intervention for vision decline Slowed vision decline Improved quality of life
Mu-opioid agonist with small-molecule polymer conjugate technology (NKTR-181) for treatment of chronic pain	Patients experiencing chronic pain	Chronic use of current 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 No ongoing trials registered; phase II trial missed primary endpoint due to unexpectedly large placebo effect in control group; manufacturer indicated additional trials in future; 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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 to be 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 registered and scheduled to start in Sept 2014. Multiple phase III trials completed outside U.S.; approved in UK, New Zealand, and Canada for treating MS spasticity; approved in Canada for relief of MS-related neuropathic pain	Pharmacotherapy (e.g., nonsteroidal anti-inflammatory drugs, opioids)	Reduced pain Reduced spasticity Improved quality of life
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 first-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, 10, and 25 mg. Intercept Pharmaceuticals, New York, NY Phase III trial ongoing; manufacturer anticipates filing new drug application by end of 2014	Antipruritic therapy Colchicine Corticosteroids Cyclosporine Immunosuppressive therapy Liver transplant Methotrexate Ursodeoxycholic acid	Decreased risk of liver transplant or death Reduced bilirubin levels Reduced serum alkaline phosphatase levels 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	Current therapy for RRMS and PPMS provides unsatisfactory results for many patients. Ocrelizumab (RG1594) represents a novel mechanism of action for this disease state. 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 Idec International GmbH, Zug, Switzerland Phase III trials ongoing; company expects to file new drug application in 2015	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
Ocriplasmin (Jetrea) for treatment of symptomatic vitreomacular adhesion including macular hole	Patients in whom focal vitreomacular adhesion (VMA) of the eye has been diagnosed	Focal VMA is a condition in which the vitreous gel, in the center of the eye, has an unusually strong adhesion to the macula, the center of the retina at the back of the eye. VMA is believed to play a key role in several back-of-the-eye conditions, such as macular hole and some forms of macular edema. A microplasmin molecule similar to human plasmin potentially breaks down fibrin clots that join the vitreous gel to the macula; thus, intravitreal injection of ocriplasmin (Jetrea®) is a potential nonsurgical treatment for VMA. The recommended dose is 2.5 mg/mL, given by intravitreal injection to the affected eye once as a single injection. ThromboGenics NV, Heverlee, Belgium FDA approved Oct 2012 for treating symptomatic VMA; Health Canada approved Oct 2013	Pharmacotherapy (e.g., Macugen®) Surgical therapy	Preserved vision Reduced need for surgery Temporary unexplained visual loss after injection 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 bevacizumab for treatment of retinopathy of prematurity	Infants weighing 1,500 g or less at birth and at gestation of 30 weeks or less in whom stage 3 retinopathy of prematurity (ROP) in zone I or posterior zone II has been diagnosed	ROP occurs in many infants born before 31 weeks' gestation; it can result in alternating episodes of tissue hyperoxia and hypoxia and induction of vascular endothelial growth factors (VEGFs), which can lead to development of abnormal retinal fibrovascular tissue and cause blindness. ROP is an acute condition with a time frame measured in days and weeks. Standard therapy (peripheral retinal ablation) for ROP is known to work but does not prevent all vision loss, and recurrence of VEGF can be as high as 40% in treated infants. Bevacizumab, used off label, is injected into the infant's vitreous to reduce incidence of blindness by suppressing VEGF. Doses of 0.375 and 0.625 mg have been studied. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland (manufacturer) BEAT-ROP cooperative (trial sponsor) Baylor College of Medicine, Houston, TX (trial sponsor) BEAT-ROP postmarket trial of off-label use completed; manufacturer is not pursuing a labeled indication	Peripheral retinal ablation with lasers (e.g., xenon, argon, diode)	Improved visual acuity Prevented recurrence of neovascularization arising from the retinal vessels 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, at a dosage of 0.8 mg/kg (with a maximum dosage of 50 mg) once weekly for 3 weeks. Amgen, Inc., Thousand Oaks, CA Phase II trial ongoing; FDA approved in 1998 for moderate to severe rheumatoid arthritis and other inflammatory conditions	Corticosteroids High-dose aspirin IVIG	Improved survival Prevented increase in coronary artery diameter Prevented new coronary artery dilation/cardiac dysfunction Reduced fever

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label naltrexone for treatment of fibromyalgia	Patients in whom fibromyalgia (FM) has been diagnosed	FM is poorly understood and current treatment options are not effective for many patients. Naltrexone is an opiate antagonist purported to block the inflammatory effects of the toll-like receptor 4 (TLR-4) on glial cells. TLR-4 is purported by investigators to be involved in pain felt by patients with FM. In clinical trials, naltrexone is administered orally, 3.0–4.5 mg, once daily. Stanford University, Stanford, CA Pilot study and small extension randomized controlled trial completed	Behavior and lifestyle modification Pharmacotherapy (e.g., duloxetine, fluoxetine, gabapentin, lorazepam, milnacipran, pregabalin, tricyclic antidepressants)	Improved ability to perform daily activities Reduced symptoms Improved quality of life
Off-label oral ketotifen for treatment of fibromyalgia	Patients in whom fibromyalgia (FM) has been diagnosed	FM is poorly understood and current treatment options are not effective for many patients. Increased numbers of mast cells have been observed in the skin biopsies of patients with FM. Mast cells are powerful inflammatory cells that can release chemokines and other chemical mediators, triggering inflammation and pain in the local area. Elevated levels of these mediators can be observed in the serum of patients with FM. Available FM treatments target only centrally acting pain pathways and neglect the potential for immunologic involvement in symptoms. Ketotifen is purportedly an antihistamine and mast cell stabilizer, which prevents mast cell degranulation (release of inflammatory meditators) and might improve FM symptoms. In clinical trials, ketotifen is administered orally as a 1 mg tablet, once or twice daily. Indiana University, Indianapolis, IN Phase III trial registered, but status unknown; approved for preventing asthma attacks and as eye drops for allergic pinkeye	Behavior and lifestyle modification Drugs: Duloxetine Fluoxetine Gabapentin Lorazepam Milnacipran Pregabalin Tricyclic antidepressants	Improved ability to perform daily activities Reduced pain 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 due to any number of diseases (e.g., postinfectious 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. Second and third 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, Korea (investigator) 2 phase II/III trials ongoing; indicated 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
Off-label simvastatin for treatment of secondary progressive multiple sclerosis	Patients in whom secondary progressive 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. Simvastatin is a statin purported to have anti-inflammatory and neuroprotective effects on the nervous system, including increased endothelial nitric oxide synthase activity, reduced excitotoxicity, and augmented remyelination, which could counter the effects of autoreactive lymphocytes in patients with MS. In clinical trials, simvastatin is administered orally at a dosage of 80 mg, daily. AstraZeneca, London, UK Phase II trial complete; phase III trial may be initiated	Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Delayed disease progression Reduced symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pasireotide for treatment of gastrointestinal injuries from acute radiation syndrome	Patients with gastrointestinal (GI) injuries from acute radiation syndrome (ARS)	ARS is a disease caused by harmful exposure to high doses of ionizing radiation, resulting in bone marrow, cardiovascular, GI, respiratory, and skin complications. Few treatments exist for irradiated bone marrow, and none exist for irradiated GI organs. Additionally, no treatments are FDA approved for use as medical radiation countermeasures for preventing or treating ARS. Pasireotide is a cyclohexapeptide engineered to bind to multiple somatostatin receptor subtypes to mimic the actions of natural somatostatin. For ARS, pasireotide is intended to reduce pancreatic secretions known to invade the irradiated intestinal wall and induce an inflammatory response. Novartis International AG, Basel, Switzerland (manufacturer) University of Arkansas for Medical Sciences, Little Rock (investigator) Clinical trial phase not reported; in Sept 2011, U.S. Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA) awarded $56.3 million in grants to 4 companies and University of Arkansas to develop ARS treatments; Novartis is providing drug for this 2-year study; data generated are intended to form basis for new drug application Novartis will submit to FDA; pasireotide is FDA approved for Cushing's disease	Pharmacotherapy (e.g., antibiotics, hematopoiesis-stimulating agents) Stem cell therapy	Decreased mortality Prevented or reduced GI flora

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pediatric Vision Scanner screening for strabismus or amblyopia	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 through its portability. 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 (manufacturer) Retina Foundation of the Southwest, Dallas, TX; Vanderbilt University, Nashville, TN; University of Southern California, Los Angeles (investigators) Unphased trials completed; additional unphased trial ongoing; FDA classifies as nonsignficant risk device (Class I) which is not subject to marketing clearance regulations	Photoscreening Standard vision examination	More appropriate referrals to ophthalmologists Reduced vision loss Improved quality of life
Pegylated recombinant phenylalanine ammonia lyase enzyme replacement therapy for treatment of phenylketonuria	Patients in whom phenylketonuria has been diagnosed	Phenylketonuria is an inherited disorder in which an enzyme that is needed to break down the essential amino acid phenylalanine is missing. Pegylated recombinant phenylalanine ammonia lyase (PEG-PAL), also called BMN 165, might be a novel enzyme replacement therapy; 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 II and III trials ongoing; FDA granted orphan drug status	Kuvan (tetrahydrobiopterin or BH4)	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
Personal activity monitors for post-stroke patient rehabilitation	Patients who are undergoing stroke rehabilitation	Stroke affects about 795,000 individuals annually in the U.S. Patients who have survived stroke need rehabilitation to achieve the best possible outcomes, yet at inpatient facilities, patients receive formal rehabilitation practice for an average of less than 15% of the waking day. Patients who increase physical activity might improve short-term outcomes such as mobility, endurance, and reduced length of stay. Stroke Inpatient Rehabilitation Reinforcement of Activity (SIRRACT) is a program that uses simple accelerometers in conjunction with the Medical Daily Activity Wireless Network (MDAWN) wireless monitoring system to measure the patient's movement in an inpatient rehabilitation setting. Small sensors are attached to the patient's arms or legs via Velcro wrist or ankle bands. The information is automatically recorded, and it can be wirelessly retrieved by the health care provider for analysis. Patients can receive feedback from health care staff on their amount of physical activity, which might encourage more activity. University of California, Los Angeles, with multiple collaborators Phase II trial completed	Robot-assisted rehabilitative therapy Standard occupational therapy Standard physical therapy	Improved care monitoring Improved patient self-care motivation

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 percent 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 2 trial Omeros Corp., Seattle, WA Phase II trial ongoing; 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
Progesterone infusion (BHR-100) for treatment of acute traumatic brain injury	Patients in whom acute traumatic brain injury (TBI) has been diagnosed	Acute TBI can cause inflammation, excitotoxicity, apoptosis, and vasogenic and cytotoxic edema. No pharmacologic agent exists to improve outcomes of acute TBI. The standard care for acute TBI is managing intracranial pressure, often with surgery to reduce pressure. BHR-100 is progesterone in a 6% lipid emulsion. It reportedly upregulates several neurotrophic factors and promotes remyelination. It is intended for 1st-line, acute treatment of severe TBI. BHR-100 is administered as a continuous intravenous infusion for 120 hours, starting within 8 hours of injury. Initial loading dose is 0.71 mg/kg for 1 hour followed by 0.5 mg/kg/hr. BHR Pharma, an affiliate of Besins Healthcare, Bangkok, Thailand (manufacturer) Emory University, Atlanta, GA (investigator), in collaboration with National Institute of Neurological Disorders and Stroke, Bethesda, MD Phase III trial ongoing; FDA granted orphan drug and fast-track statuses; EU granted orphan drug status	Neurosurgery to relieve pressure on the brain	Decreased brain swelling and need for surgery Downregulated inflammatory cascade Reduced cellular necrosis and apoptosis Improved function 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 into up to 10 powered movements. U.S. Defense Advanced Research Projects Agency, Arlington, VA (commissioned and funded research) U.S. Department of Defense, Washington, DC, and U.S. Department of Veterans Affairs, Washington, DC (conducting clinical testing); several U.S. and international research partners participating 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	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-Gestaut 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 first 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 necessitate permanent caregiver interventions. Investigators have not found cures for LGS or Dravet syndrome, although anticonvulsant drugs and ketogenic diets may provide some temporary relief from seizures. 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 Phase II and II/III trials planned; FDA granted orphan drug status for LGS and Dravet syndrome indications and fast-track status for Dravet	Anticonvulsants Ketogenic diet	Fewer seizure symptoms 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
Real-time MRI-guided laser interstitial thermal therapy for epilepsy	Patients with epilepsy who have lesions identified by MRI	An estimated 3 million people in the U.S. have 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. 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. Texas Children's Hospital, Houston Washington University School of Medicine, St. Louis, MO Mayo Clinic, Rochester, MN Pilot trial completed; another recruiting	Pharmacotherapy: Lamotrigine Levetiracetam Tiagabine Tricyclics Valproate Surgical procedures: Craniotomy Gamma Knife radiosurgery	Reduced or eliminated seizures
Recombinant, human, pancreatic elastase 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. A recombinant, human, pancreatic elastase (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. Proteon Therapeutics, Inc., Waltham, MA Phase II trials completed, phase III planned; 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
RenalGuard for prevention of contrast-induced nephropathy	Patients at risk of contrast-induced nephropathy (CIN)	CIN can occur when patients with pre-existing kidney problems undergo procedures that require imaging that uses iodinated contrast media, such as cardiac catheterizations. The only standard treatment for CIN in high-risk patients with chronic kidney disease (CKD) is hydration and avoidance of nephrotoxic drugs. The RenalGuard System™ is a closed loop, single-use, software-controlled console that automatically matches fluid loss and replacement to minimize overhydration or dehydration in patients during medical procedures in which creating and maintaining high urine output is essential. The single-use urine collection set is connected to a Foley catheter and an infusion set is connected to a standard intravenous catheter. The console is managed by monitoring software that measures urine volume in the collection set and matches patient urine output with an equal volume of hydration fluid. PLC Systems, Inc., Milford, MA (developer) sold to GCP Capital Partners, LLC, New York, NY Pivotal trial completed; phase III and phase IV trials ongoing in patients at high risk, patients undergoing surgery for cardiac resynchronization therapy implantation; and patients undergoing transcatheter aortic valve implantation; RenalGuard also investigated for use after kidney transplantation; Conformité Européene (CE) marked Jun 2013	Deferoxamine Hydration	Reduced incidence of CIN in high-risk patients with CKD Reduced occurrence and complications of CIN Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Retinal implant (Alpha IMS) for treatment of 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 commercially available in the U.S. to assist in some aspects of visual perception for RP, and another device is in development. The Alpha IMS system 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 Pilot trial completed; Conformité Européene (CE) marked Jul 2013	Argus II retinal prosthesis system	Improved visual acuity Improved quality of life and independence
Retinal prosthesis system (Argus II) to restore visual function in retinitis pigmentosa	Patients with retinitis pigmentosa (RP) who have a functioning optic nerve	No medications or devices are available to restore lost vision or halt progression of vision loss that occurs with the inherited disorder RP. The Argus™ II implant consists of an array of electrodes that is surgically inserted into the retina of 1 eye and used in conjunction with an external camera and video processing system to provide a rudimentary form of sight. By electrically stimulating the retina, visual perception is enabled for blind people with severe to profound RP. The device is intended to restore a level of vision that is sufficient to improve patients' ability to function more independently. Second Sight® Medical Products, Inc., Sylmar, CA First commercial patient implanted Jan 2014; observational studies ongoing; FDA approved Feb 2013; Conformité Européene (CE) marked 2011	Alpha IMS system (in development, received CE mark Jul 2013)	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
RPE65 therapy for treatment of Leber congenital amaurosis	Patients in whom *RPE-65*–associated Leber congenital amaurosis (LCA) has been diagnosed	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 is a treatment that purportedly can cure LCA or significantly improve visual impairment caused by LCA, through delivery of 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 dosage of 1.5 x 10^11 vector genomes per eye; eyes are dosed on separate days. Spark Therapeutics, LLC, Philadelphia, PA, collaborating with Children's Hospital of Philadelphia, PA Phase I, I/II, and III trials ongoing	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
Sebelipase alfa for treatment of late-onset lysosomal acid lipase deficiency	Patients in whom late-onset 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 (SBC-102) 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. Synageva BioPharma, Lexington, MA Phase III trials ongoing in infants, children, and adults; FDA granted orphan drug status; FDA granted fast-track and breakthrough therapy status for infants with LAL deficiency	Bone marrow transplant Palliative treatments	Improved cholesteryl ester and triglyceride levels Reduced mortality Improved quality of life
Self-regulating normothermic liver perfusion system (OrganOx Metra) for preservation of livers for transplantation	Patients who require a liver transplant	According to the U.S. Department of Health and Human Services, 4.86 per 1 million people in the U.S. received an organ transplant in 2008. Donor organs require careful handling and preservation during transport to minimize damage prior to transplantation. Current methods of organ preservation leave the organ susceptible to significant damage to the point where some organs are not useable. The OrganOx Metra system is designed to maintain a donor liver in a warm, functioning state outside of the body to optimize organ health and allow for continuous clinical evaluation prior to transplantation. The system provides blood flow, oxygen, carbon dioxide control, nutrients, and temperature control for the liver for up to 24 hours. OrganOx, Ltd., Oxford, UK Ongoing trial; 16 transplants completed	Cold-storage preservation	Improved patient outcomes Increased graft survival Increased utilization of donor organs Reduced cost of transplantation and follow up care because of healthier transplanted organs

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Smartpatch peripheral nerve stimulator for treatment of post-stroke pain	Patients experiencing pain after stroke	Approximately 10% of stroke survivors experience mild to severe pain after the stroke. The pain can be acute or chronic. The Smartpatch peripheral nerve stimulation system is proposed as a minimally invasive therapy in which a fine wire from the patch is placed on the skin near the selected nerves to deliver electrical stimulation, purportedly relieving pain. It differs from existing electrical stimulation modalities because it is not an implanted stimulator device and is placed near nerves rather than touching them. The Smartpatch is intended to be used for up to 30 days. SPR Therapeutics, LLC, Cleveland, OH Pivotal unphased trial recruiting participants; Conformité Européene (CE) marked Jan 2013	Anticonvulsants Antidepressants Corticosteroids Nonsteroidal anti-inflammatory drugs	Reduced pain Improved quality of life
Tafamidis (Vyndaqel) for treatment of various hereditary transthyretin-related amyloidoses	Patients in whom familial transthyretin (TTR)-related amyloidoses have been diagnosed	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 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. Tafamidis (Vyndaqel®) purportedly is a TTR stabilizer. Tafamidis purportedly binds to the TTR protein to promote the stabilization of functional tetrameric molecules, slowing the formation of misfolded amyloid fibrils and their deposit in organs. Pfizer, Inc., New York, NY Phase III trials completed; global phase III trial ongoing in cardiomyopathy; FDA granted orphan drug status. Tafamidis is approved for marketing in Europe and Japan; FDA did not approve Pfizer's new drug application for polyneuropathy when submitted in 2012; Pfizer now developing for cardiomyopathy.	Supportive therapy	Decreased organ failure TTR stabilization

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. 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 Phase III and IV trials ongoing; FDA approved Jan 2014 after granting priority review and orphan drug status; FDA required postmarket followup studies	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. Previous 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 and II/III trials registered; phase II trials completed; FDA granted fast-track status	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
Terlipressin (Lucassin) for reversal of hepatorenal syndrome type 1	Patients in whom hepatorenal syndrome type 1 (HRS-1) has been diagnosed	HRS-1 is a rapid, progressive renal impairment with more than 80% mortality within 3 months. Terlipressin is a synthetic vasopressin analog that acts as a systemic vasoconstrictor, mainly in abdominal circulation, which may improve renal blood flow and renal function in patients with HRS-1. No U.S.-approved drugs for HRS-1 are available. Cumulative daily doses between 3 and 12 mg are under study. Given intravenously, in combination with albumin. Ikaria, Inc., Clinton, NJ Phase III completed; phase IV and unphased trials ongoing; FDA granted orphan drug, priority review, and fast-track statuses	Liver transplantation Pharmacotherapy (e.g., dopamine, misoprostol, vasoconstrictors)	Confirmed HRS-1 reversal Increased survival to time of transplantation Increased rates of transplant-free survival up to 90 days
Tirasemtiv (CK-2017357) for treatment of amyotrophic lateral sclerosis	Patients in whom 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 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 is purportedly a fast skeletal muscle troponin activator. Tirasemtiv 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 II trial ongoing; 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 (Actrema/ RoActrema) 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. 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 (Actrema) 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 II and III trials ongoing; 2 phase II trials studying effectiveness of tocilizumab for treating polymyalgia rheumatica are also ongoing	Corticosteroids	Reduced corticosteroid doses Reduced corticosteroid-related side effects Reduced GCA 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
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. It can be 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 patients with TTR-FAP. In clinical trials, patients with TTR-FAP are administered 300 mg of ISIS-TTRRx subcutaneously, once daily, on 3 alternating days during the first week of treatment, followed by once-weekly treatments for 64 weeks. Isis Pharmaceuticals, Carlsbad, CA, in collaboration with GlaxoSmithKline, plc, Middlesex, UK Phase III trial ongoing; FDA granted fast-track and orphan drug status; ISIS-TTRRx also has orphan drug status in Europe	Supportive therapy	Improved neuropathy impairment score Improved quality of life TTR stabilization

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; Feb 2014, FDA granted orphan status for treating Friedrich's ataxia; Jun 2014, FDA granted orphan status for treating Leigh syndrome	Assistive interventions including: Physical therapy Speech therapy Wheelchair use	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
Vesicular monoamine transporter type 2 inhibitor (NBI-98854) 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. Only 1 treatment is approved for this condition, and the development of the disease is not yet well understood. More and better treatments are needed. NBI-98854 is a vesicular monoamine transporter type 2 inhibitor that regulates levels of dopamine release 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 tested 25, 50, 75, and 100 mg doses, taken orally, every morning. Neurocrine Biosciences, Inc., San Diego, CA Phase II trials completed; FDA granted fast-track status Jan 2012; manufacturer plans to submit End of Phase II meeting request to FDA and complete phase III protocol based on positive data	Benzodiazepines Cogentin® Mirapex® Omega-3 fatty acids Tarvil® Tetrabenazine	Reduced abnormal involuntary movement

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 kidney failure	Patients in whom end-stage kidney failure has been diagnosed	Conventional dialysis requires most patients to 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 trained on use might be able to use it independently in any setting, because WAKs are portable. 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 Fresenius Medical Care Holdings AG & Co. KGaA, Bad Homburg, Germany (acquired developer Xcorporeal, Inc.) Blood Purification Technologies, Inc., Beverly Hills, CA FDA approved trial for Blood Purification Technologies Feb 2014; FDA selected this technology in Apr 2012 as 1 of 3 technologies for its new innovation pathway; phase I study completed by developers Royal Free London NHS Foundation Trust (formerly Royal Free Hampstead NHS Trust) and Xcorporeal, Inc., in the UK; 5 randomized controlled trials planned, 1 pilot trial completed; AWAK and partners expect to start clinical trials in 2017	Conventional home dialysis systems Kidney transplantation	Adequate filtration of toxins from kidneys Improved mobility Reduced infection rates 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 exoskeletons to enable mobility in community or home setting for paraplegic patients	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-P™ (personal use), could provide greater mobility and freedom to individuals with paraplegia from spinal cord injury. The ReWalk-P 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. The ReWalk-P is intended for use at home or in a community setting. Other exoskeletons in early development for personal use include Ekso system, Rex Personal, Mina, Brain Controlled Exoskeleton System, and Indego. Argo Medical Technologies, Ltd., Yokneam Ilit, Israel (manufacturer of ReWalk-P) distributed in the U.S. by Bionics Research, Inc., Mt. Laurel, NJ Ekso Bionics, Richmond, CA (manufacturer of Ekso system) Florida Institute of Human & Machine Cognition, Pensacola, FL (investigator of Mina) Rex Bionics, Auckland, New Zealand (manufacturer of Rex Personal) University of Michigan, Ann Arbor (investigator of Brain Controlled Exoskeleton System) Vanderbilt University for Intelligent Mechatronics, Nashville, TN with Parker Hannifin Corp., Cleveland, OH (investigator and manufacturer of Indego) FDA cleared for marketing ReWalk under *de novo* pathway Jun 2014; FDA required postmarket studies; available in Europe since late 2012; ReWalk study for home and community use ongoing; Indego commercialization planned for 2015	Weight-supported standing systems Wheelchairs	Decreased complications from being wheelchair bound Improved independence Improved mobility Improved quality of life

Table 9. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 40 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
3D oral regimen (ABT-450/r, dasabuvir, ombitasvir) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Interferon (IFN)-based treatment options for HCV are not effective in all patients. Current treatment options 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. The 3D oral regimen is an IFN-free option intended to improve treatment success and tolerability in patients chronically infected with HCV. The regimen consists of ABT-450/r, an NS3/4A HCV protease inhibitor, co-administered with ritonavir; dasabuvir (ABT-333), a nonnucleoside NS5B polymerase inhibitor intended to bind HCV RNA-dependent RNA polymerase and inhibit replication of the viral genome; and ombitasvir (ABT-267), an NS5A inhibitor purported to block the ability of the viral NS5A protein to attach to the endoplasmic reticulum of infected hepatocytes, which is thought to be required for the formation of functional virions. Ombitasvir could inhibit the activity of all HCV genotypes. ABT-450, ritonavir, and ombitasvir are administered orally, 150 mg, 100 mg, and 25 mg, respectively, once daily, and dasabuvir is administered 250 mg, twice daily, with weight-based ribavirin (RBV) for 12 weeks. AbbVie, North Chicago, IL Enanta Pharmaceuticals, Inc., Watertown, MA Phase III trials ongoing; FDA granted breakthrough therapy status for treating HCV genotype 1 with and without RBV; FDA granted priority review Jun 2014 with a decision date of Oct 2014	Boceprevir IFN/RBV Simeprevir Sofosbuvir Telaprevir	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
Alisporivir 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 and a long duration of therapy. Effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. Cyclophilin A is a host-cell protein involved in protein folding and transport, and it has been shown to be essential in HCV replication; cyclosporine A inhibits cyclophilin activity but is immunosuppressive. Alisporivir (Debio-025) is a modified form of cyclosporin A that purportedly acts as a host-targeted antiviral with enhanced cyclophilin binding but no immunosuppressive activity, which might be due to the inability of the alisporivir-cyclophilin complex to bind calcineurin which modulates proinflammatory lymphocyte signaling. Administered orally, 400 mg, twice daily in combination with the standard-of-care pegylated interferon plus ribavirin (IFN/RBV). Debiopharm, S.A., Lausanne, Switzerland Novartis International AG, Basel, Switzerland Phase III trials completed; FDA granted fast-track status	Boceprevir IFN/RBV Simeprevir Sofosbuvir Telaprevir	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
Anthrax antitoxin monoclonal antibody raxibacumab (ABthrax) for treatment of inhalation anthrax	Patients suspected of having inhaled anthrax spores	Patients can be unaware that they have inhaled anthrax spores, leading to late treatment that may render antibiotics ineffective; treatments for later-stage inhalation anthrax are needed. Raxibacumab (ABthrax™) is a fully human, antitoxin, monoclonal antibody purported to treat inhalation anthrax by inhibiting the activity of the protective antigen of anthrax toxin, inhibiting the protein's ability to facilitate pathogenesis. In a clinical trial, raxibacumab was administered intravenously, 40 mg/kg, on days 0 and 14. Human Genome Sciences, Rockville, MD FDA approved Dec 2012 for treating adult and pediatric patients with inhalational anthrax infection due to *Bacillus anthracis* in combination with appropriate antibacterials and for prevention of inhalational anthrax when other therapies are not available or not appropriate	Anthrax vaccine Antibiotics	Protection against inhalation anthrax Rapid resolution of symptoms
Antitoxin monoclonal antibody (MK-3415) for treatment of *Clostridium difficile*–associated diarrhea	Patients in whom *Clostridium difficile*–associated diarrhea has been diagnosed	Recurrent *Clostridium 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. MK-3415 is a monoclonal antibody designed to block the activity of *C. difficile* toxin A, which is purportedly involved in CDI pathogenesis. In a clinical trial, MK-3415 was administered as a single intravenous infusion of 10 mg/kg. Merck & Co., Inc., Whitehouse Station, NJ Phase III trial recruiting	Fecal microbiota transplant Fidaxomicin Metronidazole Vancomycin	Increased clinical cure rates Reduced CDI recurrence
Antitoxin monoclonal antibody (MK-6072) for treatment of *Clostridium difficile*–associated diarrhea	Patients in whom *Clostridium difficile*–associated diarrhea has been diagnosed	Recurrent *Clostridium 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. MK-6072 is a monoclonal antibody designed to block the activity of *C. difficile* toxin B, which is purportedly involved in CDI pathogenesis. In a clinical trial, MK-6072 was administered as a single intravenous infusion of 10 mg/kg. Merck & Co., Inc., Whitehouse Station, NJ Phase III trials recruiting	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
Antitoxin monoclonal antibody combination (MK-3415A) for treatment of *Clostridium difficile*–associated diarrhea	Patients in whom *Clostridium difficile*–associated diarrhea has been diagnosed	Recurrent *Clostridium 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. MK-3415A is a combination of 2 monoclonal antibodies designed to block the activity of *C. difficile* toxins A and B, which are purportedly involved in CDI pathogenesis. In a clinical trial, MK-3415A was administered as a single intravenous infusion of 10 mg/kg. Merck & Co., Inc., Whitehouse Station, NJ Phase III trials recruiting	Fecal microbiota transplant Fidaxomicin Metronidazole Vancomycin	Increased clinical cure rates Reduced CDI recurrence
ART-123 (Recomodulin) for treating 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 mortality. ART-123 (Recomodulin®) 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/day, up to a maximum dose of 6 mg/day for 6 days. Asahi Kasei Corp., Tokyo, Japan Phase IV trial recruiting	Coagulation factor concentrates or cryoprecipitate Plasma	Reduced episodes of life-threatening bleeding Reduced mortality
Asunaprevir 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 period of time are needed. Asunaprevir is an NS3 protease inhibitor intended to block the activity of HCV protease, preventing the cleavage and maturation of functional viral particles. Administered orally, 200 mg, twice daily, in combination with daclatasvir, BMS-791325, and sofosbuvir. Bristol-Myers Squibb, New York, NY Phase III trials ongoing; FDA granted breakthrough therapy status for asunaprevir in combination with daclatasvir (NS5A inhibitor) and BMS-791325 (non-nucleoside polymerase inhibitor)	Boceprevir Interferon/ribavirin Simeprevir Sofosbuvir Telaprevir	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
Brincidofovir for prevention of cytomegalovirus after hematopoietic stem cell transplant	Patients who have recently received a hematopoietic stem cell transplant (HSCT)	Cytomegalovirus (CMV) infections 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 CMV infections, for which no treatments are approved. Brincidofovir is purported to be a broad spectrum antiviral for treating or preventing life-threatening double-stranded DNA (dsDNA) viral diseases. Brincidofovir (CMX001) 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 recruiting; FDA granted fast-track status	Cidofovir (off label) Ganciclovir	Decreased rate of organ rejection Increased time to organ rejection Reduced CMV load
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 recruiting	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
Copper surfaces in the intensive care unit for prevention of hospital-acquired infections	Patients admitted to an intensive care unit (ICU)	Hospital-acquired infections (HAIs) are the 4th leading cause of death in the U.S. behind heart disease, stroke, and cancer; nearly 1 in every 20 hospitalized U.S. patients acquires an HAI, resulting in 100,000 deaths each year. Bacteria on surfaces in ICUs are said to be responsible for 35% to 80% of patient infections. Replacing the most heavily contaminated touch surfaces in ICUs with antimicrobial copper purportedly controls bacterial growth and lowers the rates of infections acquired in the ICU. Bacterial reduction rates are intended to achieve the same outcome as current "terminal cleaning" practices, although use of copper surfaces is not intended to obviate the need for all other infection prevention and control measures. International Copper Association, New York, NY Various manufacturers Commercially available; studies at hospitals ongoing	Terminal cleaning of standard surfaces	Reduced costs associated with HAIs Reduced infection rates Reduced bacteria isolated from surfaces Reduced morbidity and mortality from HAIs
Daclatasvir for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C (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 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 the formation of functional virions. It may be used in combination with standard of care and other investigational agents including pegylated interferon (IFN) lambda, or asunaprevir, BMS-791325, and sofosbuvir. Administered orally, 60 mg, once daily. Bristol-Myers Squibb, New York, NY Phase III trials ongoing; FDA granted breakthrough therapy status for daclatasvir in combination with asunaprevir (NS3 protease inhibitor) and BMS-791325 (nonnucleoside polymerase inhibitor)	Boceprevir IFN/ribavirin Simeprevir Sofosbuvir Telaprevir	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
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 trial ongoing	Bedaquiline Ethionamide Kanamycin Ofloxacin PA-824, a nitroimidazole (in development) Pyrazinamide	Improved patient adherence with therapy Reduced spread of infection Reduced time to clinical response Resolution of active TB infection Improved quality of life
Fecal microbiota transplantation for treatment of recurrent *Clostridium difficile* infection	Patients with recurrent *Clostridium difficile* infection (CDI)	Because of antibiotic resistance, new options are needed that can improve clinical cure rates and reduce CDI recurrence. In fecal microbiota transplantation (FMT) fecal matter from a healthy donor is collected and mixed with a saline solution and transplanted into the recipient in 1 of several ways (e.g., colonoscopy, nasogastric tube, gelatin capsules) with the intended purpose of introducing healthy flora to the intestinal tract to prevent recurrence of CDI. Multiple trials ongoing at various U.S. medical centers Fecal transplantation is considered a biological product and a drug by FDA; an investigational new drug (IND) application is required to treat patients who have CDI; FDA intends to exercise enforcement discretion regarding the IND requirements for fecal microbiota transplantation for treating CDI not responding to standard therapies provided: the physician obtains adequate informed consent, the stool donor is known to either the health care provider or the patient, and the physician performing the FMT procedure directs the donor and stool screening and testing	Fidaxomicin Metronidazole Vancomycin	Reduced diarrhea Reduced dehydration Reduced reinfection

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Hand washing monitoring system (BIOVIGIL) to reduce health care–associated infections	Patients attending health care facilities	Hospital-acquired infections (HAIs) are the 4th leading cause of death in the U.S., behind heart disease, stroke, and cancer; nearly 1 in every 20 hospitalized U.S. patients acquires an HAI, resulting in 100,000 deaths each year. Hand-washing adherence by health care workers is only about 40% in many health care settings, leading to transmission of dangerous and costly infections. Many health care workers have purportedly expressed the opinion that because they are frequently exposed to infections, they are more immune to infection and, thus, do not wash their hands. The BIOVIGIL hand hygiene system operates on a remind, record, reassure, and report methodology. It reminds the health care worker to wash his or her hands, records the presence of hand sanitizer, reassures the patient of proper hand hygiene with a visual cue, and reports the data to a base station. BIOVIGIL Hygiene Technologies, LLC, Ann Arbor, MI System is available for use	Radiofrequency identification hand-washing systems Standard hand-washing practices	Increased hand hygiene compliance Reduced HAI incidence Reduced HAI morbidity and mortality Reduced health care costs associated with HAIs
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 is purported to compete 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., Tapei, Taiwan Phase II trial ongoing	Antiretroviral therapy Enfuvertide Marviroc	Decreased viral load Decreased morbidity Increased survival Slower development of resistance

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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. RBX2660 is intended to be more palatable 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 for treating recurrent CDI	Fecal microbiota transplant Fidaxomicin Metronidazole Vancomycin	Increased clinical cure rates Reduced CDI recurrence
Ledipasvir for treating chronic hepatitis C 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 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 the formation of functional virions. Ledipasvir could inhibit the activity of all HCV genotypes. Administered orally, 30 mg, once daily and intended to be used in combination with sofosbuvir in a single pill. Gilead Sciences, Inc., Foster City, CA Phase III trials ongoing; FDA granted breakthrough therapy status and granted priority review Apr 2014, with a decision date in Oct 2014	Boceprevir Pegylated interferon plus ribavirin Simeprevir Telaprevir	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
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 recruiting; 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
Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry device (MALDI Biotyper) for detection of microbial infections	Patients in whom bacterial infection is suspected	Often patients with suspected infection pose challenges for clinicians, including deciding when to provide or withhold therapy and length of treatment course, distinguishing infectious from noninfectious illness, identifying the etiologic agent, and assessing disease severity and response to therapy. Better methods to diagnose and guide judicious therapy are needed. The MALDI Biotyper™ purportedly uses high throughput matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry to guide infection diagnosis and monitoring. It purportedly takes less time than conventional culture and biochemical testing to identify bacteria. The MALDI Biotyper system is purported to be capable of identifying more than 4,600 microbial isolates from gram-negative or gram-positive bacteria, yeasts, multicellular fungi, and mycobacteria. For sample preparation, a portion of an isolated colony is placed onto a target plate, covered with a chemical matrix, and loaded into the instrument. The sample is pulsed by a laser, converting the sample into an ionic gas composed of small proteins, peptides, and other molecules. In the ionization chamber, positively charged molecules move through an electric field at a rate based on their mass-to-charge ratios. Each organism has a unique rate signature, which can be compared by the device with reference spectra in the MALDI Biotyper library, leading to rapid identification. Additionally, the device allows users to generate their own database entries to include regional isolates. The device is purportedly capable of running high-throughput workflow and could be automated. Once the instrument is loaded, identifications can typically be performed in less than 1 minute, compared with hours to days for conventional methods. The device requires minimal sample preparation and offers low consumables cost. Bruker Corp., Billerica, MA FDA granted 510(k) marketing approval Nov 2013 for MALDI Biotyper CA System for identifying Gram negative bacteria	Culture methods Microscopy Polymerase chain reaction	Rapid disease detection Fewer cases of antibacterial resistance Improved treatment outcomes
Nitazoxanide for treatment of influenza	Patients in whom viral influenza has been diagnosed	Influenza continues to cause significant morbidity and mortality in susceptible patients; better treatments are needed because of the development of resistance to existing agents. 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 recruiting	Oseltamivir (Tamiflu®) Zanamivir (Relenza®)	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
NS5A inhibitor (MK-8742) for treating 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 period of time are needed. MK-8742 inhibits HCV NS5A; 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. Although the role of the protein is poorly understood, NS5A is required for viral replication; it is proposed that MK-8742 destabilizes the association of NS5A with the ER membrane, thus inhibiting the formation of functional virions. In clinical trials, MK-8742 is administered orally, 20 or 50 mg, once daily, in combination with MK-5172, with or without ribavirin. Merck & Co., Inc., Whitehouse Station, NJ Phase III trials ongoing; FDA granted breakthrough status for treating HCV genotype 1 in combination with MK-5172	Boceprevir Pegylated interferon alfa plus ribavirin Simeprevir Sofosbuvir Telaprevir	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
Off-label maraviroc (Selzentry) for prevention of HIV infection	People at high risk of contracting HIV infection	HIV remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments. HIV-drug resistance, high lifelong cost of therapy, and adverse events continue to suggest that prophylactic HIV measures be pursued for individuals at high risk of contracting HIV infection. Maraviroc (Selzentry®) is a chemokine (C-C motif) receptor-5 (CCR-5) antagonist. CCR-5 is expressed on the surface of T cells and has been identified as 1 of the 2 co-receptors needed for HIV to enter host cells. By preventing HIV from entering T cells, maraviroc could prevent HIV infection; thus, the drug is considered an entry inhibitor. In this indication, it is intended to be used as preexposure prophylaxis for people at high risk of HIV infection. Administered orally, 300 mg, once daily. ViiV Healthcare, Middlesex, UK Phase II trial recruiting; approved for treating CCR-5-tropic HIV-1 infection in combination with other antiretroviral agents	Condoms Harm-reduction campaigns Preexposure prophylaxis (tenofovir/emtricitabine)	Reduced transmission and incidence of HIV Reduced morbidity and mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ozonated water disinfectant to prevent health care–acquired infections	Patients in a hospital or other health care facility where hospital-acquired infections (HAIs) are a concern	HAIs are a major 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. Cleaning surfaces with ozonated water purportedly cleans as effectively as using other chemicals for terminal cleaning, but ozonated water is said to be less harsh on hospital staff and patients. Additionally, ozonated water is thought to leave no harmful residue after cleaning. Ozone is a highly active form of oxygen that purportedly reacts with microorganisms leading to efficient killing. After reacting, elemental oxygen is thought to remain. Windsor Regional Hospital, Windsor, Ontario, Canada Medizone International, Inc., Sausalito, CA Manufacturer is in discussions with the U.S. Environmental Protection Agency for marketing clearance as a disinfection system	Antimicrobial copper touch surfaces Terminal cleaning procedures using bleach and cleaning of visibly soiled surfaces as necessary Ultraviolet light	Reduced costs associated with HAIs Reduced bacteria isolated from surfaces Reduced infection rates Reduced HAI morbidity and mortality
PA-824 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. 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, PA-824 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 II trials 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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pegylated interferon lambda (BMS-914143) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	HCV treatment options using pegylated interferon (IFN)a-2a are not effective in all patients and are 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. BMS-914143 (pegylated IFN lambda) is a recombinant, pegylated form of IFN lambda, a type III IFN, which binds to a unique receptor on cells with a restricted cellular distribution and may improve tolerability when compared with treatment with type I IFNs/IFNa-2a. Administered as a subcutaneous injection, 180 mcg/mL, once weekly, for 24 or 48 weeks depending on response. Bristol-Myers Squibb, New York, NY Phase III trials ongoing	IFNa-2a IFN-free HCV drug combinations	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
Polymerase inhibitor (BMS-791325) 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 period of time are needed. BMS-791325 is a HCV nonnucleoside, NS5B polymerase inhibitor intended to limit viral replication when used in combination with other investigational agents including asunaprevir, daclatasvir, and sofosbuvir. Administered orally, 75 to 150 mg, twice daily. Bristol-Myers Squibb, New York, NY Phase III trials ongoing; FDA granted breakthrough status for treating HCV in combination with daclatasvir and asunaprevir	Boceprevir Interferon/ribavirin Simeprevir Sofosbuvir Telaprevir	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
Protease inhibitor (MK-5172) for treatment of chronic hepatitis C 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 and a long duration of therapy. Effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. MK-5172 is an oral NS3/4a protease inhibitor intended to block the activity of HCV protease from genotypes 1b, 2a, 2b, and 3a, preventing the cleavage and maturation of functional viral particles. In clinical trials, MK-5172 is administered orally, 100 mg, once daily, in combination with MK-8742 with or without ribavirin. Merck & Co., Inc., Whitehouse Station, NJ Phase III trials recruiting; FDA granted breakthrough status for treating HCV genotype 1 in combination with MK-8742	Boceprevir Pegylated interferon/ribavirin Simeprevir Sofosbuvir Telaprevir	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
Rapid molecular detection test (Gene Xpert MTB/RIF) for *Mycobacterium tuberculosis* infection with rifampin resistance	Patients suspected of having *Mycobacterium tuberculosis* infection	According to the World Health Organization, tuberculosis (TB) is highly underdiagnosed. Current TB testing methods require weeks to deliver a definitive result. During that time, patients can be left untreated or placed on ineffective therapies, which could allow TB to continue to spread to others in the community. The automated molecular test (Xpert® MTB/RIF) for detecting *M. tuberculosis* infection is a nucleic acid test that runs on the manufacturer's GeneXpert® real-time polymerase chain reaction (PCR) system. The test detects the presence of *M. tuberculosis* complex species in a sputum sample and simultaneously determines whether the identified bacterium is susceptible to the 1st-line antibiotic rifampicin. The assay is intended to yield results for both the presence of TB and antibiotic resistance for positive samples in about 2 hours. Traditional susceptibility testing is still required for antibiotics other than rifampicin. Cepheid, Sunnyvale, CA FDA granted marketing approval Jul 2013 through the 510(k) de novo pathway for rapid molecular detection of TB and rifampin resistance associated mutations of the *rpoB* gene	Microscopy Tuberculin skin test (Mantoux test) Ziehl-Neelsen microscopy	Less lab staff training time Rapid detection Improved treatment Better control of antibacterial resistance

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
RTS,S (Mosquirix) for prevention of malaria caused by *Plasmodium falciparum*	Patients living in or traveling to areas endemic for malaria	Almost half of the world population is at risk of contracting malaria. Treatments for the parasite *Plasmodium falciparum* can be ineffective, particularly in young children and immunosuppressed individuals; this results in high morbidity and mortality. RTS,S (Mosquirix™) consists of a recombinant, circumsporozoite protein in which the 9 central tandem repeat and carboxyl-terminal regions are fused to the N-terminus of the hepatitis B virus S antigen. The particle is expressed in yeast along with unfused S antigen. The vaccine is formulated with the AS02A adjuvant (proprietary oil-in-water emulsion with the immunostimulants monophosphoryl lipid A and QS21). The vaccine purportedly targets the pre-erythrocytic stage of *P. falciparum* growth by inducing protective immune responses against the parasite when it 1st enters the human host's bloodstream and/or when it infects liver cells, thus inhibiting the infection cycle. Administered in 3 intramuscular injections at 0, 1, and 2 months. GlaxoSmithKline, Middlesex, UK PATH Malaria Vaccine Initiative, Washington, DC Phase III trials completed; phase II trials ongoing	Chloroquine phosphate Mosquito nets	Reduced incidence of malaria infection Increased overall survival
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 Trial expected to be completed Oct 2013; larger trials planned for 2014	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

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	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 period of time are needed. Sofosbuvir (Sovaldi™) is a uridine nucleotide analog intended to inhibit HCV NS5B polymerase activity, which may limit viral replication by inhibiting viral genome replication. Sofosbuvir is being evaluated in conjunction with standard-of-care pegylated interferon plus ribavirin (IFN/RBV) and in IFN-free regimens that include ribavirin, daclatasvir, ledipasvir simeprevir, and other agents. Administered orally, 400 mg, once daily. Gilead Sciences, Inc., Foster City, CA 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	Boceprevir IFN/RBV Simeprevir Telaprevir	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
Sovaprevir 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 period of time are needed. Sovaprevir is a NS3 protease inhibitor intended to block the activity of HCV protease, preventing the cleavage and maturation of functional viral particles. Sovaprevir is purported to have broad genotypic coverage and to induce high rates of rapid virologic responses irrespective of interleukin-28 genotype. In a clinical trial, sovaprevir is being administered 200 mg or 400 mg, once daily, in combination with ACH-3102 (NS5A inhibitor) and ribavirin (RBV) as an interferon (IFN)-free regimen. Achillion Pharmaceuticals, Inc., New Haven, CT Phase II trial ongoing; FDA granted fast-track status for chronic HCV infection; FDA placed sovaprevir on clinical hold Jul 2013 because of safety concerns when the drug was administered with ritonavir-boosted atazanavir. FDA removed the clinical hold Jun 2014.	Boceprevir IFN/RBV Simeprevir Sofosbuvir Telaprevir	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
Surotomycin (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 previously treated for recurrent CDI with antibiotics develop further recurrence after therapy is stopped, which suggests that other therapeutic options are needed. Surotomycin (CB-183,315) is a novel cyclic lipopeptide, which purportedly disrupts bacterial membrane potential, inhibiting bacterial metabolism. Administered orally, 250 mg, twice daily, for 10 days. Cubist Pharmaceuticals, Inc., Lexington, MA Phase III trials recruiting participants; FDA granted qualified infectious disease product and fast-track statuses	Fidaxomicin Metronidazole Vancomycin	Reduced CDI recurrence rate Reduced length of hospital stay Improved time to resolution of diarrhea
Tablet-based kiosks to facilitate HIV self-testing of patients in emergency departments	Patients at high risk of contracting HIV infection	Despite efforts to integrate HIV testing into routine care delivered in emergency departments (ED), barriers remain. Tablet-based kiosks in the ED could be used to identify patients who may be in need of HIV testing. Additionally, these kiosks can direct the patient through the process of HIV self-testing (OraQuick® Advance), which could reduce workload for health care personnel. Patients in the ED are provided with a mobile touch-screen tablet that collects demographic information and previous HIV preventive screening status. Patients requiring HIV testing are given the option of self-testing by the tablet, which provides an overview of the process on the screen. Patients deciding to perform self-testing are given a placard with simple directions as a visual aid and a test kit by a health care worker. Johns Hopkins University, Baltimore, MD OraSure Technologies, Inc., Bethlehem, PA Program not diffused; OraQuick Advance FDA approved Jun 2004; OraQuick In-Home HIV test FDA approved Jul 2012	Clinic-based rapid test (OraQuick) performed by health care worker Home-based blood tests (mail-in) Home-based rapid test (OraQuick)	Reduced HIV transmission Earlier intervention to control viral load Increased HIV screening rate

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tafenoquine for treatment of *Plasmodium vivax* infection	Patients in whom *Plasmodium vivax* infection has been diagnosed	Malaria caused by *P. vivax* is the second 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 II trial ongoing; FDA granted breakthrough status for treating malaria caused by *P. vivax*	Chloroquine phosphate Mosquito nets Primaquine	Reduced incidence of malaria infection Relapse efficacy Increased overall survival
Tenofovir gel 1% for prevention of HIV transmission	Women who are sexually active	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 continue to suggest that prophylactic HIV measures be pursued for individuals who are not infected with the virus. Tenofovir 1% gel is a topical formulation of the nucleotide reverse transcriptase inhibitor tenofovir that is intended to inhibit reverse transcription, an essential part of the viral life cycle, Women apply the gel vaginally 12 or fewer hours before they anticipate having sexual intercourse and within 12 hours after sexual intercourse. International Partnership for Microbicides, Silver Spring, MD Gilead Sciences, Inc., Foster City, CA Phase III trial ongoing; FDA granted fast-track status	Condoms Harm reduction campaigns Pre-exposure prophylaxis with antiretrovirals	Reduced HIV transmission
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 recruiting	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
Vaccine (PXVX0200) for prevention of cholera	People traveling to areas endemic for cholera	A cholera vaccine is not available in the U.S., and internationally available vaccines require a 2-dose regimen. PXVX0200 is a live attenuated cholera vaccine derived from the *Vibrio cholerae* CVD 103-HgR strain. PXVX0200 is purported to require a single dose for protection and is intended to enhance convenience and protection for people traveling to cholera-endemic areas on short notice. Administered orally, $2x10^8$ to $2x10^9$ colony forming units in a liquid suspension. PaxVax, Inc., Menlo Park, CA Phase III trial ongoing	Improved hygiene	Protection against challenge Reduced severity of disease
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 at a dosage of 1,800 mg, twice daily, for 1 day, and 800 mg, twice daily, on days 2 through 5. FujiFilm Pharmaceuticals U.S.A., Inc., Boston, MA MediVector, Inc., Boston, MA Phase III trials recruiting	Oseltamivir Zanamivir	Shorter hospitalization time Reduced virus titers Relieved symptoms

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
Deep brain stimulation for treatment of obesity	Patients classified as overweight or obese on the basis of body mass index	The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Current surgical and pharmacologic options for treating obesity have varying degrees of invasiveness, some of which are associated with significant adverse effects and others that have suboptimal efficacy. 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 completed	Aspiration therapy system (in development) Endoluminal sleeve (EndoBarrier) Gastric banding surgery Gastric pacemaker (in development) Intragastric balloons (in development) Pharmacotherapy Roux en Y bypass surgery Sleeve gastrectomy surgery Vagus nerve blocking	Decreased food cravings Decreased obesity-associated comorbidities (e.g., prediabetes, high blood pressure) Increased weight loss Improved quality of life
Fecal microbiota therapy 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 trial 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
Intragastric dual balloon (ReShape Duo) for treatment of obesity	Patients with a body mass index (BMI) between 30 and 40 kg/m^2 who wish to lose weight	Current surgical options for treating obesity have varying degrees of invasiveness, some of which are associated with significant adverse effects, and other surgical options have suboptimal efficacy. ReShape Duo is a nonsurgical, intragastric, dual balloon that is endoscopically inserted into the stomach in an uninflated state using a guidewire. Once the clinician positions the dual balloon appropriately with the guidewire, they are inflated with a total of 900 cc of saline, occupying stomach space with the intended purpose of increasing satiety while avoiding overdistention. 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 Pivotal U.S. trial ongoing; Conformité Européene (CE) marked in 2007; Nov 2013, company announced device met primary efficacy endpoints in ongoing pivotal trial; Jul 2014, company submitted premarket approval application to FDA	Aspiration therapy system (in development) Deep brain stimulation Endoluminal sleeve (EndoBarrier) Gastric banding surgery Gastric pacemaker (in development) Pharmacotherapy Roux en Y bypass surgery Sleeve gastrectomy surgery 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 (Victoza) 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	The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Pharmacologic options have expanded with new drug approvals in 2012; however, competing approved drugs have significant potential side effects and work in only a proportion of patients taking them. Additional pharmacologic options are needed. Liraglutide (Victoza®) is approved for treating type 2 diabetes mellitus and acts as a glucagon-like peptide 1 analog; 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 an ongoing clinical trial, liraglutide is being administered as a once-daily, subcutaneous injection of 3.0 mg. Novo Nordisk a/s, Bagsværd, Denmark Phase III trials completed; 1 phase III trial ongoing in nondiabetic obese patients; Dec 2013, company announced it had submitted new drug application to FDA	$5\text{-}HT_{2C}$ receptor agonist (Belviq®) Behavior and lifestyle modifications Combination appetite suppressant/stimulant and anticonvulsant (Qsymia®) Combination norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (Contrave®; in development) Pancreatic lipase inhibitor (orlistat, Xenical®) Surgical therapy (e.g., bariatric surgery)	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
Naltrexone and bupropion extended-release (Contrave SR) for treatment of obesity	Adults with body mass index (BMI) >30 kg/m^2 or >27 kg/m^2 with comorbidities	The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Pharmacologic options have expanded with new drug approvals in 2012; however, competing approved drugs have significant potential side effects and work in only a proportion of patients taking them. Additional pharmacologic options are needed. Contrave® is a fixed-dose combination of naltrexone sustained-release (SR) and bupropion SR. Naltrexone purportedly prevents inhibition of proopiomelanocortin (POMC) neurons by blocking the action of beta-endorphin. Bupropion purportedly acts on weight control by stimulating the POMC neuron. Naltrexone and bupropion extended release (Contrave SR®) is taken orally, once a day. In an ongoing clinical trial, naltrexone and bupropion are being administered in combination at doses of 32 and 360 mg, respectively. Orexigen Therapeutics, Inc., La Jolla, CA FDA rejected new drug application Feb 2011; requested additional trial on cardiovascular effects; enrollment began Jun 2012; Jan 2013, company announced progress with FDA on faster path to resubmission; Jan 2014, company announced resubmission of data; FDA assigned decision date of Jun 10, 2014; Jun 2014, FDA assigned new decision date of Sept 11, 2014	5-HT$_{2C}$ receptor agonist (Belviq®) Behavior and lifestyle modifications Combination appetite suppressant/stimulant and anticonvulsant (Qsymia®) Glucagon-like peptide 1 analog Liraglutide (Victoza®; in development) Pancreatic lipase inhibitor (orlistat, Xenical®)	Decreased comorbidities Total weight loss Improved quality of life
Off-label exenatide for treatment of pediatric obesity	Children and adolescents receiving a diagnosis of “extreme” obesity (body mass index [BMI] ≥1.2 times the 95th percentile or BMI ≥35 kg/m^2)	A single weight-loss pharmacotherapy is available for adolescents older than 12 years of age: orlistat (Xenical®). However, prescription medications are not recommended for child or adolescent use. Exenatide is a glucagon-like peptide-1 receptor agonist approved for type 2 diabetes mellitus treatment that purportedly reduces BMI, waist circumference, and body weight in addition to improving the glycemic index. Exenatide purportedly increases satiety sensation and appetite suppression. In trials, exenatide was administered subcutaneously, twice daily, 5 mcg/dose for the 1st month and then 10 mcg/dose for 2 months. University of Minnesota, Minneapolis Pilot trial completed; phase II trial completed	Behavior and lifestyle modifications Off-label anti-obesity medications Pancreatic lipase inhibitor (orlistat, Xenical®)	Decreased comorbidities Improved quality of life Total weight loss

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vagus nerve blocking (Maestro system VBLOC) for treatment of obesity	Adults with body mass index (BMI) between 40 and 45 kg/m^2 or ≥35 kg/m^2 with comorbidities	The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Available pharmacologic and surgical options can have serious side effects or adverse events, warranting the need for more novel approaches for treating obesity. The VBLOC™ system is an implanted device that emits high-frequency, low-energy electrical impulses, which are intended to block the vagus nerve in an effort to inhibit gastric motility and increase feelings of fullness. Electrical impulses are delivered by the implanted neuroregulator, which is powered either by an external controller (Maestro™ RF System) or an integrated rechargeable battery (Maestro RC System); implanted laparoscopically. EnteroMedics, Inc., St. Paul, MN Pivotal ReCharge trial ongoing; phase III trial completed; Jun 2013, company submitted premarket approval application to FDA; Jun 2014, FDA advisory committee voted 8-1 that the device was safe, 4-5 "against" on the issue of a reasonable assurance of efficacy, and 6-2 that the relative benefits outweigh the risks; company anticipates 2014 approval	Aspiration therapy system (in development) Deep brain stimulation Endoluminal sleeve (EndoBarrier) Gastric banding surgery Gastric pacemaker (in development) Intragastric balloons (in development) Pharmacotherapy Roux en Y bypass surgery Sleeve gastrectomy surgery	Decreased comorbidities Total weight loss Improved quality of life

Table 11. AHRQ Priority Condition: 11 Peptic Ulcer Disease and Dyspepsia: 10 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 an abnormally and chronically activated immune systems in the absence of any known invader, leading to periodic bouts of abdominal pain, diarrhea, and rectal bleeding. 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 trials ongoing; FDA granted orphan drug status	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
Andrographis paniculata extract (HMPL-004) for treatment of ulcerative colitis	Patients in whom ulcerative colitis (UC) has been diagnosed	Patients with UC have an abnormally and chronically activated immune system in the absence of any known invader, leading to periodic bouts of abdominal pain, diarrhea, and rectal bleeding. 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. HMPL-004 is a herbally derived drug from the *Andrographis paniculata* plant. The extract purportedly inhibits multiple cellular targets including specific tumor necrosis factors (TNFs) and interleukin cytokines. HMPL-004 also purportedly inhibits the activation of specific cellular proteins associated with inflammation. Specific cytokine inhibition is thought to disrupt the inflammatory signal transduction pathway, thus suppressing UC. HMPL-004 purportedly is associated with fewer adverse events than available inflammatory cytokine inhibitors. In clinical trials, it has been administered as an oral medication twice daily in doses of 400 or 600 mg. Hutchison MediPharma, Ltd., Shanghai, China 2 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
Eluxadoline (MuDelta) for treatment of diarrhea-predominant irritable bowel syndrome	Patients in whom diarrhea-predominant irritable bowel syndrome (IBS-D) has been diagnosed	IBS is considered to be a functional gastrointestinal disorder of unclear etiology with no known cure. Approximately 30% of diagnosed IBS cases can be attributed to IBS-D. Available treatments are purported to be 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. Eluxadoline is a mu-opioid receptor agonist and delta-opioid receptor antagonist that may provide relief for both pain and diarrheal symptoms of IBS-D without the constipating effects typically seen with mu-receptor agonists. Pharmacology data suggest that eluxadoline acts locally in the digestive tract, thus having a low potential for systemic side effects. In clinical trials, eluxadoline has been administered as an oral tablet, at a dose of 75 or 100 mg, twice daily. Actavis plc, Dublin, Ireland acquired developer Furiex Pharmaceuticals, Inc., Morrisville, NC Jul 2014 Pivotal phase III trials completed; 1 phase III trial ongoing; FDA granted fast-track status Jan 2011; Actavis announced plans to file NDA with FDA in Q3 2014	Antispasmodic drugs Opioids Serotonin agonists 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
Fecal microbiota transplantation for treatment of ulcerative colitis	Patients in whom ulcerative colitis (UC) has been diagnosed	Patients with UC have an abnormally and chronically activated immune system in the absence of any known invader, leading to periodic bouts of abdominal pain, diarrhea, and rectal bleeding. 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. 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/III trial ongoing; procedure may 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 Reduced 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
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	Autologous bone marrow–derived MSC stromal cells (in development) Teduglutide	Increased disease remission Improved disease symptoms Improved quality of life
Rifaximin (Xifaxan) for treatment of nonconstipating irritable bowel syndrome	Patients in whom nonconstipating irritable bowel syndrome (IBS) has been diagnosed	IBS is a considered to be a functional gastrointestinal disorder of unclear etiology 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. Salix Pharmaceuticals, Inc., Morrisville, NC Phase III trial ongoing (TARGET3)	Antispasmodic drugs Opioids Serotonin agonists 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
Teduglutide (Gattex) for treatment of short bowel syndrome	Patients in whom short bowel syndrome (SBS) has been diagnosed	SBS typically arises after extensive resection of the bowel because of Crohn's disease and is a highly disabling condition that can lead to serious, life-threatening complications as well as malnutrition, severe diarrhea, dehydration, fatigue, osteopenia, and weight loss due to the reduced intestinal absorption. Available treatments supplement and stabilize nutritional needs; however, parenteral support does not improve absorption of nutrients and is associated with infections, blood clots, liver damage, poor quality of life, and high costs. Teduglutide (Gattex™) is a recombinant analogue of human glucagon-like peptide 2 that purportedly increases nutrient absorption and intestinal cell growth in patients with SBS. Gattex is a self-administered injectable given once daily at a dose of 0.05 mg/kg. NPS Pharmaceuticals, Inc., Bedminster, NJ FDA approved Dec 2012 for treating SBS	Intravenous fluids Parenteral nutrition	Improved hydration Improved nutritional status Weight gain Reduced diarrhea Improved quality of life
Tofacitinib (Xeljanz) for treatment of ulcerative colitis	Patients in whom ulcerative colitis (UC) has been diagnosed	Patients with UC have an abnormally and chronically activated immune system in the absence of any known invader, leading to periodic bouts of abdominal pain, diarrhea, and rectal bleeding. 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
Vedolizumab (Entyvio) for treatment of moderate to severe ulcerative colitis and Crohn's disease	Patients in whom moderate to severe ulcerative colitis (UC) has been diagnosed	Patients with UC have an abnormally and chronically activated immune systems in the absence of any known invader, leading to periodic bouts of abdominal pain, diarrhea, and rectal bleeding. 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. Vedolizumab (Entyvio) is an infused monoclonal antibody purported to inhibit the binding of intestinal mucosal cell molecules thought to play a role in the inflammatory process. Vedolizumab is administered via intravenous infusion in doses of 300 mg at 0, 2, and 6 weeks, followed by 300 mg intravenous infusions every 8 weeks. Millennium Pharmaceuticals unit of Takeda Pharmaceutical Co., Ltd., Osaka, Japan FDA approved May 2014 for treating adult patients with moderate to severe ulcerative colitis; phase III trial completed	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (e.g., prednisone) Immunomodulators (e.g., azathioprine) Monoclonal antibodies (e.g., natalizumab, infliximab)	Reduced flare symptoms Maintained remission Reduced or postponed need for surgery Improved quality of life
Vercirnon (Traficet-EN) for treatment of Crohn's disease	Patients in whom moderate to severe 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. Vercirnon (Traficet-EN™, GSK1605786) is an oral CCR9 antagonist. CCR9 is a chemokine receptor that plays a central role in the inappropriate inflammatory response thought to underlie Crohn's disease. By blocking CCR9, vercirnon selectively impairs the movement of activated T cells that are involved in causing inflammation of the digestive tract. In phase III trials, it was administered in a 500 mg dose, twice daily. Chemocentryx, Inc., Mountain Valley, CA 1 phase III trial completed, 3 phase III trials terminated; GlaxoSmithKline returned all rights to Chemocentryx following failed clinical trials	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (e.g., prednisone) Immunomodulators (e.g., azathioprine) Monoclonal antibodies (e.g., natalizumab, infliximab	Delayed or avoided surgery Reduced flares Reduced side effects Disease remission Symptom improvement Improved quality of life

Table 12. AHRQ Priority Condition: 12 Pregnancy, Including Preterm Birth: 5 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bi-directional communication for management of weight (SmartMoms) 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, Canada Phase III trial recruiting	Other perinatal weight-management strategies	Improved maternal and fetal health outcomes Improved perinatal weight management Reduced morbidity Improved quality of life
Blood test (PreTRM) to predict spontaneous preterm birth	Women who are pregnant	About 1 in 10 pregnant women has a spontaneous preterm birth in the U.S. each year; however, no screening or diagnostic test is available to identify women at risk of preterm birth early in pregnancy. Clinicians and their patients could use test results to plan preterm-birth prevention strategies. PreTRM™ is a panel of proteomic markers that purportedly indicates the likelihood of spontaneous preterm birth. The proteomic assay is performed on a blood sample taken at 28 weeks of pregnancy. Sera Prognostics, Salt Lake City, UT Validation study ongoing; study completed enrollment of 5,500 patients	Assessment of cervical length Detection of bacterial vaginosis Fetal fibronectin levels Home uterine activity monitoring Salivary estriol testing	Earlier intervention for women at risk of preterm birth Reduced incidence of preterm birth Reduced neonatal complications Reduced use of neonatal intensive care services

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fetal catheterization procedures for treatment of hypoplastic left heart syndrome	Pregnant women in whom fetal hypoplastic left heart syndrome (HLHS) has been diagnosed	HLHS is a congenital condition in which parts of the heart's left side (i.e., aorta, aortic valve, mitral valve) do not completely develop. It occurs in about 1 in 6,000 live births. Once a baby with HLHS is born, the patient is admitted to the neonatal intensive care unit, placed on a ventilator, and given prostaglandin E1 to keep the ductus arteriosus patent. Texas Children's Fetal Center has created a fetal, in utero valvuloplasty program to better stabilize the baby at time of birth before undergoing phase I of HLHS surgery. Each fetal intervention procedure is specialized to the needs of the patient and depends on the specific cardiac malformation. For example, fetal aortic valvuloplasty could occur in the aortic valve for a fetus with severe aortic stenosis that typically develops into HLHS, allowing blood to circulate throughout the entire body. Catheterization could also occur across the atrial valve septum, connecting the 2 atrial chambers and allowing blood to pass through the heart's other side. In this case, a stent may also be placed to help sustain the patency of the hole created between the atrial chambers. These techniques can help blood pass to the left side of the heart, allowing the fetus to become more oxygenated and increasing odds of postnatal survival. Texas Children's Fetal Center of Texas Children's Hospital, Houston, in collaboration with Boston Children's Hospital, Boston, MA University of California, San Francisco University of Michigan C.S. Mott Children's Hospital, Ann Arbor Phase I/II trial recruiting	Heart transplantation Neonatal surgery	Increased oxygenation to fetus Increased postnatal survival Increased survival to live birth

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	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 the need for managing bone loss while treating endometriosis. In clinical trials, the drug is taken at a variable dose, daily, orally. AbbVie, North Chicago, IL Phase III trials ongoing; also under study for uterine fibroids	Drugs: Hormonal contraceptives Steroids Surgical interventions: Endometrial growth and scar tissue excision Hysterectomy	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
Recombinant antithrombin (ATryn) for treatment of preterm preeclampsia	Pregnant women in whom very early preterm preeclampsia (before 28 weeks gestation) has been diagnosed	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 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 at weight-dependent doses with the goal of restoring and maintaining functional levels of antithrombin (0.8–1.2 IU/mL). rEVO Biologics, Inc., a subsidiary of LFB S.A., Les Ulis, France Phase III trial ongoing; Feb 2014, submitted investigational new drug application to FDA	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

Table 13. AHRQ Priority Condition: 13 Pulmonary Disease, Asthma: 16 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
AeriSeal System for treatment of emphysema	Patients in whom 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. The AeriSeal System® purportedly achieves lung volume reduction using a minimally invasive approach. Damaged areas of the patient's lungs are targeted with a bronchoscope to deliver a proprietary foam sealant that purportedly seals and collapses, through reabsorption, the treated area, resulting in reduced lung volume. Lung volume reduction purportedly creates more space for healthier, adjacent lung tissue to function more effectively. Aeris Therapeutics, LLC, Woburn, MA Phase III trials terminated; unphased trial planned	Antibiotics Bronchodilators Corticosteroids Oxygen Pulmonary rehabilitation program Surgery (lung volume-reduction surgery, bullectomy, lung transplantation)	Improved lung function Improved activities of daily living Improved quality of life
Ataluren 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. Treatment is aimed at controlling infections, secretions, airway obstructions, and complications. Ataluren is a protein-restoration therapy designed to enable the formation of 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 trial ongoing; FDA granted orphan drug status	Antibiotics Gene therapies (viral vector or liposome delivery of normal CFTR) Lung transplantation Chest physiotherapy Bilevel positive airway pressure ventilators	Improved lung function Reduced need for additional therapies 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
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
Inhaled amikacin (Arikace) 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 (Arikace®), an approved antibiotic against a variety of NTM, is a semisynthetic aminoglycoside derived from kanamycin. Arikace is being developed as a sustained-release formulation of amikacin encapsulated inside small fat particles using an optimized, investigational eFlow® Nebulizer System. Arikace 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 II trial ongoing; FDA granted orphan drug and fast-track statuses. Arikace is approved for other indications and sometimes used off label for treating NTM, but existing formulation is not intended for that use and trials are ongoing for the NTM indication	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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lumacaftor for treatment of cystic fibrosis	Patients with cystic fibrosis (CF) who have the delta *F508-CFTR* gene mutation	No curative treatments exist for CF or non-CF bronchiectasis mucus accumulation. Treatment is aimed at controlling infections, secretions, airway obstructions, and complications; no product is available to effectively clear excess mucus secretions. Lumacaftor (VX-8090 is considered a corrector of the cystic fibrosis transmembrane regulator (*CFTR*) gene mutation; intended to increase CFTR protein regulator function by increasing its movement to the cell surface. Given as oral monotherapy and in combination with ivacaftor (Vertex's other CF drug). Administered orally, 600 mg, once daily, or 400 mg, twice daily, in clinical trials. Vertex Pharmaceuticals, Inc., Cambridge, MA Phase III trials ongoing; FDA granted breakthrough, orphan drug, and fast-track statuses	Antibiotics Gene therapies (viral vector or liposome delivery of normal *CFTR*) Lung transplantation Chest physiotherapy Bilevel positive airway pressure ventilators	Improved lung function Increased survival Improved quality of life
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 Pivotal phase III trial recruiting	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)

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. 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. Masitinib is administered orally, 6 mg/kg, daily, in clinical trials. AB Science S.A., Paris, France Phase III trial recruiting	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 (Bosatria) 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 (Bosatria®) 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	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 hospitalization 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 KB001-A for treatment of *Pseudomonas aeruginosa* infection	Patients in whom cystic fibrosis (CF) and *Pseudomonas aeruginosa* infection has been diagnosed	Patients with CF are susceptible to bacterial lung infections, such as *Pseudomonas aeruginosa,* that are difficult to treat with antibiotics. Better treatment options are needed for long-term management of CF. KB001-A is a pegylated monoclonal antibody fragment targeting the *PcrV* gene product of *P. aeruginosa*. PcrV is purported to be part of the bacterium's type III secretion system which is involved in releasing toxins resulting in destruction of the host's immune cells and contributing to pathogenesis. Blocking PcrV is purported to prevent immune cell destruction and reduce inflammation, preserving immune and lung epithelial cell function. Bacteria are believed to be unlikely to develop resistance to KB001-A because loss of PcrV leads to a loss in *P. aeruginosa* pathogenicity. In a clinical trial, KB001-A is being administered intravenously, 10 mg/kg up to a maximum dose of 800 mg per dose, up to 5 times over 6 weeks. KaloBios Pharmaceuticals, Inc., South San Francisco, CA Phase II trial recruiting; FDA granted orphan drug status	Antibiotics	Improved lung function Improved quality of life Increased survival Reduced need for antibiotics
Nintedanib to preserve lung function in 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%. No approved treatments are available. Nintedanib (BIBF-1120) 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 under study for treating IPF and slowing of disease progression and symptoms. Administered orally, 150 mg, twice daily. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trial ongoing and 1 phase III trial recruiting; FDA granted orphan drug and priority review statuses	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Methotrexate 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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label azithromycin for prevention of chronic obstructive pulmonary disease exacerbations	Patients in whom chronic obstructive pulmonary disease (COPD) has been diagnosed	Patients experiencing severe acute exacerbations of COPD have a greater 30-day mortality rate than patients experiencing acute myocardial infarction. Acute exacerbations of COPD dramatically change the course of the disease and are associated with a rapid decline in lung function and worsening quality of life; better treatments are needed. Antibiotics have been used to prevent COPD exacerbations; however, they were shown to be ineffective. Recently, macrolide antibiotics have been selected to prevent COPD exacerbations because of their purported antibacterial action combined with immunomodulatory and anti-inflammatory properties. Administered orally, 250 mg, once daily or 3 times weekly to prevent COPD exacerbations. University of Colorado, Denver, Health Sciences Center Phase III trial ongoing; FDA approved in 1992 for treating community-acquired respiratory infections and skin infections	Glucocorticoids Long-acting anticholinergic agents Long-acting beta-2 agonists Roflumilast	Reduced cost due to exacerbations Reduced incidence of exacerbations Increased survival Improved quality of life
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%. No 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, 800 mg, 3 times daily. InterMune, Inc., Brisbane, CA Phase III trial ongoing; new drug application submitted to FDA May 2014; FDA granted fast-track and orphan drug statuses	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Methotrexate Penicillamine Pulmonary rehabilitation Supplemental oxygen	Improved ability to perform activities of daily living Improved lung function measured by forced vital capacity 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
Portable warm blood perfusion system (Organ Care System) for living lung transplantation	Patients who require lung transplantation	According the U.S. Department of Health and Human Services, 4.86 per 1 million people in the U.S. received an organ transplant in 2008. Current methods of organ preservation during transplantation leave the organ susceptible to significant damage. 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, FDA-approved investigational device status trials recruiting	Cold-storage preservation	Increased graft survival Decreased graft dysfunction Increased utilization 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., Petach Tikva, Israel (acquired developer Cephalon, Inc., Oct 2011) Phase III trials ongoing	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 hospitalization Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 is comprised of 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 Reduced symptoms at night Reduced rescue medication use Reduced exhaled nitric oxide (inflammation)
Temperature-controlled laminar air-flow device (Airsonett) for treatment of atopic asthma	Patients in whom atopic asthma has been diagnosed	Despite pharmaceutical treatment and lifestyle modification, many patients continue to have difficulty controlling asthma symptoms. Airsonett is a temperature-controlled laminar air-flow device that is positioned over the patient while he or she sleeps. The device purportedly creates a downward flow of filtered air that surrounds the sleeping patient's breathing zone with the intention of providing air in convection currents that is free of allergens and irritants. Airsonett AB, Ängelholm, Sweden Phase III trials completed	Air purifiers Antiallergenic pillow/mattress encasements Home heating, ventilation, and air conditioning systems	Reduced asthma symptoms Improved peak nasal inspiratory flow Improved sleep quality Improved quality of life

Table 14. AHRQ Priority Condition: 14 Substance Abuse: 10 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 utilizes 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. Titan Pharmaceuticals, Inc., South San Francisco, CA (manufacturer) Braeburn Pharmaceuticals subsidiary of Apple Tree Partners, Princeton, NJ (licensee) Phase III confirmatory trial completed; new drug application submitted Oct 2012; FDA advisory panel recommended approval Mar 2013; FDA issued complete response letter stating that it could not grant approval, requested more efficacy data Apr 2013	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
Community-based overdose prevention program (Project Lazarus)	Patients with chronic opioid use or opioid dependence	Opioid overdose is an increasingly common issue with the rise of prescription opioid use and abuse in communities across the U.S. Project Lazarus is a community-targeted overdose prevention program developed in Wilkes County, NC, in response to extremely high rates of overdose deaths. The program offers 5 components: community activation and coalition building, monitoring and surveillance data, prevention of overdoses, use of rescue medication by community members for reversing overdoses, and evaluating project components. Primary care physicians receive an educational tool kit on chronic pain management and safe opioid prescribing practices. Project Lazarus in collaboration with the Community Care of North Carolina's Chronic Pain Initiative This program has expanded across North Carolina since its success in Wilkes County and is supported with significant state and local infrastructure; Project Lazarus has also been cited as a national model of effective intervention, for possible replication in locales including New Mexico	Other substance abuse prevention and treatment programs Various combinations of opioid replacement therapy and detoxification treatments	Decreased incidence of overdose and overdose-related death Improved chronic pain management Improved opioid prescribing practices

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). SmartStart, Inc., Irving, TX, with Intelligent Fingerprinting, Norwich, UK Manufacturer (Intelligent Fingerprinting) notes that a series of pilot studies will start in 2014, with wider commercial availability in 2015	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
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 options to promote abstinence in alcohol-dependent individuals 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, as well as Ethypharm, Saint-Cloud, France Multiple phase II and III trials are ongoing; FDA approved for treating muscle spasticity associated with multiple sclerosis	Acamprosate Benzodiazepines Cognitive behavior therapy Disulfiram Gabapentin Naltrexone Psychotherapy	Reduced alcohol consumption Increased abstinence rates Decreased alcohol craving Decreased alcohol withdrawal symptoms

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 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. Multiple investigators, including the National Institute on Drug Abuse, Bethesda, MD, and the University of Pennsylvania, Philadelphia Phase II trial ongoing; multiple randomized controlled trials completed in U.S. and overseas with results reported	Cognitive behavior therapy Off-label pharmacotherapy (e.g., disulfiram) Psychotherapy Modafinil Other GABAergic medications: Baclofen 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 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 options to promote abstinence in alcohol-dependent individuals 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. 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 a clinical trial, mifepristone was orally administered at a dosage of 600 mg/day for 1 week. The Scripps Research Institute, La Jolla, CA Phase II trial ongoing; preliminary results available; mifepristone is FDA approved to end early pregnancy, marketed under the brand name Mifeprex® (Danco Laboratories, New York, NY), and approved for treatment of hypoglycemia in patients in whom Cushing's Syndrome has been diagnosed, marketed as Korlym® (Corcept Therapeutics, Inc., Menlo Park, CA)	Acamprosate Benzodiazepines Cognitive behavior therapy Disulfiram Gabapentin Naltrexone Psychotherapy	Reduced alcohol 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 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 and is marketed under the brand name Mifeprex (Danco Laboratories, New York, NY)	Cognitive behavior therapy Off-label pharmacotherapy (e.g., disulfiram) Psychotherapy Modafinil Other GABAergic medications: Baclofen Tiagabine	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. In clinical trials, ondansetron is administered to patients in oral tablets at various dosages, up to 16 mcg/kg, twice daily. Adial Pharmaceuticals, LLC, Charlottesville, VA (indication-specific manufacturer) Johns Hopkins University, Baltimore, MD; National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD; University of Virginia, Charlottesville; and Medical University of South Carolina, Charleston (investigators) Phase III trials completed; phase II and III trials ongoing; approved for treating chemotherapy-induced nausea and vomiting and 1st marketed by GlaxoSmithKline (Middlesex, UK) as Zofran®	Acamprosate Benzodiazepines Cognitive behavior therapy Disulfiram Gabapentin Naltrexone Psychotherapy	Improved health outcomes associated with abstinence Reduced alcohol consumption Reduced alcohol cravings Reduced relapse Improved patient quality of life
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 is a GABAergic anticonvulsant and mood stabilizer that has been purported to be 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 Adderall XR®, an amphetamine psychostimulant. Ortho-McNeil-Janssen, a unit of Johnson & Johnson, New Brunswick, NJ Phase III trials ongoing	Cognitive behavior therapy Off-label pharmacotherapy (e.g., disulfiram) Psychotherapy Modafinil Other GABAergic medications: Baclofen Tiagabine	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 topiramate 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 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 behavioral therapy. Investigators included 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; data from phase II, III, and IV trials have been reported	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

Table 15. AHRQ Priority Condition: 15 Cross-Cutting: 7 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
3-D printing for creating bioresorbable implants	Patients requiring medical implants	Implants have limited ability to be customized to each patient's needs. Implants are either made with synthetic material foreign to the body or harvested from cadavers. 3-dimensional (3-D) printing creates an implantable, customized, bioresorbable implant, created with a computer-aided design based on a computed tomographic image that shows the patient's specific needs. Some implants are 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 implants are affixed without metal screws or plates but can still provide structural support. Implants replacing bones have an osteoconductive coating to enhance bone regeneration and proliferation throughout the porous surface. Outer ear structures can be printed with collagen gels that will be replaced with the body's cartilage over 3 months after implantation. Tissue Regeneration Systems, Inc., Kirkland, WA (founded by researchers at University of Michigan, Ann Arbor, with funding from the university) Cornell University, Ithaca, NY 2 cases reported of trachea splints; FDA granted emergency use exemption; FDA granted 510(k) marketing clearance for TRS's cranial bone void filler in Aug 2013	Cadaver tissue Traditional implants	Improved health outcomes Increased survival Improved quality of life
Computer-assisted system (Sedasys) for automated propofol sedation during gastrointestinal endoscopy procedures	Patients who are undergoing propofol-induced sedation during colonoscopy or upper gastrointestinal (GI) procedures	Propofol-induced sedation can be associated with risk of oversedation and decreased oxygen saturation. The Sedasys® system integrates physiologic patient monitoring (oxygen saturation, respiratory rate, heart rate, blood pressure, end-tidal carbon dioxide, and patient responsiveness) with personalized drug delivery (system automatically responds to signs of oversedation) for delivering propofol. The system is intended to enable nonanesthesiologists (i.e., other physicians or nurses) to administer sedation for endoscopic GI procedures. Ethicon Endo-Surgery unit of Johnson & Johnson, New Brunswick, NJ After repeated premarket approval application submissions, FDA approved May 2013; company plans to initiate limited roll-out of system in late 2014	Propofol sedation administered and monitored by anesthesiologist	Successful and safe propofol sedation without need for an anesthesiologist

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, AIDS, 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. Proteus Digital Health, Inc., Redwood City, CA FDA granted marketing clearance for the monitoring device Mar 2010; Jul 2012, the company also received marketing clearance for the ingestible sensor; expected to come to market late 2014	Conventional oral drug therapy Patient medication reminders via telephone, text message, and/or email	Improved disease management by maintaining consistent oral drug dosing and reducing missed doses
High-throughput DNA sequencers for genetic testing	Patients in need of genetic testing for diagnosis, pharmacogenetics, and 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 has 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 In Nov 2013, the Illumina MiSeqDx DNA sequencer and Universal Kit reagents became the first 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)	First-generation sequencing methods Single-gene assays	Improved diagnosis Improved treatment planning Improved pharmacogenetics

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Senior-specific emergency departments for treatment of elderly patients	Senior or elderly patients who visit an emergency department (ED)	20% of all seniors use an ED at least once a year, and half of all ED patients are seniors. General EDs can be uncomfortable or unsafe for elderly patients, and risk of hospital readmission and drug interactions are high in this population. Additionally, EDs do not always have access to geriatrician staff members. EDs for seniors are designed specifically for the elderly population. Structural, safety, and comfort changes include wider hallways (for wheelchairs), hand rails, different lighting systems, easier-to-read visuals, pressure-reducing beds, and alarms for wandering patients. Care teams and care delivery are redesigned to include clinicians and nurses with special training in geriatric medicine, including education on issues related to ageism and sensory appreciation in the elderly (so that these skills can be used to communicate more effectively with older adults and their caregivers). The different approach to care involves being more thorough with each patient and conducting on a routine basis assessments that typically are only made as needed (e.g., cognitive exams to detect issues that normally would go unchecked in other EDs). Senior-specific EDs have been opened across the U.S. 1st senior-specific ED launched in 2008; approximately 50 established senior-specific EDs exist and at least 150 are in development in U.S.; multigroup task force released Geriatric Emergency Department Guidelines in Jan 2014	General EDs	Improved health outcomes for seniors Improved quality of life
Web-based integrated monitoring platform (T3) 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. T3, 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. This information can be readily accessed remotely via a portable, Internet-enabled device. T3 purportedly allows for better decisionmaking, care-plan adjustment, and real-time, regular analysis. Boston Children's Hospital, Boston, MA, working with software developer Arcadia Solutions, Burlington, MA; licensed software to Etiometry, Inc., Boston, MA Installed in multiple academic hospitals; novel algorithms under development by ICU researchers	Multiple monitoring platforms	Improved care-plan adjustment Improved decisionmaking Improved patient outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Wireless monitoring program (Care Beyond Walls and Wires) for rural patients with chronic conditions	Patients with chronic conditions who have been recently discharged from the hospital and who live in rural areas	Up to 1/2 of patients with heart failure discharged from the hospital are rehospitalized within 3–6 months. Reasons for this include not taking medications as prescribed, improper diet, lack of awareness of heart failure signs, and lack of planned followup with a doctor. These issues are particularly salient for rural populations, such as Native Americans, who often don't have access to cars or other transportation, running water, or electricity. The Care Beyond Walls and Wires program is intended to overcome these barriers and reduce hospital readmissions. The program uses smart phones and in-home monitoring equipment to collect data on weight, blood pressure, activity, and other important health indicators and transfer the data to nurses at a medical center. The nurses monitor the data daily and work with physicians to detect declines in a patient's health status and intervene early, potentially reducing unnecessary travel, physician office visits, costs, and hospital readmissions. The cell phones and monitoring equipment are donated by manufacturers. Rural residents without electricity use solar-powered batteries. Flagstaff Medical Center, Flagstaff, AZ as part of a National Institutes of Health Public-Private Partnership 50-patient trial completed Apr 2013	In-person patient-monitoring visits Kiosk monitoring programs	Fewer office visits and hospital readmissions Improved patient monitoring Improved patient outcomes Reduced costs

Section 2. Interventions Added Since Last Update: 26 Interventions

Table 16. AHRQ Priority Condition: 01 Arthritis and Nontraumatic Joint Disease: 0 Interventions

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

Table 17. AHRQ Priority Condition: 02 Cancer: 9 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Abemaciclib for treatment of 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. The drug is being studied for use in combination with fulvestrant in various treatment settings for advanced disease. In clinical trials, abemaciclib is given orally at a dose of 200 mg, once every 12 hours, in 28-day cycles. Eli Lilly and Co., Indianapolis, IN Phase III trial registered, not yet recruiting; also being tested in advanced nonsmall cell lung cancer	Anastrozole Fluoxymesterone Fulvestrant High-dose estrogen LEE011 (in development) Palbociclib (in development) Progestin Tamoxifen Toremifene	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 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. BioAlliance Pharma SA, Paris, France (merging with Topotarget a/s, Copenhagen, Denmark, and expected to change its name to Onxeo) Phase III trial ongoing; FDA granted fast-track status	Locoregional treatment Regorafenib Sorafenib (if not used in 1st-line setting)	Increased overall survival Increased progression-free survival Improved quality of life
Epidermal growth factor receptor inhibitor (CO-1686) 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	Treatment with EGFR inhibitors has 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. And 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. 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, CO-1686 is being administered orally, at doses between 500 and 1,000 mg, twice daily. Clovis Oncology, Boulder, CO Phase I/II and phase II trials ongoing; FDA granted orphan drug and breakthrough therapy status	Afatinib 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
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, Inc., Sunnyvale, CA, in partnership with the Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ Phase III trial ongoing	Various regimens (rituximab monotherapy; rituximab and a chemotherapeutic agent such as bendamustine, fludarabine)	Increased overall survival Increased progression-free survival Improved quality of life
Nivolumab for treatment of Hodgkin's lymphoma	Patients with Hodgkin's lymphoma who have undergone previous treatment with autologous stem cell transplant and brentuximab vedotin	Patients with Hodgkin's lymphoma that has progressed following 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 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 I 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
Ruxolitinib (Jakafi) for treatment of pancreatic cancer	Patients in whom recurrent metastatic pancreatic adenocarcinoma has been diagnosed	Only about 5% of patients with pancreatic cancers 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 III trials ongoing; FDA granted orphan drug status	Various chemotherapies including 1 or more of the following: 5-Fluorouracil Capecitabine Erlotinib Gemcitabine Leucovorin Nab-paclitaxel 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
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 twice daily at a dose between 5 mg 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	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
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
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	Carboplatin in combination with any of the following: Paclitaxel Docetaxel Pemetrexed	Increased overall survival Increased complete response rate Improved quality of life

Table 18. AHRQ Priority Condition: 03 Cardiovascular Disease: 2 Interventions

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 III trials ongoing; phase II trials completed; FDA granted breakthrough therapy status	Transfusion	Reduced major bleeding

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
MST-188 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. MST-188 is a pharmaceutical agent being investigated as adjunct therapy for patients with acute limb ischemia currently treated with tissue plasminogen therapy (tPA). MST-188 purportedly improves the clot-busting action of tPA and minimizes perfusion injury. According to the manufacturer, MST-188 inhibits multiple inflammatory processes and binds to damaged cellular membranes, thus increasing blood flow to the extremities. In clinical trials, MST-188 is being injected via continuous fusion, 100 mg/kg, for 1 hour followed by 30 mg/kg/hr 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

Table 19. AHRQ Priority Condition: 04 Dementia (including Alzheimer's: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Receptor for advanced glycation-endproducts inhibitor (TTP448) for treatment of mild Alzheimer's disease	Patients in whom mild probable Alzheimer's disease (AD) has been diagnosed	No approved disease-modifying agents are available for treating AD; available therapy options are limited to symptom management. 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 have hypothesized that these accumulations trigger a cycle of chronic inflammation and inflammatory response, also involving nuclear factor kappa B (NF-κB) and the receptor for advanced glycation endproducts (RAGE). Preliminary research purportedly suggests that regulation of NF-κB or RAGE activity may reduce amyloid-beta accumulation and subsequently prevent or minimize cognitive and behavioral symptoms associated with AD. TTP448 is a small molecule drug purported to block endogenous ligands, including amyloid-beta, from binding to RAGE. In late-phase clinical trials, TTP448 is administered orally, 5 mg, once daily, for 18 months. TransTech Pharma, Inc., High Point, NC Phase III trial ongoing; FDA granted fast-track status	Donepezil Galantamine Rivastigmine	Reduced amyloid plaque accumulation Reduced caregiver burden Reduced cognitive decline Improved quality of life

Table 20. AHRQ Priority Condition: 05 Depression and Other Mental Health Disorders: 2 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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, 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 Phase III trial ongoing; 12 phase III trials (pivotal clinical development program) planned and ongoing; FDA granted fast-track status	Drugs: Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors Tricyclic antidepressants Procedures: Deep brain stimulation Electroconvulsive therapy Transcranial magnetic stimulation (investigational) Vagus nerve stimulation Psychotherapy	Improved Hamilton Depression Rating Scale scores Improved Montgomery-Asberg Depression Rating Scale scores Reduced symptom severity 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 trial 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	Reduced symptoms 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: 1 Intervention

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 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 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	Islet cell transplantation Pancreas transplantation	Increased beta cell function Improved glycemic control Reduced or eliminated need for exogenous insulin

Table 23. AHRQ Priority Condition: 08 Functional Limitations and Disability: 4 Interventions

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. Approximately 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; FDA granted orphan drug status; May 2014, European Medicines Agency granted marketing approval	Drisapersen (in development for DMD) Eteplirsen (in development for DMD) Idebenone (in development for DMD) Palliative care Physical therapy Respiratory support (respirator/ ventilators) Symptom control using corticosteroids and beta-2 agonists	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
Hypercaloric diet for treatment of amyotrophic lateral sclerosis	Patients in whom 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 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
Poloxamer compound (MST-188) 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, red blood cells are more susceptible to oxidative damage, which alters their properties leading to vaso-occlusion. A vaso-occlusion crisis (VOC) can cause severe pain and require hospitalization. Patients may progress to organ failure and early death. Despite advancements in managing complications of SCD (i.e., pain crises), the only drug FDA approved for treatment is hydroxyurea. MST-188 is a surfactant-containing, hydrophilic poloxamer that limits adhesion of sickled cells to each other and vascular endothelium, actions responsible for VOC. MST-188 may shorten duration of painful VOC and may not lead to adverse effects associated with available treatments for SCD. In clinical trials, MST-188 is administered intravenously by continuous infusion of 100 mg/kg/hr for 1 hour followed by 30 mg/kg for up to 48 hours. Mast Therapeutics, Inc., San Diego, CA Phase III trial 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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Safinamide for adjunctive treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	Up to 1 million Americans have 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 can also have severe side effects such as dyskinesia and must have dosages closely monitored and adjusted. Other pharmaceuticals, including pramipexole and rasagiline mesylate, have been prescribed, but have demonstrated poor efficacy at low dosage. Safinamide, a selective, reversible monoamine oxidase B (MAO-B) inhibitor, purportedly treats PD through a dual mechanism of action, acting to enhance dopaminergic functioning (through reducing dopamine degradation) and inhibit excessive glutamate release; it is intended for use as a treatment across all stages of PD. Safinamide is also purported to increase patient "on" times, when interventions are capable of reducing PD-related symptoms, and to reduce severe side effects associated with standard PD monotherapies. In clinical trials, safinamide is administered orally, once daily, as an adjunctive therapy to other prescribed medications. Newron Pharmaceuticals S.p.A., Bresso, Italy (developer and manufacturer) Zambon Co., S.p.A., Bresso, Italy (pending U.S. licensee) Meiji Seika Kaisha, Ltd., a subsidiary of Meiji Holdings Co., Ltd., Tokyo, Japan (Asian market licensee) Phase III trials completed; May 2014, Newron submitted a new drug application to FDA	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)	Improved motor skills Improved symptoms Reduced disease progression Reduced incidence/severity of levodopa-induced dyskinesia Improved quality of life

Table 24. 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
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 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	Standard immunosuppression followed by low-dose immunosuppression	Reduced rate of BK virus nephropathy Reduced rate of post-transplant complications

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Eravacycline for treatment of life-threatening infections	Patients in whom life-threatening infections have been diagnosed	Eravacycline is fully synthetic antibiotic derived from tetracycline purported to have very–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 first-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, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecium, Enterococcus faecalis*, and penicillin-resistant strains of *Streptococcus pneumonia*. Additionally, eravacycline is being evaluated as an empiric countermeasure for inhalation disease caused by *Bacillus anthracis*, *Francisella tularensis,* or *Yersinia pestis*. In clinical trials, eravacycline was administered intravenously, 1 mg/kg, twice daily; or 1.5 mg/kg, intravenously, once daily, plus 200–250 mg orally, twice daily, as monotherapy. Tetraphase Pharmaceuticals, Watertown, MA Phase III trials ongoing	Carbapenems Levofloxacin Tigecycline	Improved clinical response Reduced mortality
Fidaxomicin (Dificid) to prevent *Clostridium difficile* infection after bone marrow or stem cell transplantation	Patients undergoing bone marrow or hematopoietic stem cell transplantation	Patients who undergo bone marrow transplantation or hematopoietic stem cell transplantation are placed on immunosuppressive therapy, which places them at risk for serious infections, including *Clostridium difficile* infection. Infection can result in significant morbidity, mortality, and costs. Fidaxomicin (Dificid®) is a 1st-in-class macrocyclic antibiotic that inhibits bacterial RNA polymerase. Fidaxomicin has a narrow spectrum and selectively eradicates *C. difficile* infection with minimal disruption to the normal intestinal flora, which could facilitate prophylactic use. Administered orally, 200 mg, once daily with fluoroquinolone therapy. Optimer Pharmaceuticals, Inc., San Diego, CA Phase IIIb trial ongoing (DEFLECT-1); 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
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 about 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

Table 25. 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

Table 26. 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

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: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mepolizumab (Bosatria) for treatment of COPD	Patients in whom chronic obstructive pulmonary disease (COPD) has been diagnosed	Patients experiencing severe acute exacerbations of COPD have a greater 30-day mortality rate than patients experiencing acute myocardial infarction. Acute exacerbations of COPD dramatically change the course of the disease and are associated with a rapid decline in lung function and worsening quality of life; better treatments for COPD management are needed. Mepolizumab (Bosatria®) 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, administered subcutaneously, 100 mg or 300 mg, once every 4 weeks. GlaxoSmithKline, Middlesex, UK Phase III trial recruiting	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

Table 29. AHRQ Priority Condition: 14 Substance Abuse: 2 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 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. Kaléo, Richmond, VA Apr 2014, FDA approved Evzio for emergency treatment given by nonclinicians of known or suspected opioid overdose	Immediate professional medical care	Reduced opioid overdose mortality rate
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 available, 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; Cleveland Clinic may undertake additional clinical trials to study larger patient populations, patients without comorbid cirrhosis, and smokers	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)

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: 48 Interventions

Table 31. AHRQ Priority Condition: 01 Arthritis and Nontraumatic Joint: 2 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Apremilast (Otezla) for treatment of psoriatic arthritis	Patients in whom psoriatic arthritis has been diagnosed	In a subset of patients, psoriatic arthritis can progress to severe and painful symptoms that, without effective treatment, can lead to deformity and disability of the hands and fingers. Available treatment can be suboptimal. Apremilast (Otezla®) purportedly inhibits phosphodiesterase type 4 (PDE-4 enzyme), which purportedly increases intracellular cAMP. cAMP is believed to modulate multiple inflammatory mediators. Recently approved by FDA, the drug became available in 10, 20, and 30 mg strengths to enable titrating the dosage over 6 days starting at 10 mg/day until reaching the optimal recommended dose of 30 mg twice daily. Celgene Corp., Summit, NJ Phase III trials completed; FDA approved Mar 2014 for treating adults who have active psoriatic arthritis	Apremilast Corticosteroids DMARDS (e.g., methotrexate, sulfasalazine) Immunosuppressants (e.g., azathioprine, cyclosporine, leflunomide) Nonsteroidal anti-inflammatory drugs Tumor necrosis factor-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	Experts commenting thought that the degree of benefit from this therapy made its potential impact only incremental, barring comparative trials demonstrating a clear safety benefit with superior or comparable efficacy.
Artificial cervical disc (Mobi-C) for treatment of 2-level degenerative disc disease	Patients in whom 2-level degenerative disc disease (DDD) has been diagnosed	Standard of care for 2-level cervical DDD includes anterior cervical discectomy and fusion surgery, which can reduce range of motion and lead to accelerated degeneration of adjacent discs and other complications. The Mobi-C® Cervical Disc (Mobi-C) is a cervical intervertebral disc prosthesis for both 1- and 2-level disc replacement. Mobi-C is made of superior and inferior cobalt-chromium-molybdenum alloy spinal plates coated with a titanium plasma spray and hydroxyapatite coating, and it has a mobile, polyethylene insert. The controlled mobility of the insert purportedly restores the physiologic instantaneous axis of rotation of the cervical vertebrae. By restoring physiologic function and providing necessary stability, the implant can be used for patients with multi-level cervical disc disease for which there are no approved cervical disc replacement therapies. LDR Holding Corp., Austin, TX FDA approved Aug 2013 for 1- and 2-level cervical intervertebral disc replacement from C3 to C7 in skeletally mature patients	Spinal fusion	Decreased pain Reduced disability Return to work Improved quality of life	Experts commenting thought this intervention had little impact potential because it is incremental to other cervical discs that could be used off-label at multiple disc levels; payers are not covering multi-level cervical disc replacement, and diffusion has lagged.

Table 32. AHRQ Priority Condition: 02 Cancer: 11 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Carfilzomib (Kyprolis) for treatment of multiple myeloma	Patients in whom recurrent or treatment-refractory multiple myeloma has been diagnosed	Patients with relapsed/refractory multiple myeloma have few treatment options and median survival of less than 1 year. Carfilzomib (Kyprolis™) is a small-molecule inhibitor of the proteasome; the proteasome is responsible for the degradation of cellular proteins, and inhibiting it can lead to accumulation of unwanted proteins, cell cycle arrest, and apoptosis. Product labeling states that carfilzomib is administered intravenously over 2–10 minutes on 2 consecutive days each week for 3 weeks (days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (days 17–28) with a recommended cycle 1 dose of 20 mg/m^2/day and if tolerated increased for cycle 2 and subsequent cycles doses to 27 mg/m^2/day. Onyx Pharmaceuticals, Inc., subsidiary of Amgen, Inc., Thousand Oaks, CA FDA granted accelerated approval Jul 2012 for patients "with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy"	Combination therapies Cytotoxic chemotherapies (bendamustine, cyclophosphamide, doxorubicin, melphalan, vincristine) Immunomodulatory drugs (lenalidomide, pomalidomide, thalidomide) Proteasome inhibitors (bortezomib) Steroids (dexamethasone, prednisone)	Increased overall survival Increased progression-free survival Improved quality of life	Tracked 2 years after FDA approval; no longer meets horizon scanning criteria for tracking.
Doxepin oral rinse for treatment of radiation therapy–associated oral mucositis	Patients experiencing oral mucositis resulting from radiation therapy for head or neck cancer	Oral mucositis is a complication commonly experienced by patients undergoing radiation therapy for head or neck cancers. Significant mouth pain is associated with oral mucositis, and it causes difficulty eating and drinking and impairs quality of life. Current treatments for oral mucositis such as narcotics and lidocaine are associated with significant side effects and limited efficacy. In a phase III trial, a daily oral rinse containing doxepin, a tricyclic antidepressant, significantly improved mouth pain associated with oral mucositis. North Central Cancer Treatment Group (National Cancer Institute and Mayo Clinic), Rochester, MN Phase III trial ongoing	Lidocaine Narcotics	Decreased pain and oral side effects Improved ability to eat and drink Improved treatment adherence Improved quality of life	Experts commenting thought doxepin little high-impact potential because other therapies are available for oral mucositis.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Electronic brachytherapy (Esteya System, eBx System) for treatment of nonmelanoma skin cancers	Patients in whom nonmelanoma skin cancers have been diagnosed	Surgical resection is an effective treatment option for nonmelanoma skin cancers, but it may not be appropriate for treating lesions in anatomical areas with difficult wound closures or in areas prone to unwanted scarring (i.e., lesions near the eyes or on the face or hands). High-dose rate (HDR) radiotherapy is an effective treatment option for these lesions. Several manufacturers have created electronic brachytherapy devices that deliver targeted HDR brachytherapy to skin lesions. These devices include the Esteya and eBx systems, which have a purported high treatment-success rate with minimal scarring and reduced radiation exposure to healthy tissues. Nucletron, an Elekta company, Stockholm, Sweden (Esteya system) Xoft subsidiary of iCAD, Inc., Nashua, NH (eBx system) Both devices have FDA 510(k) marketing clearance	Surgical resection	Reduced scarring Reduced procedure recovery time Improved quality of life	Further searches by the horizon scanning team found that a similar device for treating melanoma had been approved several years ago; so, this device does not meet horizon scanning criteria for inclusion.
Everolimus (Afinitor) for treatment of estrogen receptor–positive breast cancer	Patients with metastatic estrogen receptor–positive breast cancer that has progressed after treatment with 1st-line aromatase inhibitors	For patients whose breast cancer progresses after 1st-line treatment with antiestrogen therapy, therapies with improved response rates are needed. Everolimus (Afinitor®) is a small-molecule inhibitor of the protein mTOR, which is a central regulator of cell growth. Inhibition of mTOR by everolimus has been demonstrated to be effective in treating multiple cancer types (e.g., renal cell carcinoma, astrocytoma). Everolimus is approved for treating hormone receptor–positive, HER2-negative breast cancer in addition to several other disease indications; it is administered at a dose of 10 mg, orally, once daily. Novartis International AG, Basel, Switzerland FDA approved Jul 2012 for treating postmenopausal women with advanced hormone receptor–positive, HER2-negative breast cancer in combination with exemestane after treatment with letrozole or anastrozole has failed	Exemestane monotherapy	Increased overall survival Increased progression-free survival Improved quality of life	Tracked 2 years after FDA approval; 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
Immature PSA ([-2]proPSA) assay as a decision aid regarding prostate cancer biopsy	Patients with serum prostate-specific antigen (PSA) levels of 4–10 ng/mL but normal results on digital rectal examination who must decide whether to undergo prostate biopsy	Prostate cancer screening using serum PSA is problematic because of its inability to distinguish between benign prostate conditions and prostate cancer. This exposes many men without prostate cancer to unnecessary prostate biopsies. [-2]proPSA is a partially processed form of PSA purported to be elevated in patients with prostate cancer that has the potential to improve upon the specificity of existing PSA-based screening. The [-2]proPSA test measures levels of the analyte using an immunoassay. Results of the assay are combined with total PSA and free PSA measurements obtained from the same sample to generate a "Prostate Health Index," which purportedly indicates the likelihood of prostate cancer. Beckman Coulter, Inc., Brea, CA FDA approved Jul 2012 as "an aid in distinguishing prostate cancer from benign prostatic conditions, for prostate cancer detection in men aged 50 years and older with total PSA between 4.0 and 10.0 ng/mL, and with digital rectal examination findings that are not suspicious for cancer"; available in Europe since 2010	PSA testing alone Free PSA testing alone Percent-free PSA testing Prostate cancer antigen 3 (PCA3) testing	Improved positive and negative predictive values Improved sensitivity and specificity Reduced number of unnecessary biopsies	Tracked 2 years after FDA approval; 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
Magnetic resonance imaging–ultrasound image fusion for image-guided prostate biopsy	Patients in whom prostate cancer is suspected, based on elevated prostate-specific antigen levels or abnormal digital rectal exam	Transrectal ultrasound (TRUS)-guided biopsy has been the standard of care for many years. However, TRUS cannot discriminate normal tissue from cancerous tissue; therefore, a random sampling procedure is used and some cancers may be missed. MRI has the potential to identify prostate tissue that may be cancerous, and some institutions have adopted the use of MRI-guided biopsy. Although this procedure may improve cancer detection rates, MRI-guided biopsy is expensive, time consuming, and cumbersome because it must be performed within the MRI machine gantry. A new procedure uses MRI data to guide prostate biopsies performed in an office setting by a urologist—rather than by a radiologist—followed by fusion of MRI image data with TRUS image data. It might enable evaluation of areas of suspicion that were identified using MRI to be targeted using TRUS-guided biopsy. Philips Healthcare unit of Royal Philips Electronics, Amsterdam, the Netherlands UroNav system received FDA approval in 2005; Phase III trial ongoing; pilot studies completed by multiple institutions (e.g., Kyoto Prefectural University of Medicine, Kyoto, Japan; University of Regensburg, Regensburg, Germany)	MRI-guided biopsy TRUS-guided biopsy	Improved positive and negative predictive values Improved sensitivity and specificity	Although some trials are ongoing for this technology, detailed searches revealed that some of these fusion devices have been approved since 2005 to assess prostate health. Technology does not meet horizon scanning system criteria for inclusion.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Pertuzumab (Perjeta) for treatment of HER2-positive breast cancer	Patients with metastatic, HER2-positive breast cancer who are receiving 1st-line trastuzumab and docetaxel and patients with high-risk, early stage, HER2-positive breast cancer who are receiving neoadjuvant treatment	No curative treatment for patients with metastatic breast cancer has been identified, and patients with HER2-positive breast cancer receiving trastuzumab-based chemotherapy have median survival times of only about 3 years. Trastuzumab is an FDA-approved monoclonal antibody specific for HER2 that purportedly functions by causing a reduction in the level of HER2 protein at the cell surface and by inhibiting proteolytic cleavage and release of the extracellular domain of HER2. Pertuzumab (Perjeta®) is a novel HER2-specific monoclonal antibody that binds to a different site on the HER2 extracellular domain; pertuzumab purportedly functions by inhibiting the heterodimerization of HER2 with other HER receptors, which is required for HER2 activation. Originally tested as a monotherapy with limited benefit, pertuzumab is approved for use in combination with trastuzumab for more comprehensive inhibition of HER2 activity. Pertuzumab is administered in an initial 840 mg dose, intravenously, then at a dose of 420 mg, intravenously, once every 3 weeks. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland FDA approved Jun 2012 for use in combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer; FDA granted accelerated approval Sept 2013 for neoadjuvant treatment in patients with high-risk, HER2-positive early stage breast cancer	Trastuzumab plus capecitabine, docetaxel, or vinorelbine Trastuzumab plus paclitaxel with or without carboplatin	Increased overall survival Increased progression-free survival Improved quality of life	Tracked 2 years after FDA approval; 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
Reconstructive laryngeal surgery after treatment of malignancies in the cricoid area	Patients undergoing reconstructive surgery after surgery for cancer in the cricoid cartilage area	Often, malignancies of the cricoid area (i.e., chondrosarcoma) require complete laryngectomy, forcing patients to communicate with voice prostheses or alternative electronic devices. A University of Michigan surgeon has created a surgical procedure that involves resecting the tumor and surrounding cricoid cartilage, harvesting the tip of the patient's shoulder blade (selected for its curvature and blood supply from surrounding muscle), reshaping the bone piece to match the shape of resected cartilage, and transplanting the portion of bone and muscle into the voice box. University of Michigan, Ann Arbor; Douglas Chepeha, M.D. 1 case report	Laryngectomy	Preserved larynx and reconstructed cricoid Improved quality of life	Further research by the horizon scanning team found no additional published reports of further development since initiating tracking 2 years ago.
ReMission 2 mobile gaming app to improve treatment adherence in adolescents and young adults with cancer	Adolescents and young adults (AYAs) in whom cancer has been diagnosed	AYAs undergoing treatment for cancer have unique care needs that often go unmet in traditional pediatric or adult cancer units. Treatment adherence and psychological issues are of particular concern in this patient population. ReMission 2: Nanobot's Revenge (Re-mission 2) is a mobile gaming application that is designed to improve behavioral outcomes in AYAs with cancer. In ReMission 2, users pilot a microscopic robot as she travels through the bodies of fictional cancer patients, combatting cancer cells and battling the side effects of cancer and cancer treatments. The program purportedly improves treatment adherence, patients' cancer knowledge and self-efficacy, and emotional state. HopeLab, Redwood City, CA, in collaboration with CIGNA Corp., Bloomfield, CT Unphased, randomized, controlled trial completed; freely available	Standard education programs and resources (e.g., patient counseling and education)	Improved health outcomes Improved treatment adherence Improved self-efficacy Improved quality of life	Further research by the horizon scanning team found that this is a second generation game of a game issued several years ago and is thus incremental and does not meet horizon scanning criteria for inclusion.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Therapeutic vaccine (GSK1572932A) for MAGE-A3-positive nonsmall cell lung cancer	Patients with stage IB, II, or IIIA nonsmall cell lung cancer (NSCLC) who have undergone complete surgical resection. Patients' tumors must express the melanoma antigenic epitope (MAGE)-A3 biomarker	The 5-year survival rate for patients with advanced NSCLC is less than 15% with current treatments. MAGE-A3 is an antigen that is expressed by a variety of tumor cells, in particular about 20% of NSCLCs. GSK1572932A is a MAGE-A3 peptide vaccine that is intended to be given to patients who have tumors that express the MAGE-A3 marker. In a phase III trial, this immunotherapy was administered as an intramuscular injection in 13 doses. GlaxoSmithKline, Middlesex, UK Phase III trial complete; in Mar 2014, GlaxoSmithKline announced the trial did not meet its primary endpoints and trial was stopped because of insufficient treatment effect	No standard maintenance therapy in this setting	Increased disease-free survival Increased overall survival Increased progression-free survival Improved quality of life	GSK halted phase III MARGIT trial when it failed to meet its primary and secondary endpoints.
Vintafolide (Vynfinit) for treatment of platinum-resistant ovarian cancer	Patients with platinum-resistant ovarian cancer who have undergone 1 or 2 rounds of platinum-based chemotherapy	Patients with platinum-resistant ovarian cancer have a poor prognosis and few treatment options. Vintafolide (Vynfinit®) is a novel, small-molecule drug conjugate that uses a peptide linker to couple a targeting ligand to a cytotoxic agent. In vintafolide, the targeting ligand is specific for the folate receptor, which is expressed on the majority of ovarian cancer cells, but not on cells of normal tissue. Based on this difference, the cytotoxic drug linked to the folate receptor targeting ligand might be preferentially delivered to malignant cells. The company is also developing a companion diagnostic test (Etarfolatide [Folcepri®]) to identify patients whose tumors express high levels of the folate receptor. In clinical trials, vintafolide is administered in combination with pegylated liposomal doxorubicin. It is administered 1 mg, intravenously, 5 days per week for the 1st 3 weeks of each 4-week cycle, then at a maintenance dose of 2.5 mg, 3 days per week, during weeks 1 and 3 of each 4-week cycle. Endoctye, Inc., West Lafayette, IN, in collaboration with Merck & Co., Inc., Whitehouse Station, NJ Phase III trial ongoing; phase III PROCEED trial halted	Docetaxel Etoposide Gemcitabine Paclitaxel Pegylated liposomal doxorubicin Topotecan	Increased overall survival Increased progression-free survival Improved quality of life	Phase III PROCEED trial terminated for failure to meet progression-free survival endpoint.

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
Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation	Patients in whom functional 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 Carillion mitral contour system is a nonsurgical, minimally invasive device intended to repair the mitral valve (implantable device and percutaneous delivery system). It consists of a proximal and distal anchor that are connected by a shaping ribbon. Using a percutaneous catheter delivery system, the device is positioned in the coronary sinus and great cardiac vein, thus plicating the tissue nearest to the mitral annulus. This action purports to reduce mitral annulus dilation, thus reducing functional mitral regurgitation. Cardiac Dimensions, Inc., Kirkland, WA FDA granted investigational device exemption to conduct U.S. clinical trials, but no trials are registered or ongoing in the U.S.; ongoing European trials not registered in U.S. National Clinical Trials database; Conformité Européene (CE) marked in 2009	Optimal medical management Minimally invasive surgery Open surgery	Reduced risk of cardiac events Reduced mitral regurgitation Reduced operative morbidity Reduced mortality Improved quality of life	Despite receiving FDA approval to conduct U.S. clinical trials under investigational device exemption, the company has not begun trials in the 3 years that the horizon scanning system has tracked this technology.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Renal denervation (Symplicity System) for treatment of heart failure	Patients in whom treatment-resistant heart failure (HF) and renal impairment have 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%. Increased sympathetic nervous system (SNS) activity, especially in the heart and kidneys, is associated with reduced cardiac output and renal function. HF is primarily managed with pharmacotherapy, such as beta blockers, which address a patient's SNS; however, outcomes are still suboptimal, possibly because of beta blockers' incomplete blockage of the SNS. The Symplicity™ Renal Denervation System consists of a catheter and generator. A physician uses the system to endovascularly deliver low-power radiofrequency energy to the renal nerves, deactivating them. According to the manufacturer, this, in turn, reduces the activity of the SNS, potentially providing benefit to patients. Medtronic, Inc., Minneapolis, MN Phase IV SYMPLICITY-HF trial ongoing in Australia	Pharmacotherapy (e.g., beta blockers) Barostim device (in development)	Reduced SNS activity Decreased HF-related morbidity Increased survival Improved quality of life	Development ongoing only outside U.S.
Treprostinil diolamine (Orenitram) 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. No approved oral prostacyclin therapies are available in the U.S.; only intravenous, injected, or inhaled formulations are available. Sustained release oral treprostinil diolamine (Orenitram™) is the 1st oral prostacyclin for PAH and is intended for use early in the PAH disease continuum. Treprostinil diolamine vasodilates pulmonary and systemic arterial vascular beds and inhibits platelet aggregation. It is intended as an add-on therapy to current oral therapies. It is orally administered at twice-daily doses of 0.125, 0.25, 1, or 2.5 mg. United Therapeutics Corp., Silver Spring, MD FDA approved Dec 2013 for treating patients with PAH to improve exercise capacity; phase III trials ongoing	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalization	Expert comments indicated no potential for high impact.

Table 34. AHRQ Priority Condition: 04 Dementia (including Alzheimer's): 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: 2 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Mifepristone (Korlym) for treatment of psychotic depression	Patients in whom psychotic depression has been diagnosed	No treatments are FDA approved for psychotic depression. This intervention represents a novel mechanism of action for the condition. Mifepristone (Korlym™, previously Corlux) is a cortisol antagonist. Patients with psychotic depression have higher levels of cortisol, a hormone that regulates bodily reactions to stress, and elevated levels of circulating cortisol can produce psychiatric disorders. The drug is intended to be administered orally, 1,200 mg, once daily. Corcept Therapeutics, Inc., Menlo Park, CA Manufactured abandoned expanded indication after failure to meet endpoints in phase III trials	Antipsychotics in combination with antidepressants Electroconvulsive therapy	Improvement in psychotic symptoms Fewer suicide attempts and completed suicides Improved quality of life	May 2014, Corcept announced it was halting development for this indication because preliminary data showed failure to meet primary endpoints.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Mobile phone therapy for bulimia nervosa	Patients in whom bulimia nervosa has been diagnosed	In people with bulimia nervosa, feelings of shame affect willingness to undergo treatment; access to treatment and its duration are significant issues with eating disorders because of their chronic nature. New behavior therapy approaches are needed that engage participants. Text messaging has been used as an adjunct and followup to treatment. In 1 program, participants sent a nightly text message to clinicians to report the number of binge-eating and purging episodes and rate their urges to binge and purge. They received automatic feedback messages tailored to their self-reported symptoms. This approach is being studied in conjunction with a cognitive behavior therapy program to keep patients engaged in therapy. In another program, text messaging was used for followup (step-down therapy) with patients after discharge from residential treatment. University of North Carolina at Chapel Hill Institute of Psychiatry, London, UK Center for Psychotherapy Research, University Hospital Heidelberg, Heidelberg, Germany Pilot studies completed	Antidepressants Nutritional counseling Psychological counseling	Reduced number of binge-eating and purging episodes Improved symptoms of depression, eating disorder, and night eating Enhanced self-monitoring and treatment, leading to improved attendance, adherence, and engagement in treatment Increased remission rates	Tracking and searches to determine further research and adoption over more than 2 years has not identified further research or diffusion; no new studies have been published on this approach since 2010.

Table 36. AHRQ Priority Condition: 06 Developmental Delays, Attention-Deficit Hyperactivity Disorder, and Autism: 2 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Mavoglurant for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	No cure exists for FXS; medications and behavior interventions alleviate individual symptoms but do not address the syndrome's cause. Individuals with FXS have DNA mutations in the *FMR1* gene that basically turn off the gene; it is the most common known heritable cause of cognitive and behavioral disability. Normal *FMR1* gene produces a protein that controls the synthesis of proteins at synapses that are stimulated via metabotropic glutamate receptors (mGluRs); without this control provided by the FMR1 protein, synaptic protein synthesis is excessive and connections do not develop normally. Mavoglurant (AFQ056), a selective, noncompetitive antagonist of the metabotropic glutamate receptor 5 (mGluR5), can potentially normalize the excessive protein synthesis and control symptoms associated with FXS. In trials, it is taken as an oral capsule, at 25, 50, or 150 mg, twice a day. Novartis International AG, Basel, Switzerland Phase II and III trials ongoing in adolescent and adult patients; drug also under study for L-dopa–induced dyskinesia in Parkinson's disease	Physical and behavior interventions addressing speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Pharmacotherapy (e.g., antipsychotics, central nervous system stimulants, clonidine [Cazares®], folic acid, selective serotonin reuptake inhibitors, melatonin)	Change from baseline in behavioral symptoms using the Aberrant Behavior Checklist	In May 2014, Novartis announced it was halting development after failed phase IIb/III trials.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Neuropsychiatric Interpretive Electroencephalograph Assessment Aid (NEBA) for assessment of attention deficit hyperactivity disorder	Children in whom attention-deficit hyperactivity disorder (ADHD) is suspected	ADHD is a commonly diagnosed neurobehavioral disorder of childhood and often persists into adulthood. ADHD can lead to medical, emotional, behavioral, social, and academic consequences for the affected person. Misdiagnosis of ADHD is common because the symptoms of the disorder—inattention, impulsivity, and hyperactivity—are difficult to quantify, overlap with other disorders, and are complicated by co-occurring disorders. Misdiagnosis leads to ineffective treatments for patients, lower rates of symptom relief, and abuse of ADHD medications. The Neuropsychiatric Interpretive Electroencephalograph Assessment Aid (NEBA) is an electroencephalographic (EEG)-based ADHD assessment tool that uses an EEG device with standardized settings to measure theta and beta brainwaves through sensors placed on a child's head over 15–20 minutes. The makers of the device claim that this information, in conjunction with a standard clinical evaluation, can be used to help accurately diagnose ADHD in children. NEBA Health, LLC, Augusta, GA Jul 2013 received FDA marketing clearance through 510(k) de novo process	Clinical assessment alone Other EEG systems	Decreased abuse of ADHD medications Increased ADHD diagnostic accuracy Increased symptom relief Improved quality of life	Experts commenting on this intervention thought it has no high-impact potential.

Table 37. AHRQ Priority Condition: 07 Diabetes Mellitus: 5 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Buccal insulin (Oral-lyn) for treatment of type 1 or type 2 diabetes	Patients with type 1 diabetes mellitus (T1DM) or uncontrolled type 2 diabetes mellitus (T2DM) who require insulin	T1DM accounts for about 5% of all diagnosed cases of diabetes mellitus, whereas T2DM makes up 95% of diagnosed diabetes mellitus. Nearly 26 million children and adults in the U.S., or 8.3% of the population, have diabetes mellitus. Approximately 18.8 million people have diagnosed diabetes mellitus, and in an additional 7.0 million people, 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 in some cases, taking insulin. Buccal insulin (Oral-lyn™ delivered via RapidMist™ device) is a fast-acting insulin that is sprayed in aerosol form on the inside of the cheek (buccal mucosa) to allow rapid absorption into bloodstream; it has a short duration of activity. It is intended for dosing before and after meals, for use adjunctively with long-acting, injectable or infused insulin, and as a substitute for injectable short-acting insulin. Buccal insulin is not intended to reach the lungs and may pose less risk of respiratory or pulmonary complications than inhaled insulin does. Generex Biotechnology Corp., Toronto, Ontario, Canada Phase III trial completed in India; positive results reported Jul 2013; Sept 2012 company announced it would conduct several short studies to meet FDA requirements; FDA approved in 2009 under the treatment investigational new drug program, which allowed Generex to provide expanded access to people with serious or life-threatening T1DM or T2DM who have no satisfactory alternative treatments and who are not eligible for participation in the company's ongoing phase III clinical trial of the drug; as of Apr 2014, the trial listing in National Clinical Trials database stated "Expanded access is no longer available for this treatment"	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 glycemic excursions related to meals Prevented onset of T2DM in prediabetic individuals Delayed insulin dependence in T2DM Improved quality of life	Ora-lyn has had Treatment IND status from FDA since 2009, which provides expanded access for an as-yet unapproved drug; development to obtain full FDA marketing approval has not progressed since 2009; expert comments deemed intervention to have little potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Cogenzia gentamicin antimicrobial sponge for treatment of infected diabetic foot ulcers	Patients in whom a moderately infected diabetic foot ulcer has been diagnosed	Approximately 3 million patients a year develop diabetic foot ulcers, and an estimated 15% require amputation of an appendage. Current treatments for diabetic foot ulcers achieve complete healing less than 30% of the time; effective treatments are needed to accelerate and complete the wound healing process. Cogenzia™ is a gentamicin-impregnated antimicrobial biodegradable sponge using the manufacturer's proprietary collagen-based drug delivery technology, CollaRx. The sponge is intended to deliver high levels of gentamicin to the wound site while avoiding systemic side effects and being resorbed. It is used in conjunction with standard wound care and administration of an oral antibiotic (levofloxacin). It is under study in 2 sizes, both of which deliver 50 mg of gentamicin sulfate. Innocoll, Inc., Ashburn, VA Phase III trial completed	Levofloxacin monotherapy Standard wound care and systemic antibiotics	Improved clinical cure rate Improved pathogen response Pathogen eradication Decreased wound surface area (increased healing rate)	Further research by the horizon scanning team and consultation with its chronic wound healing technology expert found that this technology does not address an important unmet need because many other antimicrobial wound dressing options are available.
Grafix cryopreserved placental membrane extracellular matrix for treatment of diabetic foot ulcers	Patients in whom diabetic foot ulcers have been diagnosed	Approximately 3 million patients a year have diabetic foot ulcers, and an estimated 15% will require amputation. Current treatments for diabetic foot ulcers achieve complete healing less than 30% of the time; effective treatments are needed to accelerate and complete the wound healing process. Grafix®, a cryopreserved placental membrane, is a 3-dimensional extracellular matrix intended to treat chronic diabetic foot ulcers. Grafix consists of allogeneic mesenchymal stem cells (MSC) and growth factors placed on a flexible support placental membrane. The growth factors and proteins purportedly aid cell proliferation, maturation, and mitigation. MSCs, neonatal fibroblasts, and epithelial cells purportedly coordinate the tissue repair process. In a clinical trial, Grafix was administered weekly for 12 weeks. Osiris Therapeutics, Inc., Columbia, MD Phase IV trial completed; the company stated that FDA regulates Grafix as a human cellular and tissue product (HC/TP), but FDA issued a letter to the company in Oct 2013 stating that "your products, Grafix PRIME®, Grafix CORE®, and Grafix XC™, do not meet the criterion in 21 CFR 1271.10(a)(4)(ii) [for HC/TP] because the products are dependent upon the metabolic activity of living cells for their primary function, and are not intended for autologous use or allogeneic use in a first or second degree relative."	Apligraf Carbapenems Cephalosporins Clindamycin Dermagraft EndoForm™ Dermal Template Fluoroquinolones Linezolid Lipopeptides Metronidazole Oasis Wound Matric Penicillins TheraSkin® Topical antibiotics Topical antiseptics Vancomycin	Increased healing rate Improved wound closure Improved quality of life	Further research by the horizon scanning team found that this product has been available and commercially marketed as an HC/TP for some time; thus it does not meet criteria for inclusion in the horizon scanning system. The company stated that it intended to continue marketing Grafix after receiving the FDA letter in Oct 2013.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Ranibizumab (Lucentis) for treatment of diabetic macular edema	Patients in whom clinically significant diabetic macular edema (DME) has been diagnosed	DME affects an estimated 560,000 patients in the U.S. Laser-based treatments stabilize but do not improve vision and are associated with additional loss of clarity, color, and peripheral vision. Ranibizumab (Lucentis®) is a monoclonal antibody fragment (Fab) derived from the same parent murine antibody as bevacizumab (Avastin®). It is an antiangiogenic that has been FDA approved to treat the "wet" type of age-related macular degeneration, a common form of age-related vision loss. DME was a new indication for ranibizumab, and it was the 1st FDA-approved medication for DME. The approved dosage is 0.3 mg, once monthly, administered by injection into the eye. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Novartis International AG, Basel, Switzerland FDA approved Aug 2012 for treating DME	Intravitreal triamcinolone acetonide with or without laser photocoagulation Laser photocoagulation Pharmacotherapy (e.g., vascular endothelial growth factor antagonists)	Improved vision Stabilized vision Reduced side effects of existing treatment Improved quality of life	Tracked 2 years after FDA approval; no longer meets horizon scanning criteria for tracking.
SmartSensor electronic oral glucose tolerance test for detection of 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. Late diagnosis may occur for many reasons, including patient nonadherence with recommended screening (blood draw). The SmartSensor oral glucose tolerance test (OGTT) is a home-based diagnostic device used to screen for prediabetes and T2DM. The device is intended for use in the general population and purportedly is the first home-based OGTT. The SmartSensor OGTT is provided in a kit that consists of a timer, temperature sensor, glucose biosensors, and a detachable data record. Patients self-administer the SmartSensor OGTT without training by performing a traditional finger stick. Upon completion, the information is uploaded into a mobile application using the patient's smartphone and can be electronically transmitted to health care professionals. Patients also can detach the data record and mail to health care providers for processing. OGTT kits, including the glucose load (drink), are obtained from the patient's care provider. SmartSensor telemed, Ltd., Oxfordshire, UK Pilot trial completed; company plans to begin marketing the device in 2014	Standard oral glucose tolerance test	Improved patient access to care Earlier diagnosis Improved quality of life	Upon further research, the team determined that this technology is not being developed for the U.S. market at this time; its development for market appears to limited to the U.K.

Table 38. AHRQ Priority Condition: 08 Functional Limitations and Disability: 10 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Electronic pressure sensing mat (MAP System) for prevention of decubitus ulcers	Patients at risk of developing decubitus ulcers	According to The Joint Commission, about 2.5 million patients are treated for pressure ulcers in acute-care hospitals each year, and the incidence is growing at a significant rate. Prevention and early diagnosis remain a challenge; visual assessment is the current standard of detection. The mattress-sensing MAP System is an electronic sheet with thousands of sensors that is placed over the hospital bed mattress. It generates an electrical signal proportional to the pressure, creating a signal that is displayed using a specific color scheme to identify high to low pressure points. Areas under high pressure or shear forces increase the risk of developing pressure ulcers. The MAP System has an alarm to ensure patients are repositioned on a regular basis and it keeps a log of pressure data to ensure continuous care across worker shifts. Henry Ford Health System, Detroit, MI (investigator) Enhanced Surface Dynamics, Inc., Nashville, TN, parent company of Wellsense (manufacturer) Phase II trial complete; FDA classified as Class I exempt device; available for marketing since 2012; Conformité Européene (CE) marked	Visual assessment Subepidermal moisture scanner (in development)	Prevention or early treatment of decubitus ulcers Reduced hospital stay from complications Reduced morbidity and mortality	Multiple similar products are available; does not meet horizon scanning criteria for tracking.
Gel stent implant (XEN 45) for treatment-refractory glaucoma	Patients in whom treatment-refractory glaucoma has been diagnosed	Glaucoma is treatable, but incurable. Available treatments may fail to work sufficiently, leading to disease progression and blindness. The goal of treatment is to reduce intraocular pressure (IOP) through use of medications or, if medications don't work, surgery in some patients. Tiny implantable stents are also available to aid aqueous outflow and relieve IOP. The XEN 45 gel stent is derived from collagen and can reportedly be implanted using a minimally invasive, corneal incision procedure. The stent is meant to be noninflammatory and to conform to the shape of the eye. The stent purportedly allows the aqueous fluid to drain into the subconjunctival space. It is intended as a permanent implant. AqueSys, Inc., Aliso Viejo, CA Phase III trial ongoing	iStent implant Laser surgery Pharmacotherapy (e.g., eye drops) Surgical therapy Trabectome (device)	Preserved vision Reduced IOP Slowed or halted disease progression	Upon further research, the horizon scanning team determined this stent to be similar to FDA-approved iStent technology for treatment of glaucoma, which reached the market first; thus, this technology 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
Micro-bypass implant (iStent Trabecular Micro-Bypass Stent System) for treatment of glaucoma	Patients undergoing cataract surgery who also have mild to moderate open-angle glaucoma	iStent Trabecular Micro-Bypass Stent System is intended for implantation during cataract surgery in patients with or at risk of developing open-angle glaucoma. iStent is designed to increase aqueous outflow by shunting aqueous humor from the anterior chamber to the Schlemm's canal, bypassing the trabecular meshwork. Using this procedure avoids having to move the iris, conjunctiva, or sclera and preserves other surgical and medical options for treating glaucoma. Glaukos Corp., Laguna Hills, CA FDA approved Jun 2012 "for use in combination with cataract surgery to reduce pressure inside the eye (intraocular pressure) in adult patients with mild or moderate open-angle glaucoma and a cataract who are being treated with medication to reduce intraocular pressure." Conformité Européene (CE) marked in select nations in Europe; approved in Canada	Pharmacotherapy (e.g., eye drops) Surgical therapy Trabectome (device)	Preserved vision Reduced elevated or uncontrolled IOP	Tracked 2 years after FDA approval; no longer meets horizon scanning criteria for tracking.
Off-label fingolimod (Gilenya) for treatment of amyotrophic lateral sclerosis	Adult patients in whom 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 a single agent (riluzole) is 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. Fingolimod (Gilenya®) is an agonist to sphingosine 1-phosphate receptors on the surface of thymocytes and lymphocytes. This mechanism of action is thought to reduce the number of circulating lymphocytes available to cause autoimmune reactions and destroy nerve tissue. Reduced inflammatory reactions against peripheral nerves could reduce ALS symptoms. Administered orally, 0.5 mg, daily. ALS Therapy Development Institute, Cambridge, MA Georgia Regents University, Augusta Massachusetts General Hospital, Boston Methodist Neurological Institute, Houston, TX University of California, Irvine, Orange Phase II trial ongoing; FDA approved for treating relapsing-remitting multiple sclerosis	Physical and speech therapy Medications for symptoms (muscle cramps, constipation, fatigue, excessive salivation, excessive phlegm, pain, depression) Riluzole (Rilutek®)	Reduced symptoms Slowed or halted disease progression Increased survival Improved quality of life	No significant development or noted diffusion (as an off-label intervention); no new data have been published.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Pasireotide (Signifor) for treatment of Cushing's disease	Patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative	The majority of Cushing's disease cases are caused by benign pituitary tumors that generate elevated levels of adrenocorticotropic hormone (ACTH). 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. Pasireotide (Signifor®) is a cyclohexapeptide engineered to bind to multiple somatostatin receptor subtypes to mimic the actions of natural somatostatin and has demonstrated the ability to inhibit ACTH secretion. Administered as a subcutaneous injection, twice daily; available in 3 doses: 0.3, 0.6, and 0.9 mg/dL. Novartis International AG, Basel, Switzerland FDA granted priority review, fast-track, and orphan drug statuses; FDA approved Dec 2012 for patients who do not benefit from surgery; FDA required 3 postmarket studies, which are ongoing ; approved in EU	Drugs: Ketoconazole Metyrapone Mitotane Radiation therapy Surgical therapy	Reduced ACTH levels Reduced morbidity from excess cortisol Improved quality of life	Experts commenting thought this intervention has no high-impact potential. High incidence of side effects such as hyperglycemia would limit patient acceptance and benefit; high cost and little data supporting efficacy mean low acceptance from physicians as well.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Pridopidine (Huntexil) for treatment of Huntington's disease	Patients in whom Huntington's disease (HD) has been diagnosed	No cure exists for HD, and current therapies only help to manage emotional and motor symptoms associated with the disease. Pridopidine (Huntexil®) is a small-molecule, dopamine stabilizer that purportedly increases or decreases dopamine to healthy levels in patients with HD. Pridopidine purportedly contrasts with neuroleptics that reduce dopamine activity regardless of baseline level. In clinical trials, pridopidine is administered orally, at doses of 45 or 67.5 mg, twice daily. Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel Phase III trials completed, but FDA and European Medicines Agency refused approval and requested additional phase III data; phase II open-label extension trial and new phase II trial ongoing; FDA granted orphan drug status	No FDA-approved treatments available for multiple HD symptoms Various drugs: Clonazepam Clozapine Diazepam Escitalopram Fluoxetine Haloperidol Sertraline Tetrabenazine Treatment approaches include: Occupational therapy Physical therapy Psychotherapy Speech therapy	Improved clinical global impression of change, cognitive function, behavior, and symptoms of depression and anxiety Improved voluntary motor function	Experts commenting thought this intervention has no high-impact potential. Additionally, FDA (and European Medicines Agency) have refused to approve manufacturer's submission without additional phase III data, which does not appear to be forthcoming, given registered clinical trial listings.
Recombinant porcine factor VIII (OBI-1) for treatment of acquired hemophilia A	Patients with acquired hemophilia A who develop immune reaction to human coagulation factor VIII	About 15% to 30% of patients with acquired hemophilia develop immune reaction to recombinant human coagulation factor VIII. Recombinant porcine coagulation factor VIII (OBI-1) is considered to be a physiologic replacement therapy that activates the natural hemostatic pathway without triggering an immune reaction. Administered as intravenous infusion every 2–3 hours for the 1st 24 hours of treatment. Initial dose is 200 units/kg, with variable followup doses. Baxter International, Inc., Deerfield, IL Phase II/III trial completed; Baxter submitted biologics license application to FDA Dec 2013; FDA granted orphan drug status, fast-track status, and priority review	Human coagulation factor VIIa	Adequate control of bleeding episodes Reduced morbidity and mortality	Experts commenting thought this intervention does not have high-impact potential. A similar treatment is on the market, so this is not addressing an unmet need and is not a novel option. This treatment will have no impact on costs or the way care is managed.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
SOLX gold shunt for treatment-refractory glaucoma	Patients in whom treatment-refractory glaucoma has been diagnosed	Investigators have not found a cure for glaucoma, and if untreated or refractory to treatment, it leads to blindness. The SOLX® Gold Shunt gold implant uses the eye's natural pressure differential to reduce intraocular pressure (IOP). The device is a flat, perforated, rectangular implant inserted between choroid layer and sclera in the trabecular meshwork area. It is differentiated from other surgical glaucoma options because it purportedly reduces IOP without creating a bleb, which is a source of serious complications, and can be used in patients with a wider range of IOP. SOLX, Inc., Waltham, MA Phase III trial ongoing; approved in Canada Aug 2009; Conformité Européene (CE) marked Oct 2005	Microstent Eye drops Surgical therapy Trabectome (device)	Preserved vision Reduced IOP	Horizon scanning team determined that this is similar to the iStent device, which timed out of the horizon scanning system in Jun 2014 because it has been tracked for 2 years after FDA approval.
Subepidermal moisture scanner (SEM) for prevention and early detection of decubitus ulcers	Patients at risk of developing decubitus ulcers	According to The Joint Commission, about 2.5 million patients are treated for pressure ulcers in acute-care hospitals each year, and the incidence is growing at a significant rate. Prevention and early diagnosis remain a challenge; visual assessment is the current standard of detection. The Sub-Epidermal Moisture (SEM) scanner is a handheld device intended to measure a tissue's dielectric properties and estimate the subepidermal moisture to detect potential decubitus ulcers before they become visible. This device can transmit data wirelessly to a storage system for analysis. Bruin Biometrics, LLC, Los Angeles, CA Pilot trial completed; other trials ongoing; CE Mark Nov 2013	Electronic pressure sensing mat Visual assessment	Prevention or early treatment of decubitus ulcers Reduced hospital stay from complications of decubitus ulcers Reduced morbidity and mortality from complications	Incremental to available MoistureMeterD, which also measures dielectric properties in biological tissues.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Tozadenant (SYN115) for treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	Up to 1,000,000 Americans are currently diagnosed with Parkinson's disease (PD), and approximately 60,000 new cases are diagnosed yearly. Worldwide, 7-10 million patients have been diagnosed with PD. Patients with PD experience “on” times when medication reduces symptoms and “off” times when medication becomes ineffective and symptoms worsen before the next dose of medication can be administered. Treatments that can increase the “on” time could improve quality of life and management of the disease. Tozadenant (SYN115) is an oral, adenosine 2A (A2A) receptor antagonist intended to increase “on” time for patients taking levodopa; the striatopallidal output pathway synthesizes gamma aminobutyric acid (GABA) and enkephalin as neurotransmitters and expresses the A2A subtype of adenosine receptors. Pharmacologic inhibition of A2A adenosine receptors may inhibit the overactive striatal GABAergic blocking of neurons associated with PD. Biotie Therapies Corp., Turku, Finland UCB, Brussels, Belgium (licensed worldwide rights from Biotie) Phase II/III trial completed; phase III trial planned	Adenosine A2A receptor antagonist (in development) Dopamine agonists Glutamate receptor 5 modulators (in development) Israpidine (experimental) Levodopa/carbidopa Monoamine oxidase-B inhibitors Nicotinic receptor agonist (in development)	Improved motor skills Improved symptoms Reduced disease progression Reduced incidence/severity of levodopa-induced dyskinesia Improved quality of life	Development slowed because development rights have changed companies from UCB Pharma S.A. to Biotie Therapies Corp. Phase III development is not under way yet.

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
Deleobuvir for treatment of chronic hepatitis C 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 period of time are needed. Deleobuvir (BI 207127) is a nonnucleoside NS5B polymerase inhibitor intended to allosterically bind HCV RNA-dependent RNA polymerase and inhibit replication of the viral genome. Dosed 100, 200, 400, 800, or 1,200 mg, 3 times a day; may also be administered in an interferon (IFN)-free regimen with the NS3/4 protease inhibitor faldaprevir and ribavirin (RBV). Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials ongoing; FDA granted fast-track status in combination with faldaprevir in an IFN-free combination	Boceprevir IFN/RBV Simeprevir Sofosbuvir Telaprevir	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	Boehringer Ingelheim stopped development of deleobuvir and will be developing only faldaprevir used in combination with IFN and RBV.
Faldaprevir 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 period of time are needed. Faldaprevir is a NS3/4 protease inhibitor intended to block the activity of HCV protease, preventing functional viral particles from cleaving and maturing. Administered orally, 120 or 240 mg, once daily, in combination with the standard-of-care pegylated interferon plus ribavirin (IFN/RBV). Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials ongoing; FDA granted fast-track status in combination with standard of care and in IFN-free combination with deleobuvir	Boceprevir IFN/RBV Simeprevir Sofosbuvir Telaprevir	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	Faldaprevir will not be developed with deleobuvir; it will be developed only with IFN and RBV, which makes its impact incremental because many other available HCV drugs must be used with IFN/RBV.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
OraQuick in-home rapid test for detection of HIV infection	People who may have been exposed to HIV	Despite advances in treatment, prevention, detection, and education, HIV continues to spread, and better, rapid, early detection methods might help limit this spread. The OraQuick® In-Home HIV Test was adapted from the FDA-approved OraQuick rapid HIV test available since 2009 for use in clinics. The new test is an over-the-counter version for home use. To perform the test, individuals swab their upper and lower gums and place the swab into a vial of test fluid. Results (colored lines on the test strip) can be read within 20 minutes. A positive result is intended to signal the need for the patient to have followup testing by a health care provider. The kit includes an information booklet with directions to call the manufacturer's support center 24 hours a day, 7 days a week for counseling on the test results and referral to medical services. OraSure Technologies, Inc., Bethlehem, PA FDA approved Jul 2012	Home-based blood tests (mail-in) Clinic-based rapid test (OraQuick)	Reduced HIV transmission Earlier intervention to control viral load Increased HIV screening rate	Tracked 2 years after FDA approval; no longer meets horizon scanning criteria for tracking.
Private intensive care rooms to reduce hospital-acquired infections	Patients admitted to an intensive care unit (ICU)	Despite infection-control efforts, about 1/3 of patients admitted to an ICU contract an infection, which may increase length of stay, morbidity, and cost of care. Retrofitting ICUs to create single-patient rooms may help to better isolate patients and contain their infections or prevent them from contracting new infections. McGill University Health Centre, Montreal, Quebec, Canada Early adoption ongoing	Antimicrobial copper touch surfaces Standard infection control practices Portable pulsed xenon ultraviolet light added to terminal cleaning	Reduced hospital-acquired infection rates	Topic has been tracked since Dec 2011 and this approach is diffusing, especially when new construction occurs. Further data on additional tipping points unlikely.

Table 40. AHRQ Priority Condition: 10 Obesity: 3 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Aspiration system (AspireAssist) for treatment of obesity	Patients with body mass index (BMI) of 35–55 kg/m^2	The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Current surgical options for treating obesity have varying degrees of invasiveness, some of which are associated with significant adverse effects and others that have suboptimal efficacy. The AspireAssist™ Aspiration Therapy System is a weight loss device/system that reduces food portions after a meal by removing stomach food contents approximately 20 minutes after consumption, reducing the calories available for the body to absorb. Patients can control this process through an endoscopically-implanted tube that comes through the surface of the abdominal skin, where the opening is closed with a poker chip-sized valve (Skin-Port). Patients can dump "excess" food contents into a toilet. This process is reversible and the device can be implanted or explanted with the patient under conscious sedation. Aspire Bariatrics, Inc., King of Prussia, PA Pivotal U.S. trial ongoing; Conformité Européene (CE) marked Dec 2011	Deep brain stimulation Endoluminal sleeve (EndoBarrier) Gastric banding surgery Gastric pacemaker (in development) Intragastric balloons (in development) Pharmacotherapy Roux en Y bypass surgery Sleeve gastrectomy surgery Vagus nerve blocking	Decreased comorbidities Total weight loss Improved quality of life	Experts commented that they would be reluctant to offer this therapy because it could contribute to or exacerbate eating disorders. Archived because of low potential for impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Controlled-release phentermine-topiramate (Qsymia) for treatment of obesity	Overweight adults with body mass index (BMI) >27 kg/m^2 and a comorbidity or obese adults (BMI >30 kg/m^2)	The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Pharmacologic options have expanded with new drug approvals in 2012; however, competing approved drugs have significant potential side effects and work in only a proportion of patients taking them. Additional pharmacologic options are needed. Controlled-release phentermine-topiramate (Qsymia™) is a combination of the appetite suppressant phentermine (approved for short-term use in weight loss) and topiramate (an approved antiepileptic agent with known weight-loss side effects). It is a controlled-release pill that is intended to be taken once daily and in trials reportedly resulted in more weight loss by more patients than other available antiobesity drugs. The approved dosage is phentermine 3.75/topiramate 23 mg extended release for 14 days followed by phentermine 7.5/topiramate 46 mg extended release daily. Vivus, Inc., Mountain View, CA FDA approved Jul 2012 for "for chronic weight management in adults who are obese, or overweight with at least 1 weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia" with diet and lifestyle modification; obesity is defined as BMI ≥30 kg/m^2 and overweight is BMI ≥27 kg/m^2; the approval included a risk evaluation and mitigation strategy requiring physician training, physician registration, pregnancy avoidance counseling for patients of reproductive age on the drug, and dose-escalation strategy	5-HT_{2C} receptor agonist (Belviq®) Behavior and lifestyle modifications Combination norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (Contrave®; in development) Glucagon-like peptide 1 analog Liraglutide (Victoza®; in development)Pancreatic lipase inhibitor (orlistat, Xenical®) Surgical therapy (e.g., bariatric surgery)	Decreased comorbidities Improved quality of life Total weight loss	Tracked 2 years after FDA approval; 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
Lorcaserin (Belviq) for treatment of obesity	Overweight adults (body mass index [BMI] >27 kg/m^2) with a comorbidity or obese adults (BMI >30 kg/m^2)	The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Pharmacologic options have expanded since 2012 with new drug approvals; however, competing approved drugs have significant potential side effects and work in only a proportion of patients taking them. Additional pharmacologic options are needed. Lorcaserin (Belviq®) is in a new class of selective serotonin 2C receptor agonists. It is taken twice daily in a 10 mg tablet. If 5% weight loss is not achieved by week 12 of therapy, labeling requires that the drug therapy be discontinued. Arena Pharmaceuticals, Inc., San Diego, CA (manufacturer) Eisai, Inc., U.S., a subsidiary of Eisai Co., Ltd., Tokyo, Japan (U.S. distributor) FDA approved Jun 2012 on basis of 3 completed phase III trials "as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m^2 or greater (obese), or 27 kg/m^2 or greater (overweight) in the presence of at least 1 weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes);" May 2013, U.S. Drug Enforcement Agency listed Belviq as schedule 4 controlled substance; Jun 2013, manufacturer announced U.S. launch	Behavior and lifestyle modifications Combination appetite suppressant/stimulant and anticonvulsant (Qsymia®) Combination norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (Contrave®; in development) Glucagon-like peptide 1 analog Liraglutide (Victoza®; in development) Pancreatic lipase inhibitor (orlistat, Xenical®) Surgical therapy (e.g., bariatric surgery)	Decreased comorbidities Total weight loss Improved quality of life	Tracked 2 years after FDA approval; no longer meets horizon scanning criteria for tracking.

Table 41. AHRQ Priority Condition: 11 Peptic Ulcer Disease and Dyspepsia: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
PerOral endoscopic myotomy (POEM procedure) for treatment of esophageal achalasia	Patients in whom esophageal achalasia has been diagnosed	Surgical treatment for esophageal achalasia generally requires at least 5 abdominal incisions to access the blocked esophageal pathway. PerOral endoscopic myotomy, also referred to as POEM, is a procedure proposed for treating esophageal achalasia by inserting an endoscope through the mouth and esophagus, allowing surgeons to directly cut abnormal muscle fibers of the lower esophageal sphincter at the base of the esophagus. It is intended to allow food to enter the stomach, and the procedure purportedly is less invasive, thereby potentially reducing complications, recovery time, and pain. Multiple institutions worldwide, including Northwestern Memorial Hospital, Chicago, IL, and the Mayo Clinic, Rochester, MN Phase IV trial ongoing	Heller myotomy	Improved esophageal function test (upper endoscopy, barium swallow, esophageal manometry, pH test) scores Improved quality of life	No major changes or movement after 4 years of tracking; no longer meets horizon scanning criteria for tracking.

Table 42. AHRQ Priority Condition: 12 Pregnancy, Including Preterm Birth: 2 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Bucelipase-alfa (Kiobrina) for improving growth rate of low-birthweight preterm infants	Infants born before week 32 of gestation	Infants born prematurely do not gain the nutrition that infants born at full term receive during the final weeks of gestation, including key vitamins and minerals for growth. A key issue in preterm infant growth is insufficient glucose and fatty-acid uptake essential for normal growth and development. Human bile salt–stimulated lipase (BSSL) is expressed in lactating mammary glands and secreted into breast milk; however, in babies receiving stored donor breast milk, the effects of storing can greatly decrease the concentration of BSSL. Infant formula lacks BSSL. Bucelipase-alfa (Kiobrina) is a recombinant, human BSSL intended as enzyme therapy to improve growth and development in preterm infants receiving pasteurized breast milk or formula. It is administered orally, as a powder added to breast milk or formula, at a concentration of 0.15 g/L. Swedish Orphan Biovitrum AB, Stockholm, Sweden Phase III trial completed; did not reach primary endpoint	Donor human breast milk Infant formula Maternal breast milk	Improved neonate growth Reduced health care costs Improved quality of life	Phase III trial completed but failed to reach endpoint, and planned U.S. development (phase III trial) halted.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Vending machine dispensers for emergency oral contraceptives (Plan B One Step) to prevent pregnancy	Women with potential for pregnancy	According to the U.S. Centers for Disease Control and Prevention, about 50% of pregnancies in the U.S. are unintended. Women in underserved areas are at increased risk of unintended pregnancies. Access, fear of others' perceptions, and cost are several determinants in emergency contraceptive use. Shippensburg University in Pennsylvania has incorporated an emergency contraceptive, or "morning after pill," vending machine into the student health center, charging $25 for each dose for students 17 years of age or older. The vending machine also includes other reproductive health products, including condoms and pregnancy test kits. Shippensburg University, Shippensburg, PA Dispensers not subject to FDA approval; FDA decided not to take regulatory action in Jan 2013; FDA announced in Jun 2013 that Plan B One Step would be available for purchase without age restrictions	Over-the-counter access to emergency contraceptives	Decreased risk of unplanned pregnancy Increased emergency contraceptive use Increased risk of adverse events associated with emergency contraception	Intervention has been available since 2010, but has not diffused to other settings.

Table 43. AHRQ Priority Condition: 13 Pulmonary Disease, Asthma: 0 Interventions

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

Table 44. AHRQ Priority Condition: 14 Substance Abuse: 2 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Off-label aprepitant (Emend) for treatment of alcohol use disorder in patients with posttraumatic stress disorder	Patients in whom alcohol use disorder secondary to posttraumatic stress disorder (PTSD) has been diagnosed	No therapies are indicated specifically for alcohol use disorder secondary to PTSD disorder. Aprepitant (Emend®, approved for use in chemotherapy-induced nausea and vomiting) is a substance P antagonist that blocks neurokinin 1 receptor. Substance P, released in amygdala in response to stress, acts at neurokinin 1 receptors to mediate stress responses. Blocking the receptors represents a novel approach (new target) for antistress actions; in alcoholism, it is intended to decrease alcohol cravings, attenuate cortisol response to stress, and decrease insula activation in response to negative sensory input. In a completed registered clinical trial, specific dosing information for aprepitant was not provided. Merck & Co., Inc., Whitehouse Station, NJ (manufacturer) National Institute on Alcohol Abuse and Alcoholism (investigator) Phase II trial completed Sept 2013; no data reported	Off-label pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone) Psychotherapy (e.g., cognitive behavior therapy)	Reduced alcohol consumption Reduced relapse Improved health outcomes associated with abstinence Improved quality of life	Topic has been tracked in horizon scanning system for more than 2 years with only 1 phase II trial completed (Sept 2013), and no results published; this intervention does not appear to be diffusing more widely as an off-label use.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Off-label deep brain stimulation for treatment of alcohol use disorder	Patients in whom treatment-refractory alcohol use disorder has been diagnosed	Only 36% of patients with alcohol use disorder experience full remission using available therapy options. Deep brain stimulation (DBS) uses permanently implanted electrodes to electrically interfere with activity in targeted parts of the brain. Researchers have suggested that DBS may have utility in treating alcohol dependence because the electrodes can be placed in the ventral striatum/nucleus accumbens, which is an area known to play a role in upholding addictive behaviors. Medtronic, Inc., Minneapolis, MN (manufacturer) University of Cologne, Cologne, Germany (investigator) Tangdu Hospital, Xi'an, China (investigator) National Institute on Alcohol Abuse and Alcoholism (investigator) Several small pilot studies completed and ongoing internationally; the manufacturer of the equipment used in these studies does not appear to be seeking a labeled indication change for this product, which is approved for use in Parkinson's disease and obsessive-compulsive disorder	Drugs: Acamprosate Disulfiram Naltrexone Psychotherapy (e.g., cognitive behavior therapy)	Reduced alcohol craving Reduced alcohol consumption Reduced relapse Improved health outcomes associated with abstinence Improved quality of life	Topic tracked for 2 years, with no significant developments in clinical trial data or diffusion tipping points reached in U.S. As an off-label use of an approved device, this intervention can potentially be used, but does not appear to be favored by clinicians, and reimbursement is not available for the procedure.

Table 45. AHRQ Priority Condition: 15 Cross-Cutting: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Postdischarge clinics to provide transition care after hospital stay	Patients who have been recently discharged from the hospital and require followup care but do not have access to timely primary care	1/3 of patients discharged from the hospital do not see an outpatient physician within 30 days of their hospital visit, resulting in exacerbation of conditions and a high number of hospital readmissions. Barriers to visiting an outpatient physician (e.g., primary care physician) for followup include lengthy wait times for appointments and lack of health insurance. To address this unmet need, some hospitals have created postdischarge clinics. Postdischarge clinics are located near the hospital, are staffed by hospitalists, and are available for patients who are unable to get a followup appointment with their primary care physician within a week or 10 days after discharge, especially those who have been identified as being at high risk of being readmitted to the hospital. The clinics are not intended to offer a substitute for primary or other outpatient care and are intended to be used only for a short time (although times vary from clinic to clinic) until the patient can get care from a primary care physician. Various hospitals across the country, including Beth Israel Deaconess Medical Center, Boston, MA; University of California, San Francisco; and University of New Mexico Health Sciences Center, Albuquerque Several clinics have been launched in the U.S.	Standard outpatient followup care (e.g., with primary care physician)	Improved patient outcomes Reduced hospital readmissions	Healthcare and payment reform over the past 5 years have led to broad diffusion of various models of postdischarge clinics to improve care transition. Estimating how many are open is difficult, but many have been identified in all U.S. geographic regions.