*AHRQ Healthcare Horizon Scanning System – Status Update*

# Horizon Scanning Status Update: November 2013

Prepared for:
Agency for Healthcare Research and Quality
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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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# Preface

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

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the 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. Two and a half years have passed since the initiation of the system. The horizon time frame focuses on identifying topics anticipated to be within 3 years of possible diffusion into clinical practice. A few surrogates are used to determine this horizon, such as clinical investigation in phase III trials for interventions subject to regulatory processes of the U.S. Food and Drug Administration (FDA). Topics with FDA orphan drug status, fast-track status, or innovation pathway designation are considered if phase II trials are ongoing.

The Status Update is a summary of data elements collected from implementation of the identification and monitoring protocol. Status Update reports are now 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 prior tracking period of 12 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 newly revised "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 Population, the Intervention, potential Comparators to the intervention, and potential Outcomes of interest for the patient population.

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

Topics accepted for tracking may also be designated during the meeting for further searches to collect more in-depth information about them. Such topics must be far enough along in development (typically in phase III trials for drugs, in phase II or III trials for devices, and having pilot information 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 meet an unmet need or to have impact on health outcomes or health care in the United States. Over time, a topic may be archived because development has ceased, because it no longer addresses an unmet need and is not novel, or because the intervention has diffused past early adoption and "timed out" in the horizon scanning system (i.e., 2 years after approval or initial diffusion).

Populating the horizon scanning system has been ongoing since December 2010. During that time, more than 16,200 leads have been uploaded into the system and reviewed by analysts, from which about 1,900 topics have been initially identified and moved through the system. This Status Update report contains 487 identified interventions we are tracking, which includes 35 new topics entered into the system during this reporting period. We archived 28 topics during this reporting period. 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, 4 priority areas comprise about 72% (rounded to the nearest percent) of the interventions (including programs) being tracked. Interventions related to cancer account for about 38% (183/487) 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 (16%, 78/487), infectious diseases (10%, 47/487), and cardiovascular diseases (9%, 42/487).

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 28% (137/487) of topics being tracked in the system.

In terms of overall types of interventions, about 86% (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 70% of topics are pharmaceutical/biotechnology (i.e., drug, vaccine, biologic) and about 17% are devices used as implants or used externally to deliver treatments. 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: 452 Interventions

**Table 1. AHRQ Priority Condition: 01 Arthritis and Nontraumatic Joint Disease: 14 Interventions**

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Apremilast for treating 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 of patients. Apremilast purportedly inhibits phosphodiesterase type 4 (PDE-4). By inhibiting the PDE-4 enzyme, apremilast purportedly increases intracellular cAMP, which modulates multiple inflammatory mediators. Clinical trial dosage: 20 or 30 mg, twice daily, orally.<br><br>Celgene Corp., Summit, NJ<br><br>Phase III trials ongoing; new drug application submitted to FDA Mar 2013 | Corticosteroids<br>Disease-modifying antirheumatic drugs: methotrexate, sulfasalazine<br>Immunosuppressants: azathioprine, cyclosporine leflunomide<br>Nonsteroidal anti-inflammatory drugs<br>Tumor necrosis factor-alpha inhibitors | Improved symptom scores as measured by the American College of Rheumatology 20/50/70 instruments<br>Improved scores on disability measures<br>Improved scores on quality of life measures |
| 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 degenerative disc disease 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 metal and polyethylene mobile bearing prosthesis purportedly designed as a low-profile cervical intervertebral disc replacement for both 1- and 2-level disc replacement. Mobi-C is composed of superior and inferior cobalt/chromium/molybdenum alloy spinal plates coated with a titanium plasma spray and hydroxyapatite coating, and a polyethylene mobile insert. The controlled mobility of the insert purportedly improves restoration of 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.<br><br>LDR Holding Corp., Austin, TX<br><br>Phase IV trial ongoing to fulfill FDA postmarket requirements; 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<br>Return to work<br>Reduction in disability<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Autologous conditioned serum for treatment of osteoarthritis (knee and back) | Patients in whom osteoarthritis (OA) has been diagnosed | Currently no regenerative treatments are approved 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 reinjected 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.<br><br>NY Spine Medicine, Schottenstein Pain & Neurology, New York, NY<br><br>Pilot studies completed; procedure currently diffusing in the U.S. | Analgesics<br>Lifestyle modification<br>Mesenchymal stem cell therapy<br>Physical therapy<br>Platelet-rich plasma<br>Viscosupplementation | Reduced pain<br>Increased range of motion<br>Increased tissue regeneration<br>Improved quality of life |
| Autologous mesenchymal stem cells for treatment of joint osteoarthritis | Patients in whom osteoarthritis (OA) has been diagnosed | Current conservative therapies for OA target disease symptoms such as pain and inflammation; however, they do not address the underlying pathology of the disease or halt its progression. Treatment of osteoarthritic joints with mesenchymal stem cells (MSCs) has the potential to be the 1st treatment could restore the large cartilage defects found in patients with OA. MSCs are adult stem cells, progenitor 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 several tissues, including bone marrow, synovium, periosteum, skeletal muscle, and adipose tissue. When 1st isolated from the patient, MSCs constitute a small fraction of the cells present in the sample and must be concentrated either by centrifugation or be passaged multiple times in vitro to expand the MSC population. Some companies use proprietary processes to add growth factors to culture and expand the MSCs before returning them to the patient. The condition of the patient may influence the attributes of the MSCs that are produced, and both patient age and the presence of OA have been shown to affect the ability of isolated MSCs to proliferate and differentiate into chondrocytes. MSCs that are more than minimally manipulated (i.e., that add growth factors or other substances and undergo culture expansion) must undergo FDA approval processes and submit a biologics licensing application.<br><br>CellTex Therapeutics Corp., Houston, TX<br>IntelliCell Biosciences, Inc., New York, NY (IntelliCell™)<br>Regenerative Sciences, Inc., Broomfield, CO (Regenexx™)<br>Various OA treatment centers<br><br>Various phase trials ongoing | Analgesics<br>Lifestyle modification<br>Physical therapy<br>Platelet-rich plasma<br>Viscosupplementation | Reduced pain<br>Increased range of motion<br>Increased tissue regeneration<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Autologous platelet-rich plasma therapy for treatment of joint osteoarthritis | Patients in whom knee osteoarthritis (OA) has been diagnosed | Other than joint replacement and symptom management, effective treatment for OA to restore long-term function is not available. Viscosupplementation provides temporary relief and improves short-term function for some patients, but long-term nonsurgical treatments are needed. Platelet-rich plasma (PRP) therapy involves collection, separation, and concentration of autologous platelets from a patient's blood, which usually takes place at a community blood bank (e.g., American Red Cross) 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 contains and releases (through degranulation) at least 7 different growth factors that are intended to stimulate bone and soft-tissue healing.<br><br>Orthohealing Center, Los Angeles, CA<br><br>Phase III trials ongoing | Analgesics<br>Lifestyle modification<br>Mesenchymal stem cell therapy<br>Physical therapy<br>Viscosupplementation | Reduced pain<br>Increased range of motion<br>Increased tissue regeneration<br>Improved quality of life |
| Fostamatinib disodium 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. Fostamatinib disodium, previously referred to as R788, is an oral spleen tyrosine kinase inhibitor that reversibly blocks lymphocyte signaling involved in inflammation and tissue degradation in RA. It is intended for treating early stage RA to reduce swelling and tissue destruction. Clinical trials dosage: 100 mg, twice daily, for 4 weeks followed by 150 mg, once daily.<br><br>Rigel Pharmaceuticals, Inc., South San Francisco, CA<br><br>Phase III trial ongoing | Corticosteroids<br>Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine<br>Nonsteroidal anti-inflammatory drugs<br>Tocilizumab<br>Tofacitinib<br>Tumor necrosis factor-alpha inhibitors | Improved symptom scores as measured by American College of Rheumatology 20/50/70 instruments<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Ixekizumab 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. Ixekizumab is purportedly a monoclonal antibody antagonist for the interleukin-17 (IL-17) receptor. 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 localized IL-17-mediated 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, 80 mg, monthly.<br><br>Eli Lilly and Co., Indianapolis, IN<br><br>Phase III trial registered | Corticosteroids<br>Disease-modifying antirheumatic drugs<br>Nonsteroidal anti-inflammatory drugs<br>Physical therapy<br>Secukinumab (in development)<br>Sulfasalazine (Azulfidine)<br>TNF inhibitors | Reduced signs and symptoms<br>Improved mobility<br>Improved quality of life |
| Ixekizumab for treatment of psoriatic arthritis | Patients in whom active psoriatic arthritis has been diagnosed | Psoriatic arthritis can progress to a stage of severe and painful symptoms in a subset of affected patients. These patients may then also experience deformity and disability of hands and fingers. Available treatment can be suboptimal. Ixekizumab is a monoclonal antibody purported to block the activity of interleukin 17, which is thought to contribute to psoriatic arthritis pathogenesis. In the ongoing UNCOVER-2 trial, ixekizumab is being given via subcutaneous injection in two 80 mg injections at week 0, followed by weekly 80 mg injections until week 12.<br><br>Eli Lilly and Co. Indianapolis, IN<br><br>Phase III trial recruiting | Apremilast (in development)<br>Corticosteroids<br>Disease-modifying antirheumatic drugs: methotrexate, sulfasalazine<br>Immunosuppressants: azathioprine, cyclosporine<br>Leflunomide<br>Nonsteroidal anti-inflammatory drugs<br>Tumor necrosis factor-alpha inhibitors: etanercept<br>Ustekinumab (in development) | Improved symptom scores as measured by the American College of Rheumatology 20/50/70 instruments<br>Improved disability measures<br>Improved quality of life measures |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Lesinurad for treatment of hyperuricemia and allopurinol-refractory gout | Patients in whom hyperuricemia has been diagnosed and thus are at high risk of acute gout | Only 30% to 40% of gout patients respond adequately to the available allopurinol. Lesinurad (RDEA594) is a selective urate transporter inhibitor. Inhibition leads to uric acid excretion to reduce uric acid and crystal formation to potentially alleviate symptoms of acute gout. Clinical trials dosage: 200 or 400 mg, once daily.<br><br>Ardea Biosciences, Inc., acquired Jun 2012 by AstraZeneca, London, UK<br><br>Phase III trials ongoing | Treatment:<br>Colchicine<br>Nonsteroidal anti-inflammatory drugs<br>Steroids<br>Prophylaxis:<br>Allopurinol<br>Febuxostat<br>Probenecid | Reduced uric acid accumulation and crystal formation<br>Reduced 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 and tolerability as well as convenient dosing are needed. Masitinib is an orally administered 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.<br><br>AB Science S.A., Paris, France<br><br>Phase II/III trial recruiting | Corticosteroids<br>DMARDs:<br>hydroxychloroquine, methotrexate, sulfasalazine<br>Nonsteroidal anti-inflammatory drugs<br>Tocilizumab<br>Tofacitinib<br>Tumor necrosis factor-alpha inhibitors | Improved symptom scores as measured by American College of Rheumatology 20/50/70 instruments<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Nitronaproxen (Naproxcinod) for treatment of osteoarthritis | Patients in whom osteoarthritis (OA) has been diagnosed | Other than joint replacement and symptom management, effective treatment for OA to restore function long-term is not available. Effective nonsteroidal anti-inflammatory drugs (NSAIDs) with an improved safety profile are needed to prevent cardiovascular complications. Nitronaproxen is an NSAID and derivative of naproxen with a nitroxybutyl ester, making it a nitric oxide (NO) donor. Nitronaproxen is the 1st-in-class cyclooxygenase inhibiting NO donators (CINODs); CINODs are intended to produce analgesic efficacy similar to traditional NSAIDs, but with fewer gastrointestinal and cardiovascular side effects because of the local effects of NO.<br><br>NicOx S.A., Sophia Antipolis, France<br><br>Phase III trials completed; FDA issued complete response letter to new drug application (NDA) requesting long-term safety data on cardiovascular effects; Apr 2012, manufacturer met with FDA to discuss additional data required for NDA resubmission; company seeking a partner to manage future development and commercialization | Celecoxib<br>Ibuprofen<br>Naproxen | Increased mobility<br>Decreased pain<br>Improved cardiovascular effects (i.e., blood pressure) |
| Off-label bisphosphonates for prevention of revision surgery after hip arthroplasty | Patients who have undergone knee or hip arthroplasty | Hip revision surgery is sometimes needed because of aseptic loosening of an implant. Treating a hip graft locally with an antiresorptive substance such as a bisphosphonate has been shown to decrease graft resorption in animal studies and researchers reported it led to “remained bone density in a human series of 16 patients.” Researchers are investigating whether increased bone density of a graft in hip arthroplasty through administration of a bisphosphonate decreases “micromotion” of the implant relative to the femur to reduce aseptic loosening and need for revision surgery. Bisphosphonates are known to inhibit bone resorption by inhibiting osteoclast activity. Bone remodeling can also be responsible for the need to perform arthroplasty revision. Using bisphosphonates for this purpose might provide a low-cost solution, preventing need for hip revision surgery. Investigators are using clodronate 60 mg/mL, 10 mL as a single dose mixed into the bone graft used at the time of operation.<br><br>Lund University Hospital, Lund, Sweden<br><br>Phase II trial ongoing in 32 hip operations | Standard of care following arthroplasty | Reduced need for revision surgery<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Secukinumab 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. 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.<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase III trials recruiting | Corticosteroids<br>Disease-modifying antirheumatic drugs<br>Ixekizumab (in development)<br>Nonsteroidal anti-inflammatory drugs<br>Physical therapy<br>Sulfasalazine (Azulfidine)<br>TNF inhibitors | Reduced signs and symptoms<br>Improved mobility<br>Improved quality of life |
| Ustekinumab (Stelara) for treatment of psoriatic arthritis | Patients in whom active psoriatic arthritis has been diagnosed | Psoriatic arthritis can progress to a stage of severe and painful symptoms in a subset of affected patients. These patients may then also experience deformity and disability of hands and fingers. Available treatment can be suboptimal. Ustekinumab (Stelara®) is a monoclonal antibody purported to block the activity of interleukin-12 and interleukin-23, which are thought to contribute to psoriatic arthritis pathogenesis. Clinical trial dosage: 45 mg at week 0, 4, and every 12 weeks or 90 mg every 12 weeks subcutaneously injected.<br><br>Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ<br><br>Phase III trial completed; FDA approved Sept 2013 for use alone or in combination with methotrexate for adults with psoriatic arthritis; FDA approved in 2009 for treating moderate to severe plaque psoriasis | Apremilast (in development)<br>Corticosteroids<br>Disease-modifying antirheumatic drugs: methotrexate, sulfasalazine<br>Immunosuppressants: azathioprine, cyclosporine<br>leflunomide<br>Nonsteroidal anti-inflammatory drugs<br>Tumor necrosis factor-alpha inhibitors | Improved symptom scores as measured by the American College of Rheumatology 20/50/70 instruments<br>Improved disability measures<br>Improved quality of life |

**Table 2. AHRQ Priority Condition: 02 Cancer: 169 Interventions**

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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.<br><br>Medac GmbH, Hamburg, Germany (developer)<br>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)<br><br>1 phase III trial completed, numerous phase I, II, and III trials ongoing; commercially available as Gliolan® in Europe | Standard surgical resection without fluorescence-assistance | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| 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.<br><br>F. Hoffmann-La Roche, Ltd., Basel, Switzerland<br><br>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 in adjuvant setting and 1st-line and 3rd-line treatment of metastatic disease ongoing | Lapatinib plus capecitabine<br>Trastuzumab plus chemotherapy (e.g., paclitaxel, docetaxel, vinorelbine, capecitabine)<br>Trastuzumab plus lapatinib | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 administered as an oral dose of 40–50 mg, once daily.<br><br>Boehringer Ingelheim GmbH, Ingelheim, Germany<br><br>Phase III trials ongoing for 1st-line treatment, 2nd-line treatment after a platinum-based regimen, and maintenance therapy | Various combination or monotherapy regimens including:<br>5-fluorouracil<br>Bleomycin<br>Cetuximab<br>Cisplatin<br>Docetaxel<br>Gemcitabine<br>Ifosfamide<br>Methotrexate<br>Paclitaxel<br>Vinorelbine | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| 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 the phase III clinical trial in HER2-positive breast cancer, afatinib (once daily oral dose) is being administered in combination with vinorelbine (25 mg/m$^2$ once weekly).<br><br>Boehringer Ingelheim GmbH, Ingelheim, Germany<br><br>Phase III trial ongoing | Ado-trastuzumab emtansine<br>Lapatinib plus capecitabine<br>Trastuzumab plus chemotherapy (e.g., paclitaxel, docetaxel, vinorelbine, capecitabine)<br>Trastuzumab plus lapatinib | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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. HER1 and HER2 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. *EGFR* gene mutations are present in about 10% of NSCLCs, with the majority of these gene mutations being *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.<br><br>Boehringer Ingelheim, GmbH, Ingelheim, Germany<br><br>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., United Kingdom) | 1st-line:<br>Combination chemotherapy (e.g., pemetrexed plus cisplatin)<br>Targeted immunotherapy (e.g., bevacizumab, cetuximab, erlotinib)<br><br>2nd-line:<br>Erlotinib<br>Single agent chemotherapy (e.g., docetaxel, pemetrexed) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Aldoxorubicin (INNO-206) for treatment of soft tissue sarcoma | Patients in whom unresectable or metastatic soft tissue sarcoma has been diagnosed | 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 dose of 350 mg/m$^2$, intravenously, once every 3 weeks, for up to 6 cycles.<br><br>CytRx Corp., Los Angeles, CA<br><br>Phase IIb trial ongoing; phase III trial agreement with FDA under a special protocol assessment; FDA granted orphan drug status | Doxorubicin | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Algenpantucel-L (HyperAcute-Pancreas) immunotherapy for pancreatic cancer | Patients in whom nonmetastatic adenocarcinoma of the pancreas has been diagnosed | Patients in whom pancreatic cancer has been diagnosed 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 being 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.<br><br>NewLink Genetics Corp., Ames, IA<br><br>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, and/or gemcitabine) | Increased overall survival<br>Increased progression-free survival<br>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.<br><br>Millennium Pharmaceuticals, Inc., subsidiary of Takeda Pharmaceutical Co., Ltd., Osaka, Japan<br><br>Phase III trial ongoing | Alemtuzumab<br>Brentuximab vedotin (ALCL subtype only)<br>Bortezomib<br>Cyclosporine (angioimmunoblastic T-cell lymphoma subtype only)<br>Denileukin diftitox<br>Gemcitabine<br>Pralatrexate<br>Radiation therapy<br>Romidepsin | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Anamorelin (ONO-7643) 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 current treatment options. CRCA may limit patients' tolerance of further treatment and may directly affect 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 is an orally administered, 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 dose of 100 mg, orally, daily.<br><br>Helsinn Healthcare S.A., Lugano/Pazzallo, Switzerland<br><br>Phase III trials ongoing | Anti-cytokine antibodies<br>Appetite stimulants:<br>Cannabinoids<br>Corticosteroids<br>Cyproheptadine<br>Progesterone derivatives<br>Dietary counseling<br>Melanocortin antagonists<br>Metabolic disturbance modulators:<br>Pentoxifylline<br>Thalidomide | Improved lean body mass<br>Improved muscle strength<br>Increased body weight<br>Increased overall survival<br>Improved quality of life |
| Anaplastic lymphoma kinase inhibitor (LDK378) 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. LDK378 inhibits ALK activity; in NSCLC tumors that are driven by constitutive ALK activity, it may reduce tumor growth and survival. LDK378 may provide a treatment option for patients whose NSCLC has progressed after treatment with the ALK inhibitor crizotinib. In clinical trials, LDK378 is provided as a once-daily, oral dose of 750 mg.<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase III trials ongoing in previously treated and untreated NSCLC; FDA granted breakthrough therapy status Mar 2013 | 1st-line:<br>Combination chemotherapy (e.g., pemetrexed plus cisplatin)<br>Crizotinib<br>Other targeted immunotherapy (e.g., bevacizumab, cetuximab, erlotinib)<br>2nd-line:<br>Erlotinib<br>Single-agent chemotherapy (e.g., docetaxel, pemetrexed) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 about 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). It purportedly targets neuroblastoma cells via antibody-dependent, cell-mediated cytotoxicity. In clinical trials, ch14.18 was administered in combination with cytokines (granulocyte macrophage colony-stimulating factor and interleukin-2) that enhance immune response and the standard neuroblastoma maintenance therapy isotretinoin.<br><br>United Therapeutics Corp., Silver Spring, MD, in collaboration with the National Cancer Institute, Bethesda, MD<br><br>Phase III trials ongoing; positive data from 1st phase III trial published in 2010 | Isotretinoin | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Astuprotimut-r (GSK2132231A) 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. 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.<br><br>GlaxoSmithKline, Middlesex, UK<br><br>Phase III trial ongoing but no longer recruiting; 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 increasing overall survival | Granulocyte-macrophage colony stimulating factor<br>Interferon-alpha<br>Interleukin-2<br>Radiation therapy | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 readministered to the patient. In clinical trials, AGS-003 being used in combination with sunitinib in patients with newly-diagnosed advanced/metastatic RCC who have undergone unilateral or partial nephrectomy. AGS-003 is administered by intradermal injection. A full treatment course consists of 8 injections in year 1 followed by quarterly booster injections.<br><br>Argos Therapeutics, Inc., Durham, NC<br><br>Phase III trial ongoing | Axitinib<br>Bevacizumab (with interferon alfa)<br>Everolimus<br>Interleukin-2<br>Pazopanib<br>Sorafenib<br>Sunitinib<br>Temsirolimus | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Autologous dendritic cell immunotherapy (DCVax-L) for treatment of 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.<br><br>Northwest Biotherapeutics, Inc., Bethesda, MD<br><br>Phase III trial ongoing | Bevacizumab (under investigation)<br>Other immunotherapeutics (in development, e.g., HSPPC-95, ICT107)<br>Radiation therapy<br>Surgical resection (with or without carmustine wafer)<br>Temozolomide | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Automated breast ultrasound (somo.v automated breast ultrasound system) for screening dense breast tissue | Women with dense breast tissue who are undergoing screening mammography | 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 in screening of 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.<br><br>U-Systems, Inc., acquired Nov 2012 by General Electric Co., Fairfield, CT<br><br>Sept 2012, FDA cleared for screening indication; previously FDA cleared for diagnostic use | Screening mammography alone<br>Screening magnetic resonance imaging<br>Manual breast ultrasound | Increased breast cancer sensitivity and specificity<br>Improved positive predictive and negative values for breast cancer |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 current 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. 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.<br><br>Biothera, Eagan, MN<br><br>Phase III trial ongoing | Cetuximab monotherapy<br>Regorafenib | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| 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 made available 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, bevacizumab is administered at 15 mg/kg, intravenously, on day 1 of each 3-week cycle.<br><br>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland, and National Cancer Institute, Bethesda, MD<br><br>Multiple phase III trials ongoing; manufacturer anticipates U.S. regulatory submission during 2013; U.K. National Institute for Health and Care Excellence announced in May 2013 it would not recommend use for ovarian cancer | Combination chemotherapy including 1 or more of the following:<br>Carboplatin<br>Gemcitabine<br>Paclitaxel<br>Pegylated liposomal doxorubicin<br>Topotecan<br>Paclitaxel monotherapy | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Blinatumomab for treatment of acute lymphoblastic leukemia | Patients in whom relapsed/refractory Philadelphia chromosome–negative acute lymphoblastic leukemia (ALL) has been diagnosed and patients in whom minimal residual disease (MRD)-positive 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 the most advanced molecule from 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.<br><br>Amgen, Inc., Thousand Oaks, CA<br><br>Phase II trials ongoing; FDA granted orphan drug status | Relapsed/Refractory ALL:<br>Anthracyclines (doxorubicin, daunorubicin)<br>Asparaginase<br>Cyclophosphamide<br>Cytarabine (ara-C)<br>Epipodophyllotoxins (etoposide, teniposide)<br>Vincristine<br>MRD-positive ALL:<br>No current standard of care | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Buparlisib (BKM120) 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 being administered in combination with the anti-estrogen drug fulvestrant. It is an oral agent administered at a dose of 100 mg, daily.<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase III clinical trials ongoing; drug also under study for endometrial cancer, glioblastoma, HER2-positive breast cancer, melanoma, nonsmall cell lung cancer, prostate cancer, and urothelial cancer | Everolimus plus exemestane<br>Fulvestrant monotherapy | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 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. 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.<br><br>Exelixis, Inc., South San Francisco, CA<br><br>Phase II and phase III trials ongoing | Abiraterone<br>Cabazitaxel<br>Denosumab<br>Docetaxel<br>Enzalutamide<br>Radium-223 | Reduced bone metastasis<br>Reduced bone pain<br>Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Exelixis, Inc., South San Francisco, CA<br><br>Phase III trial in RCC 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<br>Bevacizumab<br>Everolimus<br>Interleukin 2<br>Pazopanib<br>Sorafenib<br>Sunitinib<br>Temsirolimus | Increased overall survival<br>Increased progression-free survival<br>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 in combination with best supportive care.<br><br>Boston Biomedical, Inc., Cambridge, MA<br><br>Phase III trial ongoing for BBI608 monotherapy; phase II trial ongoing for combination therapy with panitumumab, cetuximab, or capecitabine | Best supportive care<br>Regorafenib | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Carfilzomib (Kyprolis) for treatment of multiple myeloma | Patients in whom recurrent or treatment-refractory multiple myeloma has been diagnosed | Patients in whom relapsed/refractory multiple myeloma has been diagnosed 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 inhibition of the proteasome can lead to accumulation of unwanted proteins, cell cycle arrest, and apoptosis. Product labeling states that it 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.<br><br>Onyx Pharmaceuticals, Inc., South San Francisco, CA (Onyx is being acquired by Amgen, Thousand Oaks, CA)<br><br>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;" phase III trials in newly diagnosed and relapsed/refractory disease ongoing | Combination therapies<br>Cytotoxic chemotherapies (bendamustine, cyclophosphamide, doxorubicin, melphalan, vincristine)<br>Immunomodulatory drugs (lenalidomide, pomalidomide, thalidomide)<br>Proteasome inhibitors (bortezomib)<br>Steroids (dexamethasone, prednisone) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Cobimetinib (GDC-0973) 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.<br><br>F. Hoffmann-La Roche, Ltd., Basel, Switzerland<br><br>Phase III trial ongoing | Dabrafenib<br>Ipilimumab<br>Trametinib<br>Vemurafenib | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Combination eflornithine/sulindac therapy (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.<br><br>Cancer Prevention Pharmaceuticals, Inc., Tucson, AZ, in collaboration with SWOG, Portland, OR<br><br>Phase III trials ongoing | No commonly used chemopreventive agent exists for preventing colorectal cancer recurrence<br>Compounds under investigation include:<br>Aspirin<br>Calcium supplements<br>Curcumin<br>Nonsteroidal anti-inflammatory drugs<br>Omega-3 fatty acids | Reduced recurrence rate of high-risk adenoma or 2nd primary colorectal cancer<br>Increased overall survival |
| 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.<br><br>Ethicon Endo-Surgery unit of Johnson & Johnson, New Brunswick, NJ<br><br>After repeated premarket approval application submissions, FDA approved May 2013; company starting limited roll-out of system in Jan 2014 | Propofol sedation administered and monitored by anesthesiologist | Successful and safe propofol sedation without need for an anesthesiologist |
| Custirsen for treatment of advanced nonsmall cell lung cancer | Patients in whom 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. 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.<br><br>OncoGenex Pharmaceuticals, Inc., Bothell, WA<br>Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel<br><br>Phase III trial ongoing (ENSPIRIT) for use as 2nd-line therapy in combination with docetaxel | Docetaxe<br>Erlotinib<br>Pemetrexed<br>Platinum doublet (plus or minus bevacizumab) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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. Custirsen is an injected agent intended as an adjunct to chemotherapy.<br><br>OncoGenex Pharmaceuticals, Inc., Bothell, WA<br>Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel<br><br>Phase III trials (AFFINITY and SYNERGY) ongoing; FDA granted fast-track status | Abiraterone<br>Cabazitaxel<br>Docetaxel<br>Enzalutamide<br>Radium-223<br>Sipuleucel-T | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Dacomitinib (PF-00299804) for treatment of nonsmall cell lung cancer | Patients in whom epidermal growth factor receptor (EGFR)-positive, 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.<br><br>Pfizer, Inc., New York, NY<br><br>Phase III trials ongoing in newly-diagnosed, advanced NSCLC and pretreated, advanced NSCLC | EGFR inhibitors (i.e., erlotinib)<br>Other angiogenesis inhibitors | Increased overall survival<br>Increased progression-free survival<br>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 and is being tested in combination with lenalidomide and dexamethasone.<br><br>Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ<br><br>Phase I/II trials ongoing; FDA granted breakthrough therapy status May 2013 | Carfilzomib<br>Pomalidomide | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Defibrotide (Defitelio) for treatment of chemotherapy-induced severe veno-occlusive disease | Patients receiving chemotherapy in whom severe veno-occlusive disease has been diagnosed | 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 current treatments. Defibrotide (Defitelio®) is an orally administered, 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 25 mg/kg, intravenously, 4 times per day.<br><br>Gentium S.p.A., Villa Guardia, Italy<br><br>Phase III trial ongoing; FDA granted orphan drug and fast-track statuses; Gentium previously submitted new drug application in 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; Conformité Européene (CE) marked Oct 2013 | Analgesia<br>Diuresis<br>Renal replacement therapy<br>Transfusion | Increased overall survival<br>Improved quality of life |
| 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 a dendritic cell–based therapeutic vaccine targeting multiple autologous tumor associated antigens including 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.<br><br>ImmunoCellular Therapeutics, Ltd., Woodland Hills, CA<br><br>Phase IIb trial ongoing, enrollment completed with interim data analysis in 2013; FDA granted orphan drug status in 2010 | Bevacizumab (under investigation)<br>Other immunotherapeutics (in development, e.g., DCVax-L, HSPPC-95)<br>Radiation therapy<br>Surgical resection (with or without carmustine wafer)<br>Temozolomide | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Amgen, Inc., Thousand Oaks, CA<br><br>Phase III trial ongoing, enrollment complete | Exemestane<br>Raloxifene<br>Tamoxifen | Increased overall survival<br>Increased bone metastasis–free survival<br>Improved quality of life |
| Doxepin oral rinse for the 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.<br><br>North Central Cancer Treatment Group (National Cancer Institute and Mayo Clinic), Rochester, MN<br><br>Phase III trial ongoing | Lidocaine<br>Narcotics | Decreased pain and oral side effects<br>Improved ability to eat and drink<br>Improved treatment adherence<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 in whom platinum-resistant ovarian cancer has been diagnosed 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 by intraperitoneal catheter. This agent is currently being tested in platinum-refractory ovarian cancer. In clinical trials, EGEN-001 is administered at a dose of 24 mg/m$^2$, weekly.<br><br>EGEN, Inc., Huntsville, AL<br><br>Phase II trial ongoing, enrollment complete; FDA granted orphan drug status; early stage trials in other treatment settings and disease indications ongoing | Docetaxel<br>Etoposide<br>Gemcitabine<br>Paclitaxel<br>Pegylated liposomal doxorubicin<br>Topotecan | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| eIF5A1 modulator (SNS01-T) for treatment-refractory multiple myeloma | Patients in whom treatment-refractory 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. eIF5A1 exists in 2 forms: a pro-apoptotic form and an antiapoptotic form, which 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, SNS01-T is administered by intravenous infusion, twice weekly.<br><br>Senesco Technologies, Inc., Bridgewater, NJ<br><br>Phase I/II trial ongoing; FDA granted orphan drug status | Various chemotherapeutic regimens, including 1 or more of the following:<br>Bendamustine<br>Bortezomib<br>Cisplatin<br>Cyclophosphamide<br>Dexamethasone<br>Etoposide<br>Lenalidomide<br>Liposomal doxorubicin<br>Thalidomide | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Elotuzumab for treatment of multiple myeloma | Patients in whom newly diagnosed 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.<br><br>Bristol-Myers Squibb, New York, NY<br><br>Phase III trials ongoing; FDA granted orphan drug status | For stem cell transplant eligible patients, 1st-line therapy such as:<br>Bortezomib/ dexamethasone<br>Cyclophosphamide/ dexamethasone<br>For patients ineligible for stem cell transplant, 1st-line therapy such as:<br>Bortezomib/ dexamethasone<br>Lenalidomide/low-dose dexamethasone,<br>Melphalan/ prednisone plus bortezomib | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Enobosarm (Ostarine) for treatment of cancer-related cachexia | Patients with cancer-related cachexia | 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.<br><br>GTx, Inc., Memphis, TN<br><br>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<br>Corticosteroids<br>Dietary modifications<br>Hormonal therapy (in development; i.e., insulin, ghrelin)<br>Progestogens | Improved physical function<br>Increased lean body mass<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Enzalutamide (Xtandi) for treatment of castration-resistant prostate cancer | Patients in whom metastatic castration-resistant prostate cancer (mCRPC) has been diagnosed | Median overall survival for patients with CRPC is only about 18 months. Most prostate cancer tumors are dependent 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 an oral drug being tested in both chemotherapy-naïve patients and patients who have previously been treated with docetaxel. Enzalutamide is administered at a dose of 160 mg (four 40-mg capsules) orally, once daily.<br><br>Medivation, Inc., San Francisco, CA<br>Astellas Pharma, Inc., Tokyo, Japan<br><br>FDA approved Aug 2012, for patients with mCRPC 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 | Abiraterone<br>Cabazitaxel<br>Docetaxel<br>Radium-223<br>Sipuleucel-T | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Etirinotecan pegol (NKTR-102) 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. Although approved for treating colorectal cancer, irinotecan is not indicated for treating breast cancer. 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 dose of 145 mg/m$^2$, once every 21 days.<br><br>Nektar Therapeutics, San Francisco, CA<br><br>Phase III trial ongoing, enrollment complete; FDA granted fast-track status; trials also investigating use in ovarian, colorectal, and other cancers | Eribulin<br>Gemcitabine<br>Ixabepilone<br>Nab-paclitaxel<br>Pemetrexed<br>Vinorelbine | Increased overall survival<br>Increased progression-free survival<br>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' disease 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. Inhibition of 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.<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase III trial ongoing, positive data reported Jun 2013; 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<br>HER2-targeted antibody therapies (e.g., trastuzumab, pertuzumab)<br>HER2-targeted tyrosine kinase inhibitors (e.g., lapatinib, afatinib) | Increased progression-free survival<br>Increased overall survival |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Novartis International AG, Basel, Switzerland<br><br>FDA approved Jul 2012 for treating postmenopausal women with advanced hormone receptor–positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole | Exemestane monotherapy | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Everolimus (Afinitor) for treatment of renal angiomyolipoma | Patients with tuberous sclerosis complex or sporadic lymphangioleio-myomatosis who develop angiomyolipomas | Angiomyolipomas are benign tumors that typically arise in the kidneys of patients with tuberous sclerosis complex or the lung disease lymphangioleiomyomatosis. Large angiomyolipomas may lead to renal failure and/or hemorrhage. No pharmacotherapies are available to treat angiomyolipomas. Loss-of-function mutations in the tuberous sclerosis complex (TSC) genes are thought to give rise to angiomyolipomas. A consequence of TSC loss of function is activation of the protein mTOR; therefore, using an mTOR inhibitor such as everolimus may be beneficial in treating these patients. Everolimus is taken once daily, as an oral tablet.<br><br>Novartis International AG, Basel, Switzerland<br><br>FDA approved for angiomyolipoma Apr 2012; everolimus is marketed as Afinitor® for multiple cancer indications | Angiomyolipoma embolization | Tumor size reduction<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Ex vivo expanded cord blood (StemEx) for allogeneic bone marrow transplant for 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 to the patient along with the remainder of the cord blood unit.<br><br>Gamida Cell, Ltd., Jerusalem, Israel, in partnership with Teva Pharmaceutical Industries, Ltd., Petah-Tikva, Israel<br><br>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<br>Unexpanded cord blood transplant | Increased overall survival<br>Improved bone marrow engraftment rate<br>Improved neutrophil recovery rate<br>Improved platelet recovery rate |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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. Better-tolerated 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.<br><br>Pfizer, Inc., New York, NY<br><br>Phase III trial ongoing, no longer recruiting; approved for other breast cancer indications; could be prescribed off-label. Phase III trial on implications of bone density effects ongoing. | Raloxifene<br>Tamoxifen | Decreased risk of developing breast cancer<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Farletuzumab (MORAb-003) 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 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, at a dose of 1.25 or 2.5 mg/kg. In platinum-sensitive disease, farletuzumab is being tested in combination with carboplatin/taxane doublet therapy.<br><br>Morphotek, Exton, PA, a subsidiary of Eisai Co., Ltd., Tokyo, Japan<br><br>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:<br>combination chemotherapy including 1 or more of the following:<br>Carboplatin<br>Docetaxel<br>Gemcitabine<br>Paclitaxel<br>Pegylated liposomal doxorubicin<br>Topotecan<br>Platinum-refractory ovarian cancer:<br>Docetaxel<br>Etoposide<br>Gemcitabine<br>Paclitaxel<br>Pegylated liposomal doxorubicin<br>Topotecan | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Fedratinib (SAR302503) for treatment of myelofibrosis | Patients who have myelofibrosis (primary myelofibrosis, post-polycythemia vera myelofibrosis, or post essential thrombocythemia myelofibrosis) | Few treatment options are available for myelofibrosis. The kinase JAK2 appears to play a central role in the majority of myelofibrosis pathophysiology; therefore, inhibiting JAK2 is seen as a promising intervention for myelofibrosis, as demonstrated by the recent marketing approval of a dual JAK1/JAK2 inhibitor (ruxolitinib, Jakafi™) for this indication. Fedratinib is a novel JAK2 kinase inhibitor, potentially altering the drug's efficacy and/or side effect profile. Fedratinib is administered in a once-daily oral dose of 400–500 mg.<br><br>Sanofi, Paris, France<br><br>Phase III trial ongoing, positive results reported May 2013 | Ruxolitinib | Increased overall survival<br>Increased progression-free survival<br>Reduced spleen size<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Ganetespib (STA-9090) for treatment of nonsmall cell lung cancer | Patients with advanced or metastatic nonsmall cell lung cancer (NSCLC) | Patients with advanced NSCLC that has progressed after prior chemotherapy have a poor prognosis and few treatment options. Ganetespib 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 in patients who have undergone 1 prior systemic therapy for advanced/ metastatic disease. Ganetespib is administered at a dose of 150 mg/m$^2$, intravenously, once weekly for 3 weeks followed by 1 week of rest.<br><br>Synta Pharmaceuticals Corp., Lexington, MA<br><br>Phase III trial ongoing; FDA granted fast-track status | Crizotinib (if ALK+)<br>Erlotinib<br>Single agent chemotherapy (e.g., docetaxel, pemetrexed) | Increased overall survival<br>Increased progression-free survival<br>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.<br><br>Pfizer, Inc., New York, NY<br><br>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<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 front-line treatment range between 10% and 60% depending on whether tumor pathology indicates that the tumor is low risk or high risk; therefore, 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 purports to lead 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.<br><br>Advantagene, Inc., Auburndale, MA<br><br>Phase III trial ongoing under FDA special protocol assessment | Androgen deprivation therapy<br>Radiation therapy<br>Surgical resection | Increased overall survival<br>Increased disease-free survival<br>Improved quality of life |
| Glembatumumab vedotin (CDX-011) 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, as 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.<br><br>Celldex Therapeutics, Inc., Needham, MA<br><br>Phase IIb trial complete; FDA granted fast-track status for treating treatment-resistant or refractory breast cancer; phase III trial to begin late 2013 | Albumin-bound paclitaxel<br>Capecitabine<br>Docetaxel<br>Doxorubicin<br>Eribulin<br>Gemcitabine<br>Ixabepilone<br>Liposomal doxorubicin<br>Paclitaxel<br>Vinorelbine | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Gonadotropin-releasing hormone analogs 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 analogs (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 analogs (i.e., goserelin or triptorelin) are administered concomitantly with standard cytotoxic chemotherapy regimens.<br><br>SWOG, Portland, OR, and International Breast Cancer Study Group IBCSG, Bern, Switzerland<br><br>Phase III trials ongoing, enrollment complete; 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 post-chemotherapy<br>Preserved fertility<br>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 these 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.<br><br>EDAP TMS S.A., Lyon, France<br><br>Phase II/III trial met primary endpoint; FDA accepted premarket approval application in Mar 2013; system available in Europe since 2000 | Brachytherapy<br>External beam radiation<br>Observation<br>Radical prostatectomy<br>Other HIFU systems (in development) | Increased overall survival<br>Increased progression-free survival<br>Improved patient quality of life |

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| 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 these 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.<br><br>SonaCare Medical, LLC (formerly USHIFU, LLC), Charlotte, NC<br><br>Phase III trial ongoing; system available in Europe since 2001 | Brachytherapy<br>External beam radiation<br>Observation<br>Radical prostatectomy<br>Other HIFU systems (in development) | Increased overall survival<br>Increased progression-free survival<br>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.<br><br>Threshold Pharmaceuticals, South San Francisco, CA, in partnership with Merck KGaA, Darmstadt, Germany<br><br>Phase III trial ongoing | Various chemotherapies including 1 or more of the following:<br>5-Fluorouracil<br>Capecitabine<br>Erlotinib<br>Gemcitabine<br>Leucovorin<br>Oxaliplatin | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Threshold Pharmaceuticals, South San Francisco, CA, with Merck KGaA, Darmstadt, Germany<br><br>Phase III trial ongoing; companies signed agreement in Feb 2012 to codevelop and commercialize TH-302 | Doxorubicin monotherapy | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| I-124 girentuximab (Redectane) positron-emission tomography for detection of clear cell renal cell carcinoma | Patients with uncharacterized renal masses; patients undergoing treatment for renal cell carcinoma | cG250 is a monoclonal antibody specific for carbonic anhydrase IX, a protein that is expressed by the majority of clear cell renal cell carcinomas (ccRCCs) and few normal tissues. Redectane® is a modified version of cG250 that incorporates a radioisotope that can be visualized by positron emission tomography (iodine-124). In combination with computed tomography (CT), imaging using Redectane could potentially be used in diagnosing ccRCC and to monitor ccRCC treatment efficacy and screen patients for ccRCC recurrence and metastasis. Redectane is administered by intravenous infusion.<br><br>Wilex AG, Munich, Germany<br><br>Phase III trial complete; company has finalized study protocol for a 2nd phase III trial under a special protocol assessment with FDA | CT imaging alone | Increased sensitivity and specificity for ccRCC |

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| Ibrutinib for treatment of chronic or small lymphocytic leukemia | Patients in whom chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) has been diagnosed | Ibrutinib is a small-molecule kinase inhibitor with activity against Bruton's tyrosine kinase (Btk). Many B-cell malignancies, including CLL and SLL, purportedly depend on B-cell receptor (BCR) signaling for survival, and Btk is essential for transduction of the BCR signaling pathway; therefore, its inhibition may be of therapeutic benefit in patients with CLL or SLL. Ibrutinib is orally administered at a once-daily dose of 560 mg in trials. Ibrutinib is under study in patients with various stages of CLL or SLL, including recurrent/refractory CLL or SLL and in patients aged 65 years or older with newly diagnosed CLL or SLL.<br><br>Pharmacyclics, Sunnyvale, CA, in partnership with the Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ<br><br>Phase III trials ongoing; FDA granted orphan drug and breakthrough therapy statuses; new drug application submitted Jul 2013 and accepted by FDA Aug 2013 | For patients with recurrent/refractory CLL/SLL:<br>Various chemotherapy regimens, including:<br>Bendamustine plus rituximab<br>Ofatumumab<br>For patients aged 65 years or older with CLL/SLL: 1 or more of the following:<br>Alemtuzumab<br>Bendamustine<br>Chlorambucil<br>Cladribine;<br>Cyclophosphamide<br>Prednisone<br>Also:<br>Fludarabine<br>Lenalidomide<br>Rituximab | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Ibrutinib 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 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).<br><br>Pharmacyclics, Inc., Sunnyvale, CA, in partnership with the Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ<br><br>Phase III trial ongoing | Combination therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone | Increased overall survival<br>Increased progression-free survival<br>Increased disease-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Ibrutinib (Imbruvica) for treatment of mantle cell lymphoma | Patients in whom newly diagnosed or recurrent/refractory mantle cell lymphoma (MCL) has been diagnosed | 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). Many B-cell malignancies (including MCL) purportedly depend on B-cell receptor (BCR) signaling for survival, and Btk is essential for transduction of the BCR signaling pathway; 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.<br><br>Pharmacyclics, Sunnyvale, CA, in partnership with the Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ<br><br>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; leading up to the approval, FDA had granted ibrutinib orphan drug and breakthrough therapy status | Various chemotherapies including 1 or more of the following:<br>Bendamustine<br>Bortezomib<br>Cyclophosphamide<br>Etoposide<br>Fludarabine<br>Lenalidomide<br>Mitoxantrone<br>Pentostatin<br>Procarbazine<br>Rituximab<br>Temsirolimus | Increased overall survival<br>Increased progression-free survival<br>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). Many B-cell malignancies (including Waldenström's macroglobulinemia) purportedly depend on B-cell receptor (BCR) signaling for survival, and Btk is essential for transduction of the BCR signaling pathway; 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.<br><br>Pharmacyclics, Sunnyvale, CA, in partnership with the Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ<br><br>Phase II trial ongoing; FDA granted breakthrough therapy status Feb 2013 | Various chemotherapy regimens, including:<br>Bendamustine<br>Bortezomib<br>Cladribine<br>Cyclophosphamide<br>Dexamethasone<br>Doxorubicin<br>Fludarabine<br>Prednisone<br>Rituximab<br>Thalidomide<br>Vincristine | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Idelalisib for treatment of chronic or small lymphocytic leukemia | Patients in whom chronic lymphocytic leukemia 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 nonblood tissues. The drug is under study in combination with rituximab or rituximab plus bendamustine for previously treated chronic or small lymphocytic leukemia. In ongoing trials, the drug is administered orally, 150 mg, twice daily.<br><br>Gilead Sciences, Inc., Foster City, CA<br><br>Phase III trials ongoing; in Oct 2013, a phase III trial of idelalisib in combination with rituximab for treating relapsed/refractory chronic lymphocytic leukemia in patients who were ineligible for chemotherapy (Study 116) was stopped early due to "highly statistically significant efficacy for the primary endpoint of progression-free survival" | Various combination chemotherapies including 1 or more of the following:<br>Cyclophosphamide<br>Doxorubicin<br>Fludarabine<br>Prednisolone<br>Rituximab<br>Vincristine | Increased overall survival<br>Increased progression-free survival<br>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.<br><br>Gilead Sciences, Inc., Foster City, CA<br><br>Phase III trials ongoing; company submitted new drug application to FDA Sept 2013 | Regimens including rituximab monotherapy or chemoimmunotherapy with rituximab and a chemotherapeutic agent (e.g., bendamustine, fludarabine) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Immature PSA ([-2]proPSA) assay as a decision aid regarding prostate cancer biopsy | Patients with elevated levels of 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 unneccesary 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.<br><br>Beckman Coulter, Inc., Brea, CA<br><br>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 ≥4.0 to ≤10.0 ng/mL, and with digital rectal examination findings that are not suspicious for cancer"; available in Europe since 2010 | PSA testing alone<br>Free PSA testing alone<br>Percent-free-PSA testing<br>Prostate cancer antigen 3 (PCA3) testing | Improved positive and negative predictive values<br>Improved sensitivity<br>Improved specificity<br>Reduced number of unnecessary biopsies |
| 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.<br><br>Soligenix, Inc., Princeton, NJ<br><br>Phase II trial ongoing; FDA granted fast-track status Jun 2013 | Lidocaine<br>Narcotics | Decreased pain and oral side effects<br>Improved ability to eat and drink<br>Improved treatment adherence<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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).<br><br>Augmenix, Inc., Waltham, MA<br><br>Phase III trial ongoing, no longer recruiting; 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 being administered once weekly, by intravenous infusion.<br><br>Pfizer, Inc., New York, NY<br><br>Phase III trial ongoing; FDA granted orphan drug status | Various combinations of the following chemotherapy agents:<br>Anthracyclines<br>Asparaginase<br>Cyclophosphamide<br>Cytarabine (ara-C)<br>Epipodophyllotoxins<br>Vincristine | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| 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 dose of 10 mg/kg, intravenously, once every 3 weeks for 4 doses, then once every 12 weeks beginning at week 24.<br><br>Bristol-Myers Squibb, New York, NY<br><br>Phase III trial ongoing | Combination chemotherapy (e.g., pemetrexed plus cisplatin)<br>Targeted immunotherapy (e.g., bevacizumab, cetuximab)<br>Targeted therapy (e.g., crizotinib [if ALK+], afatinib/erlotinib [if EGFR mutation+]) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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).<br><br>Bristol-Myers Squibb, New York, NY<br><br>Phase III trial in chemotherapy-naïve patients ongoing; Sept 2013, company announced a phase III trial of ipilimumab in patients who had previously undergone docetaxel therapy did not meet its primary endpoint of improving overall survival | Abiraterone<br>Docetaxel<br>Enzalutamide<br>Radium-223<br>Sipuleucel-T | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| 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.<br><br>AngioDynamics, Latham, NY<br><br>Unphased trial ongoing; FDA cleared for surgical ablation of soft tissue but not for any cancer indication; some cancer centers using off-label | Cryotherapy<br>RF ablation | Increased overall survival<br>Increased clinical downstaging to surgically resectable tumor<br>Improved adverse event profile<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Irreversible electroporation (NanoKnife) for treatment of pancreatic cancer | Patients in whom locally advanced pancreatic cancer that is not resectable by surgery has been diagnosed | 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.<br><br>AngioDynamics, Latham, NY<br><br>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<br>RF ablation | Increased overall survival<br>Increased rate of clinical downstaging to surgically tumor<br>Improved adverse event profile<br>Improved quality of life |
| Lenvatinib (E7080) 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 radioiodine have few treatment options and a poor prognosis. Lenvatinib is a small-molecule multikinase inhibitor with activity against multiple tyrosine kinases involved in signaling pathways that regulate cell growth and proliferation and angiogenesis (e.g., vascular endothelial growth factor receptors 2 and 3). In a late-phase clinical trial, lenvatinib is an oral medication administered as a once-daily dose of 24 mg.<br><br>Eisai Co., Ltd., Tokyo, Japan<br><br>Phase III trial ongoing, enrollment complete; FDA granted orphan drug status Feb 2013; Eisai reported 2013 target date for regulatory submission | Pazopanib (off label)<br>Sorafenib (off label)<br>Sunitinib (off label) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 prior to 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).<br><br>CEL-SCI Corp., Vienna, VA; in partnership with Ergomed Clinical Research Ltd., London, UK, for development abroad<br><br>Phase III trial ongoing; 2nd interim review of safety data in Oct 2013 raised no safety concerns | Surgical resection and chemoradiation therapy | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Liposome encapsulated irinotecan (MM-398) 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. 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-FU and leucovorin is being investigated, as well as MM-398 monotherapy, in the 2nd-line setting. In clinical trials, MM-398 is being administered by intravenous infusion at a dose of 120 mg/m$^2$, every 3 weeks.<br><br>Merrimack Pharmaceuticals, Inc., Cambridge, MA<br><br>Phase III trial (NAPOLI-1) ongoing, topline data expected late 2013/early 2014; FDA granted orphan drug status for treating 2nd-line pancreatic cancer | Capecitabine<br>Capecitabine/ oxaliplatin<br>FOLFOX (folinic acid [leucovorin], 5-fluorouracil, oxaliplatin) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 vincristine 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.<br><br>Spectrum Pharmaceuticals, Henderson, NV (Spectrum acquired the former developer Talon Therapeutics, Inc., San Mateo, CA)<br><br>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:<br>Anthracyclines<br>Asparaginase<br>Methotrexate<br>High-dose cytarabine<br>Steroids<br>Vincristine | Increased overall survival<br>Increased disease-free survival<br>Improved quality of life |
| Lorvotuzumab mertansine (IMGN901) for treatment of small cell lung cancer | Patients in whom advanced small cell lung cancer (SCLC) has been diagnosed; patients must have no previous systemic chemotherapy exposure | The 5-year survival rate for patients in whom SCLC is diagnosed is only about 15%. Lorvotuzumab mertansine (IMGN901) is a novel antibody-drug conjugate that links the highly cytotoxic agent mertansine to a monoclonal antibody specific for CD56, a cell surface marker expressed on multiple cancer types including SCLC. In current clinical trials, Lorvotuzumab mertansine is being given as an adjunct to a conventional cytotoxic chemotherapy regimen of carboplatin plus etoposide in the 1st-line setting. Lorvotuzumab mertansine is administered on days 1 and 8 of every 3-week cycle.<br><br>ImmunoGen, Inc., Waltham, MA<br><br>Phase II trial discontinued due to safety concerns and futility, manufacturer reviewing data to determine next steps; FDA granted orphan drug status | Carboplatin plus etoposide | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>XBiotech, Austin, TX<br><br>Phase III trial ongoing; FDA granted fast-track status | Appetite stimulants:<br>Cannabinoids<br>Corticosteroids<br>Cyproheptadine<br>Progesterone derivatives<br>Dietary counseling<br>Melanocortin antagonists<br><br>Metabolic disturbance modulators:<br>Anti-cytokine antibodies<br>Pentoxifylline<br>Thalidomide | Increased body weight<br>Increased lean body mass<br>Increased muscle strength<br>Increased overall survival<br>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 specifically 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 non-invasive, 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.<br><br>InSightec Ltd., Tirat Carmel, Israel<br><br>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 post-approval trial required by FDA is ongoing | Opiates and other analgesics<br>Palliative radiation therapy<br>Radiopharmaceuticals | Decreased pain<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Magnetic resonance imaging-ultrasound image fusion for image-guided prostate biopsy | Patients who are suspected of having prostate cancer based on elevated prostate-specific antigen (PSA) 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 of the need to perform the biopsy 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.<br><br>Philips Healthcare unit of Royal Philips Electronics, Amsterdam, the Netherlands<br><br>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<br>TRUS-guided biopsy | Improved positive and negative predictive values<br>Improved sensitivity<br>Improved specificity |
| 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 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.<br><br>Dune Medical Devices, Inc., Framingham, MA<br><br>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<br>Improved rate of complete surgical resection (e.g., no positive margin) |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Masitinib (AB1010) 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 an orally administered, 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 a dose of 7.5 mg/kg, daily.<br><br>AB Science S.A., Paris, France<br><br>Phase III trial ongoing | Dacarbazine<br>Interleukin-2<br>Ipilimumab<br>Nilotinib (in development) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Masitinib (AB1010) 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.<br><br>AB Science S.A., Paris, France<br><br>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:<br>5-Fluorouracil<br>Capecitabine<br>Erlotinib<br>Gemcitabine<br>Leucovorin<br>Oxaliplatin | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| MEK inhibitor (MEK162) for treatment of metastatic melanoma | Patients in whom advanced 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%. 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 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). MEK162 is also under investigation as part of combination therapy regimens with RAF inhibitors for treating BRAF-mutated melanoma.<br><br>Novartis International AG, Basel, Switzerland; licensed by Array BioPharma, Inc., Boulder, CO<br><br>Phase II and phase III trials ongoing in patients with NRAS mutation–positive melanoma and BRAF mutation–positive melanoma | Dacarbazine<br>Interleukin-2<br>Ipilimumab<br>Other BRAF/MEK inhibitor combinations in development<br>Temozolomide<br>Vemurafenib | Increased overall survival<br>Increased progression-free survival |
| 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).<br><br>Novartis International AG, Basel, Switzerland; licensed by Array BioPharma, Inc., Boulder, CO<br><br>Phase II and phase III trials ongoing | Bevacizumab (Avastin)<br>Chemotherapy (monotherapy or combination therapy)<br>Radiation<br>Surgery (debulking) | Increased overall survival<br>Increased progression-free survival |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>California Stem Cell, Inc., Irvine, CA<br><br>Phase III trial registered, not yet recruiting | Dabrafenib (if BRAF-positive)<br>Dacarbazine<br>Interleukin-2<br>Ipilimumab<br>Other immunotherapies in development (i.e., vaccines that target MAGE-A3 or MUC-1)<br>Temozolomide<br>Trametinib (if BRAF-positive)<br>Vemurafenib (if BRAF-positive) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Methylated septin 9 plasma DNA test (Epi proColon 2.0) for colorectal cancer screening | All patients undergoing routine colorectal cancer (CRC) screening | Many patients who are recommended to undergo screening for colorectal cancer do not follow the recommended screening guidelines 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.<br><br>Epigenomics AG, Berlin, Germany; company has entered a commercialization agreement with Polymedco, Inc., Cortlandt Manor, NY, for distribution of test in North American markets<br><br>Epigenomics submitted premarket approval application Jan 2013 for the test kit for Epi proColon 2.0; FDA granted priority review status; available in Europe as Epi proColon 2.0 CE since 2011 | Colonoscopy<br>Computed tomographic colonography<br>Fecal DNA tests<br>Sigmoidoscopy | Increased sensitivity and specificity<br>Increased predictive values<br>Avoided unnecessary followup procedures<br>Improved adherence with CRC screening<br>Earlier intervention for identified cancer |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase III trial ongoing; FDA granted orphan drug status | Cytarabine/daunorubicin | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| 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 an intravenous medication given at a dose of 3,000 $mg/m^2$, on days 1 and 4 of the 1st 3 weeks of each 4-week cycle.<br><br>Cornerstone Pharmaceuticals, Inc., Cranbury, NJ<br><br>Phase I/II trials ongoing in hematologic malignancies; phase II trial ongoing in myelodysplastic syndrome; phase I/II trial ongoing in pancreatic cancer; FDA granted orphan drug status for AML, myelodysplastic syndrome, and pancreatic cancer | Various chemotherapy regimens | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>National Cancer Institute, Bethesda, MD<br><br>Phase III trial ongoing | No approved therapies exist for chemotherapy-resistant hairy cell leukemia | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| 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 the 3 cycles, then every 12 weeks for 3 cycles.<br><br>Prima BioMed, Ltd., Melbourne, Australia<br><br>Phase II/III trial ongoing; in Oct 2013, enrollment in the phase II/III trial was suspended after top-line analysis of results from a 2nd phase II trial did not demonstrate an improvement in progression-free survival; the company is making amendments to the clinical development plan before resuming trial | Other ovarian cancer vaccines (in development) | Decreased recurrence rates<br>Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| MUC1 therapeutic vaccine (TG4010) for nonsmall cell lung cancer | Patients with metastatic, chemotherapy-naïve nonsmall cell lung cancer (NSCLC) who are mucin-1 (MUC-1)-positive | The 5-year survival rate for patients with advanced NSCLC is less than 15% with current 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 of treatment initiation. 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.<br><br>Transgene SA, Cedex, France<br><br>Phase IIb/III trial ongoing, phase IIb data expected 2nd half of 2013; FDA granted fast-track status | Combination chemotherapy (e.g., pemetrexed plus cisplatin)<br>Targeted therapy (e.g., afatinib, bevacizumab, cetuximab, crizotinib, erlotinib) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| 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 for patients with RCC. 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.<br><br>Immatics Biotechnologies GmbH, Tübingen, Germany<br><br>Phase III trial ongoing, enrollment completed Nov 2012; FDA granted orphan drug status | Sunitinib | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Nabiximols oromucosal spray (Sativex) for persistent chronic cancer pain | Patients with cancer who have persistent chronic pain | Effective pain management for chronic cancer pain is challenging because of side effects of available narcotic therapies and some patients' reluctance to avail themselves of narcotic therapy. For patients with advanced cancers, narcotic therapies may provide inadequate pain relief. Sativex, which is sprayed under the tongue, is a whole plant medicinal cannabis extract that contains tetrahydrocannabinol (THC) and cannabidiol as its main component. It is administered orally as a spray at a 100-mcL dose, which contains 2.5 mg cannabidiol and 2.7 mg THC.<br><br>GW Pharmaceuticals, plc, Salisbury, UK, and Otsuka Holdings Co., Ltd., Tokyo, Japan<br><br>Phase III U.S. trials ongoing; approved in Europe and Canada for pain and symptom relief for patients with multiple sclerosis and neuropathic-related cancer pain | Oral and transdermal opioids | Avoidance of side effects from narcotic pain medications<br>Reduced pain<br>Improved quality of life |
| Nab-paclitaxel (Abraxane) for the 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. In addition to its approved indication for treating metastatic pancreatic cancer, nab-paclitaxel is also being tested in the adjuvant setting after surgical resection to promote disease free survival.<br><br>Celgene Corp., Summit, NJ<br><br>Phase III trial ongoing in the adjuvant setting to promote disease-free survival after surgical resection; received FDA approval Sept 2013 for treating metastatic pancreatic cancer | Various chemotherapies including 1 or more of the following:<br>5-Fluorouracil<br>Capecitabine<br>Erlotinib<br>Gemcitabine<br>Leucovorin<br>Oxaliplatin | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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. Necitumumab 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, this agent 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.<br><br>Eli Lilly and Co., Indianapolis, IN; formerly in partnership with Bristol-Myers Squibb, New York, NY<br><br>Phase III trials ongoing in squamous and nonsquamous NSCLC; Lilly announced that the SQUIRE phase III trial in squamous NSCLC met its primary endpoint of increasing overall survival | Combination chemotherapy (e.g., pemetrexed plus cisplatin)<br>Targeted immunotherapy (e.g., bevacizumab, cetuximab) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| 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. 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.<br><br>RXi Pharmaceuticals Corp. subsidiary of Galena Biopharma, Lake Oswego, OR<br><br>Phase III ongoing under FDA special protocol assessment; phase II trial ongoing for combination therapy with trastuzumab | Aromatase inhibitors<br>Tamoxifen | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 current 1st-line treatments. Nintedanib (Vargatef™) is a tyrosine kinase inhibitor that has activity against vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor tyrosine kinases, which regulate tumor growth and angiogenesis. In late-phase clinical trials, nintedanib is being tested as an adjunct to the conventional 1st-line therapy of intravenous carboplatin plus paclitaxel. Nintedanib is administered as an oral tablet, at a dose of 200 mg, twice daily.<br><br>Boehringer Ingelheim GmbH, Ingelheim, Germany<br><br>Phase III trial ongoing, enrollment completed | Combination chemotherapy including 1 or more of the following:<br>Carboplatin<br>Docetaxel<br>Gemcitabine<br>Paclitaxel<br>Pegylated liposomal doxorubicin<br>Topotecan | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| 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 following 1st-line chemotherapy have few treatment options. Nintedanib is a tyrosine kinase inhibitor that has activity against vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor tyrosine kinases, which 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 monotherapy, docetaxel monotherapy). Nintedanib is administered as an oral tablet, twice daily.<br><br>Boehringer Ingelheim GmbH, Ingelheim, Germany<br><br>Phase III trials ongoing, positive data reported in Jun 2013 from the LUME-Lung 1 trial | Various combination therapies including:<br>Bevacizumab<br>Carboplatin<br>Crizotinib<br>Docetaxel<br>Erlotinib<br>Pemetrexed | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Niraparib (MK-4827) 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.<br><br>TESARO, Inc., Waltham, MA<br><br>Phase III trial registered, not yet recruiting | Combination or single agent chemotherapy with 1 of the following:<br>Alkylating agents (e.g., cyclophosphamide)<br>Anthracyclines (e.g., doxorubicin)<br>Antimetabolites (e.g., fluorouracil, gemcitabine)<br>Taxanes (e.g., docetaxel, paclitaxel) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Niraparib (MK-4827) 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 the 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.<br><br>TESARO, Inc., Waltham, MA<br><br>Phase III trial ongoing | Bevacizumab | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Nivolumab (BMS-936558, MDX-1106) 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, the utility of ipilimumab is limited by its 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 nonresectable advanced melanomas and in patients whose disease progressed following prior anti-CTLA-4 therapy. In clinical trials, nivolumab is administered intravenously at a dose of 3 mg/kg, once every 2 weeks.<br><br>Bristol-Myers Squibb, New York, NY<br><br>Phase III trials ongoing in several treatment settings as monotherapy and combination therapy with ipilimumab; FDA granted fast-track status | Dacarbazine<br>Dabrafenib (if BRAF-positive)<br>Ipilimumab<br>Trametinib (if BRAF-positive)<br>Vemurafenib (if BRAF-positive) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Nivolumab (BMS-936558, MDX-1106) 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. One of the hallmarks 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.<br><br>Bristol-Myers Squibb, New York, NY<br><br>Phase III trials ongoing; FDA granted fast-track status | Docetaxel<br>Erlotinib<br>Pemetrexed<br>Platinum doublet (plus or minus bevacizumab) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Nivolumab (BMS-936558; MDX-1106) for treatment of advanced renal cell carcinoma | Patients in whom advanced or metastatic clear cell renal cell carcinoma (ccRCC) has been diagnosed and who have undergone prior treatment with at least 1 antiangiogenic kinase inhibitor | Patients in whom advanced renal cell carcinoma has been diagnosed and whose disease has progressed after 1st-line treatment with a tyrosine kinase inhibitor have few treatment options and a poor prognosis. One of the hallmarks 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.<br><br>Bristol-Myers Squibb, New York, NY<br><br>Phase III trial ongoing; FDA granted fast-track status | Axitinib<br>Bevacizumab<br>Everolimus<br>Interferon<br>Interleukin-2<br>Pazopanib<br>Sorafenib<br>Sunitinib | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Obinutuzumab (Gazyva) for treatment of chronic lymphocytic leukemia | Patients with newly diagnosed chronic lymphocytic leukemia (CLL) who are unable to undergo intensive chemotherapy regimens (i.e., patients older than 70 years of age and younger patients with significant comorbidities) | CLL is the most frequently diagnosed leukemia among adults in the U.S., and about 4,600 patients die of the disease each year. CLL is a malignancy that affects cells in the B cell lineage, which express the surface antigen CD20. For several years, the CD20-specific monoclonal antibody rituximab has been used to target such malignancies. Rituximab is thought to act through a process of antibody-dependent cell-mediated cytotoxicity (ADCC). Obinutuzumab (Gazyva™) is a next-generation CD20-specific monoclonal antibody that has been glycoengineered to improve its ADCC inducing activity. Obinutuzumab is administered by intravenous infusion in a combination regimen with chlorambucil. Following a dose-escalation cycle, obinutuzumab is administered once monthly at a dose of 1,000 mg.<br><br>Genentech subsidiary of F. Hoffman La-Roche, Basel, Switzerland<br><br>Phase III trial ongoing, positive data reported; FDA granted breakthrough therapy status in May 2013; FDA approved on Nov 1 for treating patients with previously untreated CLL | Various treatment regimens (in order of preference according to the National Comprehensive Cancer Network Guidelines for CLL):<br>Chlorambucil plus or minus rituximab<br>Bendamustine plus or minus rituximab<br>Cyclophosphamide and prednisone plus or minus rituximab<br>Alemtuzumab<br>Rituximab<br>Fludarabine plus or minus rituximab<br>Lenalidomide<br>Cladribine | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 tissues involved in GVHD. Maraviroc is a CCR5 antagonist that may limit lymphocyte recruitment to target tissues, potentially limiting the extent of recipient tissue damage. In clinical trials, daily maraviroc is administered at a dose of 300 mg, orally, in combination with standard GVHD prophylaxis.<br><br>University of Pennsylvania, Philadelphia<br><br>Phase II trial ongoing; FDA approved in 2007 for treating HIV; marketed by Pfizer, Inc. (New York, NY), as Selzentry®, but the manufacturer does not appear to be seeking a labeled indication for this use | Methotrexate<br>Tacrolimus | Reduced rate of acute GVHD<br>Increased overall survival<br>Improved quality of life |
| Off-label metformin for treatment of breast cancer | Patients in whom breast cancer has been diagnosed | 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.<br><br>National Cancer Institute, Bethesda, MD, and multiple other academic institutions<br><br>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<br>Various hormone therapies | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA (investigator)<br>National Cancer Institute, Bethesda, MD (investigator)<br><br>Phase III trial ongoing | No commonly used chemopreventive agent exists for treating colorectal cancer<br>Compounds under investigation include:<br>Aspirin<br>Calcium supplements<br>Curcumin<br>Nonsteroidal anti-inflammatory drugs<br>Omega-3 fatty acids | Reduced recurrence rate of adenomatous polyps<br>Increased overall survival |
| Olaparib (AZD-2281) for treatment of ovarian cancer | Patients in whom BRCA-mutated ovarian cancer has been diagnosed and who have had a complete or partial response to platinum-based cytotoxic therapy | Patients in whom advanced ovarian cancer has been diagnosed often have recurrent disease and poor prognosis. Olaparib is a novel orally administered, small-molecule drug intended to inhibit PARP, which functions in a DNA repair pathway; no PARP inhibitors are currently 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.<br><br>AstraZeneca, London, UK<br><br>Phase III trials ongoing | Bevacizumab<br>Paclitaxel | Increased progression-free survival<br>Increased overall survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Cephalon unit of Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, (developed by ChemGenex Pharmaceuticals, Ltd., which was acquired by Cephalon)<br><br>FDA approved Oct 2012 for treating adults with CML whose disease is resistant to or who cannot tolerate other FDA-approved drugs for CML | Allogeneic stem cell transplantation<br>Ponatinib | Increased overall survival<br>Increased progression-free survival<br>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) that has progressed after 1st-line systemic chemotherapy | 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 1-armed monoclonal antibody that blocks ligand-mediated activation of the MET receptor tyrosine kinase. In a late-stage trial, it is being studied in combination with the EGFR inhibitor erlotinib in the 2nd-line setting. Earlier stage trials are investigating this agent as part of combination therapy with bevacizumab and systemic chemotherapy. Onartuzumab is administered at 1 mg/kg, intravenously, on day 1 of each 3-week cycle.<br><br>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland<br><br>Phase III trials ongoing in combination with erlotinib in multiple treatment settings; earlier stage trials ongoing in combination with bevacizumab and/or systemic chemotherapy | Crizotinib<br>Docetaxel<br>Erlotinib monotherapy<br>Pemetrexed | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 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).<br><br>F. Hoffmann-La Roche, Ltd., Basel, Switzerland<br><br>Phase III trial ongoing | Various chemotherapy regimens, including 1 or more of the following:<br>Capecitabine<br>Carboplatin<br>Cisplatin,<br>5-Docetaxel,<br>Epirubicin<br>Fluoropyrimidine<br>5-FU<br>Irinotecan<br>Oxaliplatin<br>Paclitaxel | Increased overall survival<br>Increased progression-free survival<br>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 specifically 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 administered to patients in the 2nd-line treatment setting following 1st-line treatment with a platinum-based chemotherapy. In this trial, Reolysin was administered in combination with paclitaxel and carboplatin.<br><br>Oncolytics Biotech, Inc., Calgary, Alberta, Canada<br><br>Phase III trial ongoing; top-line data for secondary endpoint reported in Dec 2012 | Various combination or monotherapy regimens including:<br>5-fluorouracil<br>Bleomycin<br>Cetuximab<br>Cisplatin<br>Docetaxel<br>Gemcitabine<br>Ifosfamide<br>Methotrexate<br>Paclitaxel<br>Vinorelbine | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Ovarian tissue cryopreservation for fertility preservation in women undergoing gonadotoxic cancer treatment | Females undergoing gonadotoxic cancer treatment who wish to preserve fertility | As 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.<br><br>Various research institutions, including Weill Medical College of Cornell University, New York, NY, and Boston IVF, Boston, MA<br><br>Several unphased trials ongoing; case series of successful pregnancies and births | Oocyte cryopreservation<br>Ovarian suppression with gonadotropin releasing hormone analogs or antagonists | Successful pregnancy<br>Live births |
| Palbociclib (PD-0332991) 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 duration is typically limited to about 1 year. Palbociclib is a dual inhibitor of cyclin-dependent kinase (CDK) 4 and CDK 6, 2 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 or fulvestrant in various treatment settings for 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.<br><br>Pfizer, Inc., New York, NY<br><br>Phase III trial ongoing for use in combination with letrozole in 1st-line treatment setting for advanced disease; phase III trial ongoing for use in combination with fulvestrant for treating endocrine therapy-refractory advanced disease; FDA granted breakthrough therapy status | Anastrozole<br>Fluoxymesterone<br>Fulvestrant<br>High-dose estrogen<br>Letrozole<br>Progestin<br>Tamoxifen<br>Toremifene | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Panobinostat for treatment of recurrent multiple myeloma | Patients with recurrent multiple myeloma | Although treatments for multiple myeloma have improved, the median life expectancy for patients with multiple myeloma is only 5–7 years. Additionally, as 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 (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.<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase III trial ongoing; FDA granted orphan drug status | Chemotherapy at standard or high doses including 1 or more of the following:<br>Bendamustine<br>Bortezomib<br>Carfilzomib<br>Cisplatin<br>Cyclophosphamide<br>Dexamethasone<br>Doxorubicin<br>Etoposide<br>Lenalidomide<br>Thalidomide | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Pazopanib (Votrient) for preventing recurrence of ovarian cancer | Patients with stage II–IV ovarian cancer, fallopian tube, or primary peritoneal carcinoma who have undergone surgical debulking and successful treatment with platinum agent–taxane combination therapy | Patients with ovarian cancer often have disease that responds to 1st-line treatment of cytoreduction and chemotherapy; however, a large number of these patients will experience disease recurrence. Therapies intended to prolong remission are needed. Pazopanib (Votrient™) is a tyrosine kinase inhibitor with activity against multiple kinases including vascular endothelial growth factor (VEGF) receptor 1 (VEGFR1), VEGFR2, VEGFR3, platelet-derived growth factor receptor-alpha/beta, and c-KIT. Inhibition of these kinases may limit tumor angiogenesis and/or tumor growth. In late-phase clinical trials, pazopanib is administered as an oral tablet, at a dosage of 800 mg, daily, for 24 months.<br><br>GlaxoSmithKline, London, UK<br><br>Phase III trial ongoing; topline data announced Jun 2013; survival data collection ongoing; FDA approved for renal cell carcinoma and soft tissue sarcoma | Bevacizumab as maintenance therapy after bevacizumab-containing treatment regimens<br>Paclitaxel<br>Watchful waiting | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Pazopanib (Votrient) for treatment of soft tissue sarcomas | Patients with advanced soft tissue sarcoma (excluding gastrointestinal stromal tumors [GIST] and liposarcomas) who have undergone prior systemic chemotherapy | 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. Pazopanib (Votrient™) is a multikinase inhibitor that has activity against multiple receptor tyrosine kinases (vascular endothelial growth factor receptor 1 [VEGFR1], VEGFR2, VEGFR3, platelet-derived growth factor receptor, c-KIT) and has the potential to inhibit tumor angiogenesis and growth. Although other multikinase inhibitors (e.g., sorafenib, sunitinib) have been used off label to treat soft tissue sarcoma, no such compound has been approved by FDA. Pazopanib is administered at a dose of 800 mg, once daily; its indicated for treating patients who have received prior chemotherapy.<br><br>GlaxoSmithKline, Middlesex, UK<br><br>FDA approved Apr 2012 for treating soft tissue sarcoma in the 2nd-line setting | 2nd-line treatments:<br>Sorafenib (off label)<br>Sunitinib (off label) | Increased overall survival<br>Increased progression-free survival<br>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.<br><br>Polaris Pharmaceuticals, Inc., San Diego, CA<br><br>Phase III trial initiated under FDA special protocol assessment; FDA granted orphan drug status; also under investigation for hematological malignancies, mesothelioma, melanoma, and lung and prostate cancer | Locoregional therapy<br>Sorafenib (if not used in 1st-line setting) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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. In clinical trials, this agent is administered at 0.8 mcg/m², intravenously, every 3 weeks until confirmed evidence of disease progression or unacceptable toxicity occurs.<br><br>MolMed, S.p.A., Milan, Italy<br><br>Phase III trial ongoing in 2nd-line setting; phase II trial ongoing in 1st-line setting; received patent from European Patent Office in Jun 2012 | 1st-line:<br>Pemetrexed plus cisplatin<br>2nd-line:<br>Single-agent chemotherapy (e.g., doxorubicin, gemcitabine, vinorelbine) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Pertuzumab (Perjeta) for treatment of HER2-positive breast cancer | Patients with metastatic HER2-positive breast cancer who are receiving 1st-line trastuzumab and docetaxel | 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.<br><br>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland<br><br>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 people with high-risk, HER2-positive early-stage breast cancer | Trastuzumab plus capecitabine, docetaxel, or vinorelbine<br>Trastuzumab plus paclitaxel with or without carboplatin | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Steba Biotech S.A., Cedex, France<br><br>Phase III trials ongoing | Radiation therapy<br>Radical prostatectomy<br>Watchful waiting | Increased overall survival<br>Increased progression-free survival<br>Fewer therapy-related side effects<br>Improved quality of life |
| 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, as 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.<br><br>PharmaMar subsidiary of Grupo Zeltia, Madrid, Spain<br><br>Phase III trial ongoing; FDA granted orphan drug status | Combination chemotherapy including 1 or more of the following:<br>Bendamustine<br>Bortezomib<br>Carfilzomib<br>Cisplatin<br>Cyclophosphamide (including high dose)<br>Dexamethasone<br>Etoposide<br>Lenalidomide<br>Pomalidomide<br>Thalidomide | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Celgene Corp., Summit, NJ<br><br>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 strategies certification for prescribers | Combination chemotherapy including 1 or more of the following:<br>Bendamustine<br>Bortezomib<br>Cisplatin<br>Cyclophosphamide (including high dose)<br>Dexamethasone<br>Doxorubicin<br>Etoposide<br>Thalidomide | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Ponatinib (Iclusig) for treatment of chronic myelogenous leukemia or Philadelphia chromosome–positive acute lymphoblastic leukemia | Patients in whom chronic myelogenous leukemia (CML) or Philadelphia chromosome–positive negative acute lymphoblastic leukemia (ALL) has been diagnosed | 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, who 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.<br><br>Ariad Pharmaceuticals, Inc., Cambridge, MA<br><br>FDA granted accelerated approval in Dec 2012 for patients with CML or Philadelphia chromosome–positive 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; on Oct 31, 2013, U.S. marketing of ponatinib was suspended pending further investigation of vascular adverse events | Bosutinib<br>Dasatinib<br>Imatinib<br>Nilotinib | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

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| 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.<br><br>Colorado Area Health Education Center, Department of Family Medicine, University of Colorado, Denver<br><br>Trials completed | Colonoscopy performed by gastrointestinal specialists | Earlier diagnosis of CRC<br>Increased screening rates |
| Prophage G-series therapeutic vaccine (HSPPC-96) for treatment of gliomas | Patients diagnosed with primary or recurrent gliomas, including glioblastoma multiforme (GBM) | Gliomas, which include GBM, can be very difficult to treat and are often associated with a poor patient prognosis. Prophage (HSPPC-96) is a cancer vaccine that is derived from antigens displayed by the patient's individual tumor. A tumor sample is collected and sent to the laboratory, where workers coimmunoprecipitate the antigens with heat shock protein GP96. Vaccination 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.<br><br>Agenus, Inc., Lexington, MA, in collaboration with University of California, San Francisco (UCSF), and the National Cancer Institute, Bethesda, MD<br><br>Phase I/II trials (in collaboration with UCSF) in adults with newly diagnosed gliomas ongoing, no longer recruiting; phase II trial (in collaboration with NCI) as combination therapy with bevacizumab in adults with recurrent gliomas ongoing; FDA granted orphan drug status | Adjuvant:<br>Radiation therapy<br>Temozolomide<br>Recurrence:<br>Bevacizumab<br>Bevacizumab plus chemotherapy<br>Combination PVC<br>Cyclophosphamide<br>Nitrosourea<br>Platinum-based regimens<br>Temozolomide | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

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| Prostate cancer antigen 3 (Progensa PCA3) assay to determine need for repeat prostate biopsy | Patients undergoing digital rectal examinations for prostate cancer screening | The assay is a urine test that is performed after a digital rectal examination; it detects a nonprotein coding messenger RNA, prostate cancer antigen 3, that is highly overexpressed in the "vast majority" of prostate cancers. Assay was developed as a test kit. The FDA indication approved in Feb 2012 is "for use in conjunction with other patient information to aid in the decision for repeat biopsy in men 50 years of age or older who have had 1 or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on the current standard of care, before consideration of the assay results. A negative Progensa PCA3 assay result is associated with a decreased likelihood of a positive biopsy. A prostate biopsy is required to diagnose cancer."<br><br>Gen-Probe subsidiary of Hologic, Inc., Bedford, MA<br><br>FDA approved Feb 2012; Conformité Européene (CE) marked in 2006 | Digital rectal examination alone<br>Prostate-specific antigen blood test screening | Increased sensitivity and specificity<br>Improved predictive values<br>Avoided unnecessary followup (i.e., biopsy) |
| 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.<br><br>BN ImmunoTherapeutics unit of Bavarian Nordic A/S, Kvistgård, Denmark<br><br>Phase III trial ongoing | Abiraterone<br>Enzalutamide<br>Sipuleucel-T | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| 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 harbor a FLT3 mutation. Quizartinib is an orally administered selective inhibitor of FLT3 kinase activity that is currently under study as a treatment for AML.<br><br>Ambit Biosciences, San Diego, CA<br><br>Phase II 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<br>High dose cytarabine and anthracycline<br>Fludarabine, cytarabine, and G-CSF plus or minus idarubicin<br>Mitoxantrone, etoposide, and cytarabine | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 following administration of ThermoDox, it induces local hyperthermia (39.5–42.0 °C) and targeted release of the cytotoxic agent. ThermoDox is being testing in patients with treatment-naïve HCC whose disease is not eligible for surgical resection.<br><br>Celsion Corp., New York, NY<br><br>Jan 2013, phase III trial failed to meet primary endpoint of progression-free survival; secondary survival analysis ongoing; Jun 2013, manufacturer reported potential benefit for subgroup of patients with optimized RF ablation procedure time | RF tumor ablation<br>Systemic chemotherapy<br>Targeted immunotherapy (e.g., sorafenib)<br>Transcatheter arterial chemoembolization | Decreased need for liver transplantation<br>Reduced side effects<br>Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| 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 specifically targeting bone metastases are available. 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.<br><br>Algeta ASA, Oslo, Norway, in collaboration with Bayer AG, Leverkusen, Germany<br><br>May 2013, FDA granted approval (after priority review) for treating bone metastases associated with advanced hormone-refractory metastatic prostate cancer; investigation in osteosarcoma and breast cancer with bone metastases ongoing | Standard therapy plus denosumab or cabozantinib (Cometriq™)<br>Standard therapy with and without Radium-223 dichloride | Increased overall survival<br>Increased progression-free survival<br>Increased rate of alkaline phosphatase normalization<br>Reduced pain from bone metastases<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Ramucirumab (IMC-1121B) for the treatment of gastric cancer | Patients in whom metastatic gastric cancer has been diagnosed and 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 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 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.<br><br>ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN<br><br>Phase III trials ongoing; company announced that 2 phase III trials have met their primary endpoints: REGARD (ramucirumab in combination with best supportive care) and RAINBOW (combination therapy with ramucirumab and paclitaxel); FDA granted fast-track status; FDA has granted the biologic license application for ramucirumab in combination with best supportive care priority review status; company indicates that a 2nd regulatory submission for use of ramucirumab in combination with paclitaxel is forthcoming | Taxane (e.g., docetaxel, paclitaxel) monotherapy<br>Various irinotecan-based single and combination therapies | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Ramucirumab (IMC-1121B) for treatment of hepatocellular carcinoma | Patients with advanced stage hepatocellular carcinoma (HCC) whose disease is not amenable to locoregional therapy and has been previously treated 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.<br><br>ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN<br><br>Phase III trial ongoing, enrollment complete | No consensus exists on treatment for this patient population | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Ramucirumab (IMC-1121B) 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 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 gastric cancer, ramucirumab is intravenously administered at a dose of 8 mg/kg once every 2 weeks as an adjunct to the standard 2nd-line FOLFIRI (folinic acid [leucovorin], 5-fluorouracil, and irinotecan) regimen.<br><br>ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN<br><br>Phase III trial ongoing, enrollment complete | Various FOLFIRI-based therapies with or without cetuximab or panitumumab | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Ramucirumab (IMC-1121B) 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 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.<br><br>ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN<br><br>Phase III trials ongoing, enrollment complete; primary completion Jan 2014 | Crizotinib (if ALK+)<br>Erlotinib<br>Single agent chemotherapy (e.g., docetaxel, pemetrexed) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

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| 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.<br><br>University of Michigan, Ann Arbor; Douglas Chepeha, M.D.<br><br>1 case report | Laryngectomy | Preserved larynx and reconstructed cricoid<br>Improved quality of life |
| Regorafenib (Stivarga) for treatment of gastrointestinal stromal tumors | Patients with advanced gastrointestinal stromal tumors (GIST) that has 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®) is an inhibitor of 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., 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.<br><br>Bayer AG, Leverkusen, Germany<br><br>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<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Regorafenib (Stivarga) for treatment of hepatocellular carcinoma | Patients with unresectable hepatocellular carcinoma (HCC) that has progressed after treatment with sorafenib | Patients with HCC that cannot be surgically resected have few treatment options and a poor prognosis; no 2nd-line therapy is available after sorafenib. Regorafenib (Stivarga®) inhibits multiple tyrosine kinases, including the pro-angiogenic kinases vascular endothelial growth factor receptor and TIE-2 (as well as RAF, RET, and KIT); inhibition of both primary angiogenic kinase pathways is a novel combination in multikinase inhibitor drugs (e.g., imatinib, sunitinib). Regorafenib for treatment of gastrointestinal stromal tumors (GIST) is administered at a daily dose of 160 mg, orally, for 3 weeks of every 4-week cycle.<br><br>Bayer AG, Leverkusen, Germany<br><br>Phase III trial ongoing; FDA approved for treating GIST and metastatic colorectal cancer | Locoregional treatment | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Regorafenib (Stivarga) for treatment of metastatic colorectal cancer | Patients in whom metastatic colorectal cancer (mCRC) has been diagnosed and 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. 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.<br><br>Bayer AG, Leverkusen, Germany<br><br>FDA approved for treatment of mCRC in Sept 2012; phase III trial ongoing in patients who have undergone resection of CRC liver metastases | No standard salvage therapies in this setting | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Mesoblast, Ltd., Melbourne, Australia (formerly developed by Osiris Therapeutics, Inc., Columbia, MD, whose stem cell unit was acquired by Mesoblast)<br><br>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<br>Corticosteroids<br>Methotrexate and cyclosporine<br>Mycophenolate mofetil<br>Other immunosuppressants<br>Photopheresis | Increased overall survival<br>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.<br><br>Onconova Therapeutics®, Inc., Newtown, PA<br><br>Phase III trial ongoing, top-line survival data expected 4th quarter 2013 or 1st quarter 2014 | Hematopoietic stem cell transplant<br>Immunosuppressive therapy (e.g., antithymocyte globulin plus or minus cyclosporine) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Rigosertib (Estybon) for treatment of pancreatic cancer | Patients in whom previously untreated, metastatic pancreatic cancer has been diagnosed | Only about 5% of patients with pancreatic cancer respond to the current standard of care (gemcitabine chemotherapy), and the prognosis for these patients is very poor. Rigosertib (Estybon®) is a small-molecule, multikinase inhibitor with activity against both the alpha and beta isoforms of the phosphoinositide 3 kinase (PI3K) and polo-like kinase 1 (Plk1). Inhibiting PI3K may disrupt cell signaling that promotes cell growth and survival, and inhibiting Plk1 may disrupt mitosis, leading to cell-cycle arrest. In clinical trials, rigosertib is being administered at a dosage of 1,800 mg/m$^2$, via 2-hour continuous intravenous infusion infusions, twice weekly, for 3 weeks of a 4-week cycle.<br><br>Onconova Therapeutics®, Inc., Newtown, PA<br><br>Phase III trial ongoing, interim survival analysis expected 4th quarter 2013 or 1st quarter 2014 | 5-fluorouracil/ leucovorin/oxaliplatin<br>Capecitabine<br>Capecitabine/oxaliplatin<br>Gemcitabine<br>Gemcitabine plus erlotinib | Increased progression-free survival<br>Increased overall survival<br>Improved quality of life |
| Rilotumumab (AMG 102) for treatment of gastric cancer | Patients with previously untreated unresectable, locally advanced or metastatic gastric cancer that expresses high levels of mesenchymal epithelial transition factor (MET) | 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. Rilotumumab 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. Rilotumumab is administered intravenously at a dose of 15 mg/kg, once every 21 days. In clinical trials it is being used in combination with a chemotherapy regimen consisting of epirubicin, cisplatin, and capecitabine.<br><br>Amgen, Inc., Thousand Oaks, CA<br><br>Phase III trial ongoing | Various chemotherapy regimens, including 1 or more of the following:<br>Capecitabine<br>Carboplatin<br>Cisplatin<br>Docetaxel<br>Epirubicin<br>Fluoropyrimidine<br>5-Flurouracil<br>Irinotecan<br>Oxaliplatin<br>Paclitaxel | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

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| Rindopepimut (CDX-110) 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. EGFRvIII is an oncogenic splice variant of EGFR. This variant represents a potential target antigen for anticancer therapy. Rindopepimut is a peptide-based vaccine designed to stimulate an immune response to cells expressing the EGFRvIII variant. 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 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.<br><br>Celldex Therapeutics, Inc., Needham, MA<br><br>Phase III trial ongoing in 1st-line setting; phase IIb trial with expansion cohort ongoing in recurrent GBM; FDA granted orphan drug and fast-track statuses | Bevacizumab<br>Temozolomide monotherapy | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Rose Bengal (PV-10) for treatment of advanced melanoma | Patients in whom advanced or metastatic melanoma has been diagnosed | Patients with advanced melanoma have few treatment options and a poor prognosis. PV-10 is a solution of the fluorescein derivative Rose Bengal. Rose Bengal preferentially accumulates in cancer cells because of the increased lipid content of its 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 because of 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.<br><br>Provectus Pharmaceuticals, Knoxville, TN<br><br>Phase II completed; phase III trial special protocol assessment is being discussed with FDA; FDA granted orphan drug status | Dacarbazine<br>Granulocyte colony stimulating factor<br>Interleukin-2<br>Ipilimumab<br>Temozolomide<br>Vemurafenib | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Sorafenib (Nexavar) for the treatment of differentiated thyroid cancer | Patients with radioactive iodine-refractory differentiated thyroid cancer | Radioactive iodine (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.<br><br>Bayer AG, Leverkusen, Germany, and Onyx Pharmaceuticals, Inc., South San Francisco, CA<br><br>FDA approved expanded indications to late-stage (metastatic) differentiated thyroid cancer Nov 2013; sorafenib was approved in 2005 to treat advanced kidney cancer in 2005 and in 2007 to treat surgically unrescectable liver cancer | Ablation<br>Chemotherapy<br>Off-label sunitinib (trials ongoing)<br>Radiation therapy<br>Surgical intervention | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Specialized care model for adolescents and young adults with cancer | Adolescents and young adults with cancer | Adolescents and young adults undergoing treatment for cancer have unique care needs that often go unmet in traditional pediatric or adult cancer units. The Teenage Cancer Trust and Teen Cancer America work with hospitals to develop specialized cancer units and care programs that address the specific needs of this patient population. Program features include redesigned inpatient and outpatient facilities, provider training, clinical trial counseling/enrollment, and psychosocial support.<br><br>Teen Cancer America and Ronald Reagan UCLA Medical Center, Los Angeles, CA<br><br>25 specialized teen cancer units are open in the United Kingdom; several U.S. centers established, with additional sites in development | Adult cancer units<br>Pediatric cancer units | Improved physical and emotional health outcomes<br>Improved treatment adherence<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Spicamycin-derived, nonopioid, nonnarcotic (KRN5500) for treatment of chronic cancer pain | Patients with chronic cancer pain, especially chemotherapy-induced neuropathic pain | Current 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.<br><br>DARA BioSciences, Inc., Raleigh, NC<br><br>Phase IIa trial completed; FDA granted fast-track status in 2011; manufacturer submitted application for orphan drug status in Nov 2012 | NSAIDs<br>Opioid analgesics | Reduced pain<br>Improved quality of life |
| Stool DNA molecular test (Cologuard) for colorectal cancer screening | All 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-gene plus 1 biomarker test performed on stool samples. This test kit is the next generation of the ColoSure™ test, which looked for epigenetic modification in only a single genetic locus.<br><br>Exact Sciences Corp., Madison, WI<br><br>10,000-patient DeeP-C trial complete; premarket approval application submitted to FDA Jun 2013 | Colonoscopy<br>Computed tomographic colonography<br>Fecal occult blood testing<br>Sigmoidoscopy | Increased sensitivity and specificity for precancerous lesions and CRC<br>Improved positive and negative predictive values<br>Reduced unnecessary followup for screening |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>MolMed, S.p.A., Milan, Italy<br><br>Phase III trial ongoing | Hematopoietic SCT | Increased overall survival<br>Decreased time to immune reconstitution<br>Increased engraftment rate<br>Reduced incidence of acute GVHD<br>Reduced incidence of chronic GVHD<br>Improved quality of life |
| Tabalumab (LY-2127399) 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. 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 once intravenously over 30 minutes on day 1 every 21 days for 8 cycles in combination with dexamethasone and bortezomib.<br><br>Eli Lilly and Co., Indianapolis, IN<br><br>Phase II trial ongoing; FDA granted orphan drug status for treatment of multiple myeloma | Carfilzomib<br>Pomalidomide | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Amgen, Inc., Thousand Oaks, CA<br><br>Phase III trial ongoing; manufacturer reported positive topline data in Mar 2013 | Dacarbazine<br>Dabrafenib (if BRAF-positive)<br>Interleukin-2<br>Ipilimumab<br>Temozolomide<br>Trametinib (if BRAF-positive)<br>Vemurafenib (if BRAF-positive) | Increased overall survival<br>Increased progression-free survival<br>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.<br><br>Active Biotech, AB, Lund, Sweden<br><br>Phase III trial ongoing | Abiraterone<br>Enzalutamide<br>Sipuleucel-T | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Tecemotide (L-BLP25, Stimuvax) for treatment of advanced nonsmall cell lung cancer | Patients in whom unresectable, stage III NSCLC has been diagnosed and 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 current 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. It is administered after a single intravenous infusion of 300 mg/m$^2$ of cyclophosphamide 3 days prior to the 1st immunization; then the vaccine is administered in 8 consecutive weekly subcutaneous injections (1,000 mcg tecemotide); the vaccine is then administered at 6-week intervals beginning at week 14 until antitumor responses are observed.<br><br>Merck KGaA, Darmstadt, Germany<br>Oncothyreon, Seattle, WA<br><br>Dec 2012, initial phase III trial missed primary endpoint of improving overall survival; new phase III trial being initiated in a subset of patients who had received prior concurrent chemoradiotherapy | No approved maintenance therapy in this setting | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Telotristat etiprate (X1606/LX1032) 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.<br><br>Lexicon Pharmaceuticals, Inc., The Woodlands, TX<br><br>Phase III trial ongoing; FDA granted orphan drug and fast-track statuses | Chemotherapy (e.g., capecitabine, dacarbazine, 5-fluorouracil, temozolomide)<br>Interferon alpha<br>Octreotide | Decreased rate of bowel movements<br>Decreased 5-HIAA levels<br>Decreased rate of flushing episodes<br>Improved quality of life (e.g., less pain, discomfort) |
| 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.<br><br>NewLink Genetics Corp., Ames, IA<br><br>Phase II/III trial ongoing | Various combination therapies including:<br>Bevacizumab<br>Carboplatin<br>Crizotinib<br>Docetaxel<br>Erlotinib<br>Pemetrexed<br>Various immunotherapies (in development) | Improved overall survival<br>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. The vaccine is administered by intradermal injection as adjuvant therapy following surgical resection and radiation.<br><br>Polynoma LLC subsidiary of CK Life Sciences Int'l (Holdings), Inc., Hong Kong<br><br>Phase III trial ongoing | High-dose interferon | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>GlaxoSmithKline, Middlesex, UK<br><br>Phase III trial ongoing in the maintenance setting following surgical resection and any adjuvant chemotherapy | No standard maintenance therapy in this setting. | Increased disease-free survival<br>Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Tivantinib for treatment of hepatocellular carcinoma | Patients with unresectable hepatocellular carcinoma 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 the c-met receptor tyrosine kinase; c-met has been implicated in a number of tumor-associated biologic processes (e.g., cell dissociation, cell migration, inhibition of apoptosis, cell proliferation). No c-met inhibitor is currently available. In clinical trials, tivantinib is given at a dose of 240 mg, orally, twice daily.<br><br>ArQule, Inc., Woburn, MA, in partnership with Daiichi Sankyo Co., Ltd., Tokyo, Japan<br><br>Phase III trial ongoing | Locoregional therapy | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 with mCRC respond 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 signalling 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.<br><br>MOLOGEN AG, Berlin, Germany<br><br>Phase II trial completed; phase III trial in planning | Bevacizumab<br>Chemotherapy-free interval<br>Leucovorin plus 5-fluorouracil | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Trametinib (Mekinist) for treatment of advanced melanoma with activating BRAF mutation | Patients with unresectable or metastatic melanoma that harbors an activating BRAF mutation | Patients with metastatic melanoma have a poor prognosis with current treatments. Melanomas harboring activating BRAF mutations are driven in part by activation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway of which MEK is a member; trametinib (Mekinist™) is an inhibitor of MEK 1 and MEK 2, which may have antineoplastic activity in tumors dependent on MAPK/ERK pathway activation. Trametinib is administered as an oral dose of 2 mg, once daily.<br><br>GlaxoSmithKline, Middlesex, UK<br><br>Trametinib monotherapy FDA approved May 2013 in conjunction with a companion diagnostic test to detect $BRAF^{V600E/K}$ mutations (THxID BRAF, bioMerieux); phase III trial ongoing for combination therapy with BRAF inhibitor dabrafenib; company announced Jun 2013 filing of a supplemental new drug application (sNDA) for dabrafenib plus trametinib combination therapy; Sept 2013 FDA granted priority review for sNDA | High dose interleukin-2<br>Dacarbazine<br>Dabrafenib<br>Ipilimumab<br>Temozolomide<br>Vemurafenib | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Trebananib (AMG 386) 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 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.<br><br>Amgen, Inc., Thousand Oaks, CA<br><br>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) | Docetaxel<br>Etoposide<br>Gemcitabine<br>Liposomal doxorubicin<br>Paclitaxel<br>Topotecan | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Urocidin for treatment of nonmuscle-invasive bladder cancer | Patients in whom nonmuscle-invasive bladder cancer (cancer on the surface of the bladder) has been diagnosed | Treatments that can provide better outcomes and 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 previous bacillus Calmette-Guérin (BCG) treatment. Urocidin is administered by transurethral catheter directly into the bladder at a dose of 8 mg, weekly.<br><br>Bioniche Life Sciences, Inc., Belleville, Ontario, Canada<br><br>Phase II/III trial complete; a 2nd phase III trial was discontinued in Nov 2012; company seeking a meeting with the FDA to develop a plan for U.S. registration, which may require additional clinical trials | BCG treatment<br>Cystectomy<br>Intravesicular chemotherapy<br>Radiation therapy | Increased overall survival<br>Increased progression-free survival<br>Avoidance of cystectomy<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Vintafolide (EC145) 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 in whom platinum-resistant ovarian cancer has been diagnosed have a poor prognosis and few treatment options. Vintafolide (EC145) 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. In clinical trials, this agent is administered in combination with pegylated liposomal doxorubicin. Vintafolide is administered at a dose of 1 mg, intravenously, 5 days/week for the 1st 3 weeks of each 4-week cycle, then at a maintenance dose of 2.5 mg, 3 days/week, during weeks 1 and 3 of each 4-week cycle.<br><br>Endoctye, Inc., West Lafayette, IN, in collaboration with Merck & Co., Inc., Whitehouse Station, NJ<br><br>Phase III trial ongoing | Docetaxel<br>Etoposide<br>Gemcitabine<br>Paclitaxel<br>Pegylated liposomal doxorubicin<br>Topotecan | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Vismodegib (Erivedge) for treatment of basal cell carcinoma | Patients in whom advanced/ metastatic basal cell carcinoma has been diagnosed | No systemic treatment was approved for treating basal cell carcinoma before the approval of vismodegib, and patients with advanced/metastatic disease not amenable to surgical resection had few treatment options. Vismodegib (Erivedge) inhibits the protein Smoothened, which is essential for transducing hedgehog signaling. Activation of the hedgehog signaling pathway, which is normally silenced after early development, has been implicated in the development and survival of a large percentage of basal cell carcinomas. Vismodegib is an oral capsule administered once daily at 150 mg.<br><br>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland<br><br>Phase II trials ongoing; FDA approved Jan 2012 based on phase II results for locally advanced and metastatic cancer; approval includes black box warning of potential risk to unborn fetuses of death or severe birth defects | No other approved systemic treatment option available | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Volasertib (BI 6727) 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 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, volasertib is being used in combination with low-dose cytarabine.<br><br>Boehringer Ingelheim GmbH, Ingelheim, Germany<br><br>Phase III trial ongoing; FDA granted breakthrough therapy status Sept 2013 | 5-azacytidine<br>Decitabine<br>Low-dose cytarabine | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| 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.<br><br>Sunesis Pharmaceuticals, Inc., South San Francisco, CA<br><br>Phase III trial ongoing | Cladribine, cytarabine, and granulocyte colony-stimulating factor (GM-CSF) plus or minus mitoxantrone or idarubicin<br>Clofarabine, cytarabine, and GM-CSF<br>Etoposide and cytarabine plus or minus mitoxantrone<br>Fludarabine, cytarabine, and GM-CSF plus or minus idarubicin<br>High-dose cytarabine and GM-CSF plus or minus anthracycline | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Case Comprehensive Cancer Center of Case Western Reserve University, Cleveland, OH<br><br>Phase III trial completed; initial results reported at ASCO 2013 | Physician counseling<br>Patient research | Increased consideration of clinical trial enrollment<br>Improved preparedness to discuss clinical trial opportunities<br>Increased rates of clinical trial enrollment |
| Zoptarelin doxorubicin (AEZS-108) 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 between a luteinizing hormone–releasing hormone (LHRH) analog 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 dose of 267 mg/m$^2$, every 3 weeks, up to 9 treatment cycles.<br><br>AEterna Zentaris, Inc., Quebec, Quebec, Canada, in partnership with Ergomed Ltd., Frankfurt, Germany<br><br>Phase III trial ongoing | Doxorubicin | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

**Table 3. AHRQ Priority Condition: 03 Cardiovascular Disease: 42 Interventions**

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 | Current 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 quicker recovery time. Patients with small vessel anatomy have not been eligible for endovascular repair of AAAs because of the relatively large size of available stent systems for endovascular repair. 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.<br><br>TriVascular, Inc., Santa Rosa, CA<br><br>FDA granted humanitarian device exemption in Nov 2011; FDA granted premarket approval Oct 2012 | Open surgical repair | Decreased perioperative risks<br>Decreased mortality<br>Faster recovery |
| Alferminogene tadenovec (Generx) for treatment of chronic angina pectoris | Patients in whom coronary artery disease and stable angina has 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 (Ad5FGF-4, Generx®) is a DNA-based angiogenic growth factor that purportedly increases myocardial blood flow through the development of collateral blood vessels around the heart to try to relieve angina symptoms. Alferminogene tadenovec is administered through intracoronary infusion with percutaneous angioplasty and a novel adenovector delivery method that uses transient ischemia to enhance delivery of vector to the heart.<br><br>Cardium Therapeutics, Inc., San Diego, CA<br><br>Phase III trial ongoing (ASPIRE) using a new transient ischemia method for delivery | Angioplasty<br>Beta blockers<br>Calcium channel blockers<br>Coronary bypass surgery<br>Coronary stents<br>Long-acting nitrates<br>Ranolazine | Decreased angina<br>Fewer cardiovascular events<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Anacetrapib (MK0859) 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 per year. Anacetrapib is a cholesterol ester transfer protein inhibitor intended to raise high-density lipoprotein by 100% and reduce low-density lipoprotein, 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.<br><br>Merck & Co., Inc., Whitehouse Station, NJ<br><br>Phase III trials (DEFINE, REVEAL) ongoing for indications including dyslipidemia, hypercholesterolemia, homozygous familial hypercholesterolemia | Lifestyle changes<br>Pharmacotherapy (e.g., statins) | Reduced risk of heart attack<br>Improved cardiovascular outcomes |
| Angiotensin receptor blocker/ 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 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 development; in Stage A, the primary goal is to treat and manage the underlying risk factors. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers may be used at this stage. LCZ696 is a 1st-in-class angiotensin receptor blocker/neprilysin inhibitor purported to treat HF. In clinical trials, it is being administered at twice-daily doses of 50, 100, or 200 mg.<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase III trials ongoing | ACE inhibitors<br>Angiotensin II receptor blockers<br>Beta blockers<br>Diuretics<br>Inotropes<br>Nesiritide<br>Vasodilators | Decreased morbidity<br>Decreased mortality<br>Improved heart failure symptoms<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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).<br><br>Aastrom Biosciences, Inc., Ann Arbor, MI<br><br>Phase III trial ongoing, FDA granted fast-track status for CLI | Percutaneous angioplasty and stenting<br>Pharmacotherapy (e.g., cilostazol and pentoxifylline)<br>Surgery | Tissue regeneration<br>Improved circulation<br>Reduced need for amputation<br>Reduced morbidity and mortality |
| Autologous bone marrow–derived stem cell therapy (C-Cure) for heart failure | Patients in whom severe heart failure (HF) has been diagnosed | No treatments are available that can repair heart tissue to reverse HF. Patients with end-stage HF have few options—ventricular assist device implant, total artificial heart implant, or a heart transplant. C-Cure® consists of stem cells derived from a patient's bone marrow and cultured in a proprietary laboratory process to become cardiac lineage cells intended to improve heart function when injected into the patient's heart. The company states that the process "reprograms" cells so they become heart precursor cells with "the aim of replicating the normal process of cardiac development in the embryo" and purportedly stimulating heart-tissue repair. The company has developed a proprietary catheter called C-Cath®ez® to deliver the processed cells to the patient.<br><br>Cardio3 BioSciences, S.A., Mont-Saint-Guibert, Belgium<br><br>Phase III trial (CHART-1) began in Jun 2013 | Cardiac rhythm therapy devices<br>Heart transplant<br>Implanted cardioverter defibrillator<br>Medical therapy<br>Total artificial heart implantation<br>Ventricular assist device | Increased left ventricular ejection fraction and other heart-function outcomes<br>Improved activities of daily living<br>Increased survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 chronic HF, are unable to achieve desired optimal medical therapy goals, and are not candidates for cardiac resynchronization therapy. According to the manufacturer, "it is typically implanted in the right pectoral region and is connected to 3 standard pacemaker leads that are threaded through veins into the right side of the heart. One lead is used to sense atrial activity, and the other two are used to sense ventricular activity…." It 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.<br><br>Impulse Dynamics, NV, Willemstad, Netherlands Antilles<br><br>Phase II/III trial ongoing; Conformité Européene (CE) marked | Implanted pacemakers and/or defibrillators<br>Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics) | Symptom relief<br>Improved 6-minute walk test<br>Fewer hospitalizations<br>Delayed progression of HF<br>Delayed need for ventricular assist devices<br>Improved quality of life |
| Cardiac resynchronization therapy for heart failure with atrioventricular block | Patients with atrioventricular block and heart failure (HF) | Atrioventricular block is typically treated with right ventricular pacing; however, ventricular dyssynchrony caused by right ventricular pacing is thought to adversely affect left ventricular function and geometry; therefore, it may present problems in patients with existing cardiac dysfunction. Cardiac resynchronization therapy (CRT) is an approved therapy for patients with HF who have a diminished ejection fraction and a prolonged QRS duration. Patients with atrioventricular block and HF often do not have the QRS indication for treatment with CRT, and thus CRT therapy is now being investigated as a new therapy for patients with atrioventricular block and HF.<br><br>Medtronic, Inc., Minneapolis MN<br><br>Unphased trials completed; Oct 2013, FDA Circulatory System Devices advisory panel voted that biventricular pacing would be both safe and effective | Right ventricular pacing | Fewer HF-related hospitalizations<br>Decreased mortality<br>Improved functional status<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 different types of pharmacotherapy are used in conjunction to try to achieve desired goals for lowered blood pressure. Yet, many cases of hypertension are not controlled with these interventions and some of these cases are considered to be treatment resistant. Because treatment resistant hypertension is associated with high morbidity (e.g., end-organ damage) and mortality, novel interventions are warranted. Renal sympathetic nerves are believed to play a role in treatment-resistant hypertension. 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.<br><br>Medtronic, Inc., Minneapolis, MN<br><br>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 | Pharmacotherapy (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers)<br>Renal artery stents | Controlled hypertension with fewer or no medications<br>Reduced rates of blindness, heart attacks, kidney failure, and stroke |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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%. 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. Treatment options include medical management and surgical revision. This intervention has the potential to be the 1st minimally invasive, catheter-based treatment for ischemic HF. According to its manufacturer, the Parachute™ Ventricular Partitioning Device is an implant that 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.<br><br>CardioKinetix, Inc., Menlo Park, CA<br><br>Phase III clinical trials ongoing (PARACHUTE IV pivotal trial in U.S.; other trials ongoing in Europe and Asia) | Heart transplant<br>Pharmacotherapy (e.g., beta blockers)<br>Surgical ventricular revision | Improved HF symptoms<br>Increased cardiac output<br>Increased survival<br>Reduced left ventricular volume<br>Reduced morbidity |
| 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. 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 atherosclerotic 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.<br><br>GlaxoSmithKline, Middlesex, UK<br><br>Phase III trial ongoing (STABILITY) | Pharmacotherapy (e.g., statins) | Improved plaque stability<br>Reduced atherosclerosis<br>Reduced morbidity and mortality |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 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. 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.<br><br>H. Lundbeck a/s, Valby, Denmark<br><br>1 phase III trial complete; other phase III trials ongoing (DIAS 3 and DIAS 4); company anticipates filing new drug application in 2014 | tPA therapy | Increased blood flow to the brain<br>Reversed damage<br>Improved stroke-related outcomes |
| Electrical stimulation of carotid baroreceptors (Barostim neo System) for treatment of drug-resistant hypertension | Patients in whom severe, drug-resistant hypertension has been diagnosed | 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 treating hypertension that has not responded to medical therapy. 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.<br><br>CVRx, Inc., Minneapolis, MN<br><br>Pivotal trials ongoing under FDA granted investigational device exemption status | Optimal medical management | Reduced hypertension<br>Reduced stoke incidence<br>Fewer cardiovascular events<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Evacetrapib (LY2484595) for prevention of cardiovascular events | Patients in whom 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.<br><br>Eli Lilly and Co., Indianapolis, IN<br><br>Phase III (ACCELERATE) trial ongoing; completion anticipated in 2016 | Pharmacotherapy<br>Sclerotherapy | Improved HDL profile<br>Reduced cardiovascular morbidity and mortality<br>Improved quality of life |
| Extra-aortic balloon counter-pulsation heart assist device (C-Pulse) for treatment of heart failure | Patients with New York Heart Association class III or ambulatory class IV heart failure (HF) | Available implanted devices for HF (e.g., intra-aortic balloon pump, left ventricular assist device) come into contact with the patient's blood, leading to a risk of stroke and blood clots, and are intended for use in patients with more advanced HF. The C-Pulse® heart-assist system consists of a mechanical balloon cuff that is wrapped around the outside of the aorta during a minimally invasive or full sternotomy procedure and is intended to reduce the workload of the left ventricle. The system's driver sits outside the body. According to the manufacturer, when the balloon is inflated, blood flow to the coronary arteries is increased, 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).<br><br>Sunshine Heart, Inc., Eden Prairie, MN<br><br>Feasibility trials completed; pivotal phase III trial (COUNTER HF™) initiated Nov 2012 | Intra-aortic balloon pumps<br>Left ventricular assist devices | Decreased morbidity<br>Increased cardiac output<br>Increased survival<br>Reduced cardiac workload<br>Reduced risk of stroke or thrombi |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Freedom portable driver system 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.<br><br>SynCardia Systems, Inc., Tucson, AZ<br><br>FDA approved TAH-t in 2004; Freedom portable driver Conformité Européene (CE) marked in Mar 2010; investigational device exemption trial completed required enrollment of 30 patients in 2012 with followup ongoing; worldwide 100 patients have received the system for out-of-hospital use | TAH-t used with in-hospital driver | Restored mobility<br>Possible recovery at home (reduction in hospitalization costs)<br>Extended survival for patients awaiting heart transplantation |
| Human monoclonal antibody anti-PCSK9 (AMG 145) for treatment of hyperlipidemia | 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.<br><br>Amgen, Inc., Thousand Oaks, CA<br><br>Phase III clinical trial ongoing | Mipomersen (in development)<br>MTP-I inhibitors (in development)<br>Statins | Decreased cardiovascular events |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase III trials completed and ongoing | Calcium channel blockers<br>Endothelin receptor antagonists<br>Phosphodiesterase type 5 inhibitors<br>Prostanoids | Improved exercise capacity<br>Reduced mortality<br>Fewer hospitalizations |
| 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. Patients who have had 1 MI are often at high risk of another MI. 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.<br><br>Angel Medical Systems, Shrewsbury, NJ<br><br>Phase III pivotal trial ongoing; Conformité Européene (CE) Sept 2010 | Conventional, external MI detection technologies<br>Patient report<br>Routine physician followup | Earlier detection of impending heart attack<br>Prevention of heart damage<br>Increased overall survival |
| Injectable biopolymer (Algisyl-LVR) for prevention or treatment of heart failure | Patients with 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%. 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 to thicken upon injection, forming gel-like bodies that remain in heart muscle as permanent implants. It is 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).<br><br>Cardio Polymers, now part of LoneStar Heart, Inc., Laguna Hills, CA<br><br>Phase II/III trial ongoing (Augment-HF) | Drug therapy to prevent HF | Increased left ejection fraction<br>Reduced progression of HF<br>Reduced regression of HF<br>Improved cardiovascular outcomes<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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."<br><br>Aegerion Pharmaceuticals, Inc., Cambridge, MA<br><br>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<br>Liver transplant<br>Pharmacotherapy (e.g., statins) | Reduced low-density lipoprotein levels<br>Improved cardiovascular outcomes<br>Improved quality of life<br>Improved long-term health outcomes |
| 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 | 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.<br><br>HeartFlow, Inc., Redwood City, CA<br><br>Phase IV clinical trial completed; DISCOVER-FLOW study complete; PLATFORM study ongoing | FFR-guided coronary angiography | Improved coronary revascularization<br>Decreased morbidity associated with invasive angiography |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Off-label methotrexate for treatment of cardiovascular disease | Patients with type 2 diabetes 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 the inflammation will decrease the risk of cardiovascular disease. Conditions such as type 2 diabetes and metabolic syndrome are associated with an enhanced proinflammatory response, and patients with these conditions are at increased risk of experiencing myocardial infarctions and stroke. The anti-inflammatory agent methotrexate is being investigated as a drug to prevent stroke, myocardial infarction recurrence, and cardiovascular death in patients with type 2 diabetes or metabolic syndrome who have a history of myocardial infarction. In a new clinical trial, methotrexate will be administered orally at a dosage of 15–20 mg weekly.<br><br>This study is funded by the National Heart, Lung, and Blood Institute, Bethesda, MD<br><br>Phase III clinical trial ongoing | Anticoagulants<br>Antidiabetes agents<br>Antihypertensives<br>Antiplatelets<br>Cholesterol-lowering agents<br>Lifestyle changes | Decreased risk of stroke<br>Decreased risk of myocardial infarction recurrence<br>Decreased risk of cardiovascular death<br>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.<br><br>National Institute of Allergy and Infectious Diseases, Bethesda, MD (trial sponsor)<br><br>Phase II trial ongoing | Calcium channel blockers<br>Endothelin receptor antagonists<br>Phosphodiesterase type 5 inhibitors<br>Prostanoids | Improved exercise capacity<br>Reduced mortality<br>Reduced hospitalization |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| PCSK9 inhibitor (REGN727/SAR236553) 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. REGN727/SAR236553 represents a new mechanism of action for hypercholesterolemia treatment. The drug is a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. 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. REGN727/SAR236553 is administered subcutaneously.<br><br>Sanofi, Paris, France<br>Regeneron Pharmaceuticals, Inc., Tarrytown, NY<br><br>ODYSSEY worldwide phase III clinical trials program announced in Jul 2012 comprising 10 trials enrolling 22,000 patients | Pharmacotherapy (e.g., statins) | Improved lipid levels<br>Reduced morbidity<br>Reduced mortality |
| Percutaneous annuloplasty (Carillon Mitral Contour System) to treat functional mitral regurgitation | Patients in whom functional mitral regurgitation has been diagnosed | Mitral regurgitation can require invasive surgery when it is severe. 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). The device purports to reduce mitral annulus dilation, thus reducing functional mitral regurgitation.<br><br>Cardiac Dimensions, Inc., Kirkland, WA<br><br>European clinical trials ongoing, but not FDA registered; Conformité Européene (CE) marked in 2009 | Optimal medical management<br>Minimally invasive surgery<br>Open surgery | Reduced risk of cardiac events<br>Reduced mitral regurgitation<br>Reduced operative morbidity<br>Reduced mortality<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Percutaneous left atrial appendage ligation (Lariat Suture Delivery Device) for prevention of atrial fibrillation-associated stroke | Patients in whom atrial fibrillation has been diagnosed | 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. 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 atrial fibrillation.<br><br>SentreHEART, Inc., Redwood City, CA<br><br>FDA approved in 2009 for soft tissue ligation; an ongoing clinical trial is comparing the Lariat and Watchman devices | Amplatzer Cardiac Plug (in development)<br>Anticoagulants<br>Atriclip Left Atrial Appendage Exclusion System<br>Watchman device (in development) | Decreased atrial fibrillation-associated stroke occurrence<br>Decreased morbidity |
| Percutaneous left atrial appendage occlusion (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). The Watchman device is implanted in a percutaneous catheterization procedure, using a standard transseptal technique and fluoroscopic guidance.<br><br>Boston Scientific Corp., Natick, MA<br><br>Phase III trials ongoing; FDA advisory panel meeting regarding approval recommendations scheduled for Dec 11, 2013 | Long-term anticoagulation therapy | Reduction in stroke risk |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Renal denervation (Symplicity System) for treatment of heart failure | Patients in whom treatment-resistant heart failure (HF) and renal impairment have been diagnosed | 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.<br><br>Medtronic, Inc., Minneapolis, MN<br><br>Phase IV trial (SYMPLICITY-HF) recruiting; the system is also in later-phase development for treatment-resistant hypertension | Pharmacotherapy (e.g., beta blockers) | Decreased HF-related morbidity<br>Improved quality of life<br>Increased survival<br>Reduced SNS activity |
| 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.<br><br>Bayer AG, Leverkusen, Germany<br><br>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 | Calcium channel blockers<br>Endothelin receptor antagonists<br>Phosphodiesterase type 5 inhibitors<br>Prostanoids | Improved exercise capacity<br>Reduced mortality<br>Reduced hospitalizations |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Selective prostacyclin (PGI2) receptor agonist (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.<br><br>Actelion Pharmaceuticals, Ltd., Allschwil, Switzerland<br><br>Phase III trials ongoing | Calcium channel blockers<br>Endothelin receptor antagonists<br>Phosphodiesterase type 5 inhibitors<br>Prostanoids | Improved exercise capacity<br>Reduced mortality<br>Reduced hospitalization |
| Serelaxin (RLX303) for treatment of acute heart failure | Patients in whom acute heart failure (HF) has been diagnosed | 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 the treatment of acute HF. In clinical trials, serelaxin (30 mcg/kg) was administered intravenously for 48 hours after acute HF diagnosis.<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase III RELAX-AHF trial completed; FDA granted breakthrough therapy status Jun 2013 | Diuretics<br>Vasodilators | Relief of dyspnea<br>Decreased mortality |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 limited efficacy in preventing embolic debris during surgery. Embolic protection devices include balloons, baskets, and filters. The Silk Road System device is intended to provide cerebral embolic protection during CAS. It purports to provide the clinician with the ability to regulate the speed of carotid blood flow and stop it temporarily. The device consists of a circuit of arterial and venous sheaths, which are connected by surgical tubing and an in-line flow controller for clinician manipulation. The system purportedly differs from other embolic protection systems by allowing blood flow control without external carotid artery manipulation.<br><br>Silk Road Medical, Sunnyvale, CA<br><br>Pivotal trial ongoing | Embolic protection devices (e.g., balloons, baskets, filters) | Increased embolic protection |
| Stem cell mobilization by granulocyte-colony stimulating factor for treatment of peripheral artery disease | Patients in whom peripheral artery disease with critical limb ischemia has been diagnosed | Patients with critical limb ischemia are at high risk of amputation, and are limited in their ability to ambulate because of ulceration and pain. Small-vessel disease and other coexisting morbidities preclude many patients from surgical treatment, and noninvasive treatment options are needed. The use of granulocyte-colony stimulating factor (G-CSF) to mobilize angiogenic stem cells blood and promote angiogenesis in areas of ischemia is a new, noninvasive treatment option to improve blood flow in patients with critical limb ischemia. In an ongoing clinical trial, G-CSF is being injected subcutaneously at a dosage of 5 mcg/kg/day for 10 days.<br><br>Sponsored by Washington University School of Medicine, St. Louis, MO<br><br>Phase III clinical trial completed | Angioplasty with stent placement<br>Bypass surgery<br>Percutaneous transluminal angioplasty | Improved blood flow<br>Improved ambulation<br>Decreased ulceration<br>Decreased pain<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy | Patients with cardiomyopathy who are at risk of sudden cardiac arrest | 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.<br><br>Boston Scientific Corp., Natick, MA (acquired developer Cameron Health Jun 2012)<br><br>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 | Quicker recovery after implantation<br>Reduced risk of unnecessary shocks<br>Reduced risk of failures to shock<br>Improved quality of life |
| Synthetic urodilatin (ularitide) for treatment of acute decompensated 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.<br><br>Cardiorentis, Ltd., Zug, Switzerland<br><br>Patients are being recruited for a phase III clinical trial started Jul 2012 | Diuretics<br>Inotropes<br>Nesiritide<br>Vasodilators | Improvement in heart failure symptoms<br>Decreased morbidity<br>Decreased mortality<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis | Patients in whom severe aortic stenosis (AS) has been diagnosed | AS 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 AS 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 AS are not suitable candidates for valve implantation performed as an open-heart surgery procedure. The transcatheter aortic valve (CoreValve®) implantation procedure uses fluoroscopic guidance 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.<br><br>Medtronic, Inc., Minneapolis, MN<br><br>Phase III trials ongoing; although not yet FDA approved, Medicare covers the valve under “cover with evidence development” rules; Conformité Européene (CE) marked in 2007; available outside U.S. in 34 countries | Open surgery<br>Optimal medical management<br>Other transcatheter aortic valves | Improved cardiac function<br>Increased survival<br>Improved quality of life |
| 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 can require invasive surgery when it is severe. 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. The device is intended for patients whose valve disease originates mainly from the center of the valve.<br><br>Abbott Laboratories, Abbott Park, IL<br><br>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<br>Pharmacotherapy | Decreased cost of HF complications<br>Improved quality of life for patients who are not good surgical candidates<br>Reduced mitral regurgitation<br>Slowed disease progression |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Treprostinil diolamine 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, if approved, could be 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.<br><br>United Therapeutics Corp., Silver Spring, MD<br><br>Phase III trials ongoing; FDA sent Complete Response Letters declining United Therapeutics' new drug application initial submission and resubmission were sent in Oct 2012 and Mar 2013. United Therapeutics plans to continue to pursue FDA approval | Calcium channel blockers<br>Endothelin receptor antagonists<br>Phosphodiesterase type 5 inhibitors<br>Prostanoids | Improved exercise capacity<br>Reduced mortality<br>Reduced hospitalization |
| Ultrasound (ClotBust-ER) for treatment of acute ischemic stroke | Patients in whom acute ischemic stroke has been diagnosed | Transcranial ultrasound is a new treatment for 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 (EDs). An unmet need exists to extend this therapy to smaller EDs. ClotBust™-ER is an ultrasound device that employs multiple transducers operating at 2 MHz, and 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 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.<br><br>Cerevast Therapeutics, Inc., Redmond, WA<br><br>Phase I/II trial completed; phase III trial ongoing | Sonographer-administered ultrasound<br>Tissue plasminogen activator therapy | Improved clot lysis<br>Reduced stroke-related morbidity and mortality |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Vagus nerve stimulation (CardioFit) for treatment of heart failure | Patients in whom severe congestive heart failure (HF) has been diagnosed | 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.<br><br>BioControl Medical, Yehud, Israel<br><br>Phase III trial ongoing | Heart transplantation<br>Minimally invasive heart surgery<br>Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics)<br>Ventricular assist devices | Improved left ventricular ejection fraction<br>Improved 6-minute walk test<br>Reduced need for medication<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Wireless monitoring system (Champion) for management of heart failure | Patients in whom moderately severe heart failure (HF) has been diagnosed | In hospitalized patients, catheters placed temporarily within the heart to monitor left atrial pressure are the gold standard for tracking blood movement (hemodynamics) and worsening HF; however, no devices are available for monitoring ambulatory patients. About 1/3 of patients with HF who have been discharged from the hospital are readmitted within 30 days, usually for worsening signs and symptoms of congestion. This congestion is caused by increases in intracardiac and pulmonary artery pressures, which are apparent several days to weeks before the onset of worsening signs, symptoms, and hospital admission. Thus, researchers suggest, monitoring these pressures might reduce the risk of readmission to hospital. The Champion device is a self-contained, paper clip–sized device placed in the pulmonary artery during a catheter-based procedure. A patient holds the external electronic module over the chest to wirelessly power the sensor and collect pressure data using radiofrequency energy. The handheld unit then transmits data to the CardioMEMS Champion Web site, which the physician monitors. This device may give clinicians more timely access to changes in symptoms and physiologic parameters, allowing them to quickly adjust medications and potentially reduce HF-related hospitalizations. This would be the 1st FDA-approved, permanent monitor implant for this indication.<br><br>CardioMEMS, Inc., Atlanta, GA<br><br>Premarket approval application submitted to FDA; Dec 2011 advisory panel voted 6-4 to not recommend approval because of potential bias in the trial design; company is deciding next steps; Jun 2012 FDA sent warning letter to company about “serious violations” of the Code of Federal Regulations pertaining to investigational device exemption trials and protection of human subjects; in an Oct 2012 interview with The Atlanta Journal-Constitution, a company spokesperson indicated the company sent a response to FDA and plans to continue pursuing marketing requirements; Oct 2013 advisory panel voted 11-0 that the device is safe and 6-4-1 that benefits outweigh risks, but also 7-4 that the device is not effective | Weight monitoring (for fluid retention)<br>Symptom monitoring | Improved clinician access to changes in patient symptoms<br>Earlier medical intervention<br>Reduced HF-related hospitalizations<br>Improved morbidity and mortality |

**Table 4. AHRQ Priority Condition: 04 Dementia (including Alzheimer's): 13 Interventions**

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| [18F] FDDNP positron emission tomography imaging agent for diagnosis of chronic traumatic encephalopathy | Patients at risk of 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. At this time, the disease is diagnosed only after evaluation of brain tissue posthumously, with evidence of tissue degeneration and elevation of tau protein. Researchers recently studied positron emission tomography (PET) imaging with 2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene)malononitrile (FDDNP), a radiotracer that binds to tau protein and amyloid deposits for its usefulness in locating these tau protein deposits in the brain's subcortical region and in the amygdala. Compared with tau protein deposits in control patients, the imaging revealed tau protein deposits in these regions in all of the participating 5 retired National Football League players.<br><br>University of California, Los Angeles<br><br>Unphased trial completed | Posthumous diagnosis | Improved treatment protocol<br>Reduced mild cognitive impairment and other CTE symptoms<br>Improved quality of life |
| 18F-florbetapir (Amyvid) positron emission tomography imaging agent for detecting beta-amyloid plaques | Patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline associated with beta-amyloid plaques | No definitive method exists for diagnosing AD in a living person. Diagnosis is made on the basis of clinical signs and symptoms, sometimes aided by positron emission tomography (PET) using a contrast agent. Florbetapir F18 (Amyvid™) is a radiopharmaceutical that binds specifically to beta amyloid and is visualized by PET imaging. Contrast agent would be indicated for visualization of beta-amyloid aggregates; a negative result could help to rule out presence of pathologically relevant levels of beta-amyloid plaques.<br><br>Avid Radiopharmaceuticals, a subsidiary of Eli Lilly and Co., Indianapolis, IN<br><br>FDA approved Apr 2012 for detecting beta-amyloid plaques | Blood tests for AD biomarkers<br>Cerebrospinal fluid tests for AD biomarkers<br>Neuropsychological test battery<br>Positron emission tomography scans with beta amyloid–binding contrast agents | Increased sensitivity and specificity of beta-amyloid plaque detection |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 18F-flutemetamol (Vizamyl) positron emission tomography imaging agent for detecting beta-amyloid plaques | Patients in whom Alzheimer's disease (AD) is suspected | No definitive method exists for diagnosing AD in a living person. Diagnosis is made on the basis of clinical signs and symptoms, sometimes aided by positron emission tomography (PET) using a contrast agent. Flutemetamol is a PET imaging agent intended to detect normal or raised beta-amyloid plaques in the brain to confirm a diagnosis of AD.<br><br>General Electric Co., Fairfield, CT<br><br>Received FDA approval Oct 2013 | Blood tests for AD biomarkers<br>Cerebrospinal fluid tests for AD biomarkers<br>Neuropsychological test battery<br>PET scans with beta amyloid–binding contrast agents | Sensitivity and specificity of PET for diagnosing AD<br>Improved positive and negative predictive values<br>Earlier diagnosis of AD<br>Earlier intervention for managing early AD |
| Beta-amyloid precursor protein site–cleaving enzyme inhibitor (MK-8931) for treatment of Alzheimer's disease | Patient in whom prodromal or mild to moderate 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. MK-8931 is an oral beta-amyloid precursor protein site–cleaving enzyme (BACE) inhibitor that is being investigated for the treatment of AD and prodromal AD. The company states that the drug is intended to exert its effects by inhibiting BACE, an enzyme that is known to play a role in the initiation of synthesis of amyloid beta peptide. Because abnormal accumulation of amyloid beta peptide is thought to play a role in the progression of AD, 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.<br><br>Merck & Co., Inc., Whitehouse Station, NJ<br><br>Phase II/III and phase III trial ongoing | Non-disease modifying pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine) | Reduced amyloid beta load in brain<br>Regression or slowing of disease progression<br>Reduced morbidity and mortality<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Deep brain stimulation for treatment of Alzheimer's disease | Patients in whom Alzheimer's disease (AD) has been diagnosed | The currently approved therapies for AD are unable to modify disease progression and have a minimal impact on symptoms. Therapeutic options are limited in 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 think to be an issue in Alzheimer's disease.<br><br>Various study sponsors:<br>Functional Neuromodulation Ltd., Toronto, Ontario, Canada (ADvance study using Medtronic DBS system)<br>Ohio State University, Columbus (appears to be an independent study)<br><br>1 trial completed, 1 phase I/II study ongoing; 1 unphased trial ongoing | Behavior therapy<br>Nutrition therapy<br>Pharmacotherapy (i.e., Donepezil, memantine, rivastigmine) | Delayed progression to AD<br>Reduced morbidity<br>Improved 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; available therapy options are limited to symptom management. 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.<br><br>F. Hoffmann-La Roche, Ltd., Basel, Switzerland<br><br>Phase III trial ongoing | Cholinergic agents (e.g., donepezil, galantamine, tacrine)<br>NMDA inhibitor (e.g., memantine) | Slowed disease progression, or regression<br>Reduced morbidity<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Handheld event-related potential/ quantitative electroencephalo-graphy system (Cognision) for diagnosis of Alzheimer's disease | Patients in whom a diagnosis of Alzheimer's disease (AD) is suspected | No definitive method exists for diagnosing AD in a living person. Diagnosis is made on the basis of clinical signs and symptoms, sometimes aided by positron emission tomography (PET) using a contrast agent. 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 via noninvasive technology using electrodes attached to a hat-like frame, which is placed on the head. The system is designed to measure 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 analyzes data and classifies the patient's brainwaves based on similarities to known neurologic risk profiles.<br><br>Neuronetrix, Inc., Louisville, KY<br><br>Trial ongoing (no phase listed) | Blood tests for AD biomarkers<br>Cerebrospinal fluid tests for AD biomarkers<br>Neuropsychological test battery<br>PET scans with beta amyloid–binding contrast agents | Improved ability to diagnose, rule out, and/or screen for AD<br>Earlier intervention<br>Improved outcomes<br>Improved quality of life |
| MRI-based algorithm to screen for Alzheimer's disease or frontotemporal lobar degeneration | Patients in whom a diagnosis of Alzheimer's disease (AD) is suspected | No definitive method exists for screening or diagnosing AD in a living person. Despite the lack of effective AD treatment, an unmet need exists for less invasive diagnostic/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. Screening and diagnosing AD currently rely on interpretation of clinical signs and symptoms, sometimes aided by positron emission tomography (PET) using a contrast agent. More invasive diagnostic measures include lumbar puncture to analyze cerebrospinal fluid (CSF) to detect total tau and beta-amyloid protein accumulation. The ability to better screen patients noninvasively is needed to determine patients in whom lumbar puncture is indicated so that unnecessary lumbar punctures can be avoided. Magnetic resonance imaging using an algorithm to measure the ratio of total tau and beta-amyloid protein present in a patient's brain is under study to do this. Researchers purport that this method could be useful to more accurately screen for early presence of disease and disease progression.<br><br>Perelman School of Medicine, University of Pennsylvania, Philadelphia<br><br>Clinical trial completed 2012 | Blood tests for AD biomarkers<br>Cerebrospinal fluid tests for AD biomarkers<br>Neuropsychological test battery<br>PET scans with beta amyloid–binding contrast agents | Improved ability to diagnose, rule out, and/or screen for AD or frontotemporal lobar degeneration<br>Earlier intervention<br>Improved outcomes<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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; available therapy options are limited to symptom management. 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 given orally at a dose of up to 100 mg, daily.<br><br>Eli Lilly and Co., Indianapolis, IN (manufacturer)<br>Emory University, Atlanta, GA, with the National Institute on Aging, Bethesda, MD (investigators)<br><br>Phase II trial ongoing; manufacturer does not appear to be seeking a labeled indication change | Off-label AD pharmacotherapy;<br>Pharmacotherapies in development | Improved cognitive performance<br>Delayed progression to AD<br>Reduced morbidity |
| Off-label carvedilol (Coreg) for the treatment of Alzheimer's disease | Patients in whom mild Alzheimer's disease (AD) has been diagnosed | The available therapies for Alzheimer's disease (AD) do not modify the disease or halt progression and are known to have minimal impact on symptoms. Carvedilol is a beta-adrenergic receptor antagonist indicated for hypertension and certain types of heart failure. Research suggests that inhibition of 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 tables, 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.<br><br>GlaxoSmithKline, Middlesex, UK (manufacturer)<br>Johns Hopkins University, Baltimore, MD, in collaboration with Mount Sinai School of Medicine, New York, NY (study sponsors)<br><br>Phase IV trial ongoing | Amyloid beta monoclonal antibodies (in development)<br>Donepezil<br>Galantamine<br>Memantine<br>Nutritional supplements (in development)<br>Other off-label beta blockers<br>Other pharmacotherapies (in development)<br>Rivastigmine<br>Tacrine | Decreased beta amyloid levels in cerebrospinal fluid<br>Delayed disease progression<br>Improved episodic memory<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Off-label intranasal insulin for treatment of Alzheimer's disease | Patients in whom 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. This intervention represents a new mechanism of action for treating AD. Insulin is known to play a role in normal brain function, modulating glucose utilization 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 and/or exacerbation of peripheral insulin resistance. Therefore, researchers have begun delivering insulin intranasally (branded insulin, delivered via a nasal drug delivery device), administered at 20 or 40 IU total dose, twice daily.<br><br>HealthPartners Research Foundation, Minneapolis, MN<br>University of Kansas, Lawrence<br>University of Washington, Seattle<br>Wake Forest University, Winston-Salem, NC, in collaboration with Alzheimer's Disease Cooperative Study, a service of the National Institute on Aging and<br>University of California, San Diego<br><br>Phase II and II/III trials ongoing; insulin manufacturers do not appear to be pursuing expanded labeling of insulin to treat AD | Cholinergic agents (e.g., donepezil, galantamine, tacrine)<br>NMDA inhibitor (e.g., memantine) | Slowed disease progression, or regression<br>Improved memory<br>Improved long-term outcomes<br>Improved quality of life |
| Solanezumab (LY2062430) for treatment of Alzheimer's disease | Patients in whom mild 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. Solanezumab is a fully humanized anti-beta-amyloid antibody that binds specifically 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 is administered 400 mg intravenously every 4 weeks for 80 weeks in clinical trials.<br><br>Eli Lilly and Co., Indianapolis, IN<br><br>Phase III trial in mild AD ongoing; additional phase III trials completed (EXPEDITION 1 and 2); Aug 2012 report of top-line results indicated drug failed to reach endpoints in EXPEDITION trials, but showed improvement in pooled results; EXPEDITION-EXT ongoing | Cholinergic agents (e.g., donepezil, galantamine, tacrine)<br>NMDA inhibitor (e.g., memantine) | Decreased brain beta-amyloid load<br>Slowed or halted disease progression<br>Improved memory and cognition<br>Improved survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Tau aggregation inhibitor (LMTX, TRx0237) for treatment of Alzheimer's disease | Patients in whom Alzheimer's disease (AD) has been diagnosed | No disease-modifying agents are approved for treating AD; available therapy options attempt to mitigate some symptoms, but have minimal impact. LMTX™ (leuco-methylthioninium, TRx0237) is a tau aggregation inhibitor said to dissolve tau protein tangles and oligomers, which are believed to be precursors of tau tangles in the brain. Tau proteins, found mostly in neuronal cells, are believed to stabilize microtubules, but if they become defective, they no longer perform this function. Some researchers think this leads to AD and dementia. In clinical trials, LMTX is administered at an oral dose of 75 to 125 mg, twice daily.<br><br>TauRx Pharmaceuticals Ltd., Singapore, Republic of Singapore<br><br>Phase III trials ongoing | Cholinergic agents (e.g., donepezil, galantamine, tacrine)<br>NMDA inhibitor (e.g., memantine) | Increased survival<br>Slowed progression of AD<br>Improved quality of life |

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

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Amitifadine (EB-1010) for treatment of depression | Patients with major depressive disorder whose disease does not respond adequately to selective serotonin reuptake inhibitors | Despite the many available therapeutic options for major depression, treatment side effects and low remission rates remain an issue. 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 a clinical trial, EB-1010 is given as an oral dose of 25–50 mg, twice daily.<br><br>Euthymics Biosciences, Inc., Cambridge, MA<br><br>Phase IIb/IIIa trial ongoing; top-line results failed to meet primary endpoint | Pharmacotherapy (e.g., serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants)<br>Psychotherapy | Increased serotonin, norepinephrine, and dopamine neurotransmission<br>Improvement in symptoms, as measured by standard depression rating scales<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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 current psychopharmaceuticals. Furthermore, despite an apparently high medication response rate, 80% of individuals with schizophrenia are functionally unable to work. Thus, new treatments for schizophrenia are urgently needed for full recovery and adaptive functioning. 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 the avatar's frightening voice and messages. Avatar therapy purportedly reduces the frequency and severity these patient's auditory hallucinations, in seven 30-minute sessions.<br><br>University College London, London, UK<br>Institute of Psychiatry, King's College London, London, UK<br><br>Pilot study with 16 patients completed | Cognitive behavior therapy<br>Cognitive remediation<br>Computerized cognitive training | Fewer symptoms<br>Improved functioning<br>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) has been diagnosed | Many pharmacologic and psychotherapeutic options are available for major depressive disorder and major depression in bipolar disorder, yet fewer than half of patients achieve remission, and many treatments have undesired side effects. Bright-light therapy (BLT) has long been diffused for seasonal affective disorder but not for nonseasonal 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. Studies have been completed and several are ongoing by various entities using bright light therapy as an adjunct to other treatments, including pharmacotherapy and behavior therapy.<br><br>Douglas Mental Health University Institute, Montreal, Quebec, Canada<br>National Institute of Mental Health, Bethesda, MD<br>New York State Psychiatric Institute, New York, NY<br>University of British Columbia, Vancouver, Canada<br>University of Pittsburgh, PA<br><br>Trials completed and ongoing | Cognitive behavior therapy<br>Pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants)<br>Psychotherapy | Improved depression rating scale scores<br>Improved sleep patterns<br>Improved quality of life<br>Reduced rate of suicide attempts and completed suicides |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Deep brain stimulation (Reclaim System) for treatment-resistant major depressive disorder | Patients in whom treatment-resistant depression has been diagnosed | Despite the many available therapeutic options for major depression, treatment side effects and low remission rates remain an issue. Once multiple medications, psychotherapy, and electroconvulsive therapy have failed, no proven treatment options exist for major depressive disorder. The neurostimulator (Reclaim system) is implanted subcutaneously in chest and delivers controlled electrical stimulation to targeted parts of the brain via thin wire electrodes.<br><br>Medtronic, Inc., Minneapolis, MN<br><br>Phase III trial ongoing; FDA approved for treating obsessive compulsive disorder | Deep brain stimulation (with other systems, or in other brain areas)<br>Electroconvulsive therapy<br>Repetitive transcranial magnetic stimulation<br>Vagus nerve stimulation | Improved depression rating scale scores<br>Improved sleep patterns<br>Improved quality of life<br>Reduced rate of suicide attempts and completed suicides |
| 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 being adequately managed 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 and bilateral, continuous and intermittent, and various targets in the brain (e.g., globus pallidus, thalamus). The type of DBS device being used is not indicated in all ongoing studies, but Medtronic, Inc., 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.<br><br>Johns Hopkins University, Baltimore, MD<br>University Hospitals, Cleveland, OH<br>University of Florida Center for Movement Disorders and Neurorestoration, Gainesville, FL<br>Various universities worldwide<br><br>Completed phase I and II trials; several ongoing phase II and III trials | Botulinum toxin type A injections<br>Pharmacotherapy (antidepressants, central adrenergic inhibitors, fluphenazine, pimozide, stimulant medications) | Reduced symptom burden<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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 major depressive disorder (MDD) has been diagnosed | Despite many available therapeutic options for MDD, treatment side effects and low remission rates remain an issue. 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. DBS leads are surgically placed within a target area in the brain and connected to a neurostimulator that is typically implanted under the skin near the collarbone. For depression, the manufacturer is investigating placement of the leads in Brodmann area 25 of the subcallosal cingulate gyrus.<br><br>St. Jude Medical, Inc., St. Paul, MN<br><br>Unphased trials ongoing | DBS (with other systems, or in other brain areas)<br>Electroconvulsive therapy<br>Repetitive transcranial magnetic stimulation<br>Vagus nerve stimulation | Improved depression rating scale scores<br>Improved sleep patterns<br>Improved quality of life<br>Reduced rate of suicide attempts |
| 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 treatment options 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. 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. Current treatment focuses on positive symptoms. In trials, the drug is being given orally once daily at several unspecified dose levels.<br><br>F. Hoffmann-La Roche, Ltd., Basel, Switzerland<br><br>Phase III trials ongoing | Pharmacotherapy (e.g., atypical antipsychotics) | Decreased symptom severity<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Lisdexamfetamine (Vyvanse) for treatment of binge-eating disorder | Patients in whom binge-eating disorder has been diagnosed | No pharmacotherapies are FDA approved for binge-eating disorder, and off-label pharmacotherapies are associated with limited efficacy, undesirable side effects, and low adherence. Lisdexamfetamine (Vyvanse®) is a prodrug of dextroamphetamine; it is FDA approved for treating attention-deficit hyperactivity disorder. The agent is thought to induce the release of dopamine and norepinephrine, which contribute to maintaining alertness, focus, thought, effort, and motivation; however, the company has not yet described the mechanism of action through which this agent is expected to exert its effects in this population. In trials, the drug is being administered orally, once daily at 50 or 70 mg for up to 52 weeks.<br><br>Shire, plc, Dublin, Ireland<br><br>Phase III trial completed, extension study ongoing; positive data reported from large phase II trial | Off-label pharmacotherapies (e.g., antiepileptics, norepinephrine reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors) | Decreased morbidity<br>Fewer binge-eating episodes<br>Improved quality of life |
| 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. Elevated levels of circulating cortisol can produce psychiatric disorders. The drug is intended to be administered orally, at a dose of 1200 mg, once daily.<br><br>Corcept Therapeutics, Menlo Park, CA<br><br>Expanded phase III trial ongoing; FDA granted fast-track status for this indication; FDA approved for Cushing's syndrome in Feb 2012 | Antipsychotics in combination with antidepressants<br>Electroconvulsive therapy | Improvement in psychotic symptoms<br>Reduced suicide rate<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Mobile apps to aid in treatment of depression | Patients in whom major depressive disorder has been diagnosed | Psychotherapy traditionally involves in-person meetings between a therapist and patient or client. This method has limitations, including 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 purport to provide psychotherapeutic benefit to patients with depression. These apps range in their capabilities and intended benefits. Features may 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.<br><br>Various research institutions, including Northwestern University, Evanston, IL; University of California, San Francisco; National Institute of Mental Health, Bethesda, MD<br><br>Clinical trials ongoing | In-person psychotherapy<br>Internet-delivered (nonmobile device) psychotherapy | Improved performance on mental health rating scales<br>Reduced morbidity<br>Reduced mortality<br>Improved quality of life |
| Mobile phone therapy for bulimia nervosa | Patients in whom bulimia nervosa has been diagnosed | Feelings of shame affect willingness to undergo treatment, and access to treatment and duration of treatment 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.<br><br>University of North Carolina at Chapel Hill<br>Institute of Psychiatry, London, UK<br>Center for Psychotherapy Research, University Hospital Heidelberg, Heidelberg, Germany<br><br>Pilot studies completed | Antidepressants<br>Nutritional counseling<br>Psychological counseling | Reduced number of binge eating and purging episodes<br>Improved symptoms of depression, eating disorder, and night eating<br>Enhanced self-monitoring and treatment, leading to improved attendance, adherence, and engagement in treatment<br>Increased remission rates |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Nicotinic alpha-7 agonist (EVP-6124) for treatment of cognitive symptoms of schizophrenia | Patients in whom schizophrenia has been diagnosed | 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 that is intended to enhance synaptic transmission in the brain and act as a co-agonist in combination with acetylcholine (ACh) to enhance cognition. According to the manufacturer, the agent sensitizes the alpha-7 receptor, thereby 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. 2 dose levels being tested as a once-daily oral drug.<br><br>EnVivo Pharmaceuticals, Watertown, MA<br><br>Phase III trials ongoing | Pharmacotherapy (e.g., atypical antipsychotics) | Improved cognitive symptoms<br>Improved social functioning<br>Improved quality of life |
| Off-label armodafinil (Nuvigil) for treatment of binge-eating disorder | Patients aged 18–65 years 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 being given orally, at a variable dosage of 150–250 mg/day.<br><br>Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel (manufacturer)<br>Lindner Center of Hope, Mason, OH (investigator)<br><br>Phase III trial ongoing | Off-label pharmacotherapies (e.g., antiepileptics, norepinephrine reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors) | Improved symptoms of binge eating<br>Reduced morbidity<br>Reduced mortality |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Off-label botulinum toxin A (Botox) for treatment of depression | Patients in whom depression has been diagnosed | Fewer than half of patients with major depressive disorder achieve remission with currently approved antidepressant therapy, and available pharmacotherapies are often associated with undesirable side effects. The neurotoxin botulinum toxin A targets the neuromuscular junction, blocking neurotransmission for several months. Paralysis of the facial musculature responsible for frowning may regulate mood through a feedback mechanism and alleviate depression symptoms. Botulinum toxin injection to the glabellad region of the brow is under study as an adjunctive treatment for major depression.<br><br>Allergan, Inc., Irvine, CA<br><br>1 ongoing trial, several completed (cumulative n=140); initial results published in May 2012 | Antidepressants<br>Combination therapy<br>Deep brain stimulation<br>Electroconvulsive stimulation<br>Psychotherapy<br>Transcranial magnetic stimulation<br>Vagus nerve stimulation | Improved scores on validated depression instruments<br>Improved quality of life |
| 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 different intervals (e.g., twice daily).<br><br>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 Hil<br><br>Clinical trials ongoing; pilot data published | Other medications for negative symptoms<br>Behavioral therapy | Improved social cognition<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Off-label ketamine for treatment-resistant depression | Patients in whom treatment-resistant major depressive disorder (MDD) or bipolar depression (BPD) has been diagnosed | Despite the many available therapeutic options for depression, treatment side effects and low remission rates remain an issue. Available options for treatment-resistant MDD or BPD (e.g., deep brain stimulation [DBS], vagus nerve stimulation [VNS], transcranial magnetic stimulation [TMS], or repetitive transcranial magnetic stimulation [rTMS]) are surgically invasive and must be performed in a hospital setting. Ketamine is under study for rapid relief of severe treatment-resistant depression and suicidal ideation. The drug is under study in 2 formulations: intravenous administration of 0.1-1.0 mg/kg once or more weekly, and intranasal administration up to 50 mg per single dose. Ketamine is being studied as a monotherapy and as an augmentive therapy to ECT.<br><br>Various institutions conducting trials sponsored by National Institute of Mental Health, Bethesda, MD<br><br>Phase II–IV trials ongoing | DBS<br>Electroconvulsive therapy<br>Pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants)<br>Psychotherapy<br>TMS<br>VNS | Rapid improvement in depression symptoms<br>Improved treatment adherence<br>Improved quality of life |
| Off-label riluzole (Rilutek) for treatment of major depressive disorder | Patients in whom treatment-resistant depression has been diagnosed | Despite the many available therapeutic options for major depression and bipolar depression, treatment side effects and low remission rates remain an issue. Available options for treatment-resistant MDD (e.g., deep brain stimulation [DBS], vagus nerve stimulation [VNS], transcranial magnetic stimulation [TMS], or repetitive TMS) are surgically invasive and must be performed in a hospital setting. The mechanism of action of riluzole (Rilutek®) would be novel for this disease state. Riluzole is a glutamatergic modulator FDA approved for treating amyotrophic lateral sclerosis; glutamate is the primary excitatory neurotransmitter in the brain, and the glutamatergic system plays a major role in MDD. Riluzole has been shown to inhibit glutamate release, enhance glutamate reuptake, and protect glial cells against glutamate excitotoxicity. In clinical trials, riluzole is administered as an oral dose of 50–100 mg, daily.<br><br>Sanofi, Paris, France (manufacturer)<br>Multiple investigators:<br>Brigham and Women's Hospital, Boston, MA<br>National Institute of Mental Health, Bethesda, MD<br>Yale University, New Haven, CT<br><br>Phase II trials ongoing; several phase II trials completed | DBS<br>Electroconvulsive therapy<br>Pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants)<br>Psychotherapy<br>TMS<br>VNS | Glutamatergic modulation<br>Improved MDD symptoms<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Off-label scopolamine (intravenous, transdermal, oral) for treatment of depression | Patients with major depressive disorder whose disease does not respond adequately to selective serotonin reuptake inhibitors | Despite the many available therapeutic options for major depression, treatment side effects and low remission rates remain an issue. 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).<br><br>Massachusetts General Hospital, Boston<br>National Institutes of Health, Bethesda, MD<br><br>Clinical trials ongoing; positive findings published from several studies | Deep brain stimulation<br>Electroconvulsive therapy<br>NMDA receptor antagonist (in development)<br>Psychotherapy<br>Serotonin-norepinephrine reuptake inhibitors<br>Tricyclic antidepressants | Improvement in symptoms, as measured by standard depression rating scales<br>Improved quality of life<br>Reduced remission rates |
| Vortioxetine (Brintellix) for treatment of major depressive disorder | Patients in whom major depressive disorder (MDD) has been diagnosed | Despite the many available therapeutic options for major depression, treatment side effects and low remission rates remain an issue. Vortioxetine (Brintellix®) is a 5-$HT_3$ and 5-$HT_7$ receptor antagonist, 5-$HT_{1A}$ receptor agonist, 5-$HT_{1B}$ receptor partial agonist, and 5-HT transporter inhibitor that has been shown to increase brain levels of serotonin, noradrenaline, dopamine, acetylcholine, and histamine. Clinical trials have suggested that the drug may be associated with low (similar to placebo) rates of sexual dysfunction, compared with available products. Vortioxetine is administered as a once-daily oral dose of 10–20 mg.<br><br>Takeda Pharmaceutical Co., Ltd., Osaka, Japan, jointly with H. Lundbeck a/s, Valby, Denmark<br><br>Received FDA approval Sep 2013 for treating MDD | Pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants)<br>Psychotherapy | Improved depression rating scale scores<br>Improved sleep patterns<br>Improved quality of life<br>Reduced rate of suicide attempts and completed suicides |

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

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| EEG-based assessment aid for diagnosis of ADHD | 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 Neurolex electroencephalographic (EEG)-based ADHD Assessment Aid is an EEG device with standardized settings to measure theta and beta brainwaves through sensors placed on a child's head, in 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.<br><br>NEBA Health, LLC, Augusta, GA<br><br>Received FDA marketing approval Jul 2013 through de novo classification process | BrainScope portable EEG system<br>Comet portable EEG system<br>Mitsar portable EEG System<br>Neurotravel Mini<br>NeuroVigil portable EEG systems<br>Neurovirtual's EEG and sleep diagnostic devices<br>Nicolet EEG Wireless Amplifier for monitoring epileptic seizures<br>Personal Neuro Devices, Inc., device<br>Other EEG types | Decreased abuse of ADHD medications<br>Increased ADHD diagnostic accuracy<br>Increased symptom relief<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Mavoglurant (AFQ056) 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. 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 doses of 25, 50, or 150 mg, twice a day.<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase II/III trial ongoing in adolescents; drug also under study for L-dopa induced dyskinesia in Parkinson's disease | Physical and behavior interventions including 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 [Catapres®], folic acid, selective serotonin reuptake inhibitors, melatonin) | Change from baseline in behavioral symptoms using the Aberrant Behavior Checklist |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Off-label intranasal oxytocin (Syntocinon) for treatment of autism spectrum disorders | Patients in whom autistic spectrum disorder (ASD) or Asperger's syndrome has been diagnosed | According to the U.S. Centers for Disease Control and Prevention, autism spectrum disorders are diagnosed in about 9 of 1,000 people in the U.S. Current 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 brain 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).<br><br>Children's Hospital of Pennsylvania, Philadelphia<br>Massachusetts General Hospital, Boston<br>Mount Sinai School of Medicine, New York, NY<br>Montefiore Medical Center, Bronx, NY<br>Stanford University School of Medicine, Stanford, CA<br>University of Illinois at Chicago<br>University of Minnesota - Clinical and Translational Science Institute, Minneapolis<br><br>Multiple phase I and II trials ongoing | Behavior and physical interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living<br>Central nervous system pharmacology<br>Melatonin<br>Selective gamma aminobutyric acid type B receptor agonist (in development) | Improved Diagnostic Analysis of Nonverbal Accuracy results<br>Improved Social Responsivity Scale scores<br>Improved Clinical Global Impressions Scale - Improvement scores |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Off-label N-acetylcysteine for treatment of autism spectrum disorders | Children in whom autism has been diagnosed | According to the U.S. Centers for Disease Control and Prevention, autism spectrum disorders are diagnosed in about 9 of 1,000 people in the U.S. Current 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. For children with 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).<br><br>Stanford University School of Medicine, Stanford, CA<br>Indiana University School of Medicine, Indianapolis<br>National Alliance for Autism Research, Princeton, NJ<br><br>Phase II trials completed | Behavior and physical interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living<br>Central nervous system pharmacology<br>Melatonin<br>Selective gamma aminobutyric acid type B receptor agonist (in development) | Improved Clinical Global Rating Scale results<br>Improved Repetitive Behavioral Scale score<br>Improved social responsiveness<br>Improved speech and language<br>Improved metabolic measures<br>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 asking to have their software to be regulated as devices delivering therapy.<br><br>Akili Interactive Labs, Boston, MA<br>Brain Plasticity, Inc., San Francisco, CA<br>Posit Science Corp., San Francisco, CA<br><br>Pilot trials ongoing | Behavior therapies<br>Combination therapies<br>Drug therapies | Improved attentiveness and academic performance<br>Reduced behavioral abnormalities<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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 has been diagnosed | According to the U.S. Centers for Disease Control and Prevention, autism spectrum disorders (ASDs) are diagnosed in about 9 of 1,000 people in the U.S. Current 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 virtual 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.<br><br>South Downs Community Special School, Eastbourne, UK<br><br>Various testing projects ongoing | Educational and behavior programs for autistic children | Improved social skills and human interaction<br>Improved activities of daily living<br>Improved quality of life |

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

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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 | Current therapies for T1DM have had variable results, and other therapies are needed to more effectively treat and slow progression of T1DM. 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.<br><br>Kamada, Ltd., Ness Ziona, Israel<br>National Institute of Allergy and Infectious Disease, Bethesda, MD<br>University of Colorado, Denver, in collaboration with Omni Bio Pharmaceuticals, Inc., Greenwood Village, CO<br><br>Phase II trials ongoing; FDA granted orphan drug status Aug 2011 | Insulin modifications<br>Islet cell transplantation<br>Pancreas transplantation | Reduced daily insulin usage<br>Improved glycated hemoglobin ($HbA_{1c}$) levels<br>Reduced complications of diabetes<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Artificial pancreas device system for treatment of diabetes | Patients with type 1 or type 2 diabetes mellitus (T1DM, T2DM) who require insulin and are highly motivated to use a closed system and monitor its function | T1DM accounts for about 5% of all diagnosed cases of diabetes mellitus, whereas T2DM makes up 95% of diagnosed diabetes mellitus. Currently, 25.8 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. 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.<br><br>Various manufacturers in collaboration with the Juvenile Diabetes Research Foundation, New York, NY<br><br>More than 25 early and mid-phase trials ongoing; FDA placed 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<br>Islet cell transplantation<br>Pancreas transplantation | Improved quality of life<br>Halted or delayed progression of secondary complications<br>Reliable glycemic control at desired levels<br>Reduced risk of acute and nighttime hypoglycemia<br>Reduction in postprandial (after meal) hyperglycemia |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Buccal insulin (Oral-lyn) for treatment of type 1 or type 2 diabetes | Individuals with type 1 diabetes mellitus (T1DM) or uncontrolled type 2 diabetes mellitus (T2DM) who require 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.<br><br>Generex Biotechnology Corp., Toronto, Ontario, Canada<br><br>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 allows Generex to provide early 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 | Diet and lifestyle changes<br>Exenatide<br>Insulin<br>Insulin sensitizers (pioglitazone, rosiglitazone)<br>Metformin<br>Sitagliptin<br>Sodium glucose co-transporter 1 and/or 2 inhibitors (in development)<br>Sulfonylurea drugs (glimepiride) | Achieved target glycated hemoglobin ($HbA_{1c}$) levels<br>Reduced glycemic excursions related to meals<br>Prevented onset of T2DM in prediabetic individuals<br>Delayed insulin dependence in T2DM<br>Improved quality of life |
| 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. Although theoretically logical, little evidence exists to support the use of topical antimicrobials for treating diabetic foot ulcers, and no topical treatment is approved for this indication. 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.<br><br>Innocoll, Inc., Ashburn, VA<br><br>FDA agreed to special protocol assessment in Jul 2013 for company's phase III development program | Levofloxacin monotherapy<br>Standard wound care and systemic antibiotics | Improved clinical cure rate<br>Improved pathogen response<br>Pathogen eradication<br>Decreased wound surface area (increased healing rate) |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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 | Current 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.<br><br>Cebix, Inc., La Jolla, CA<br><br>Phase II trial ongoing; FDA granted fast-track status for diabetic peripheral neuropathy | Analgesics<br>Duloxetine (antidepressant)<br>Lidocaine patches<br>Pregabalin (anticonvulsant)<br>Selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, antiepileptics | Reduced pain<br>Improved quality of life |
| Degludec ultra-long-acting insulin (Tresiba) and degludec plus aspart (Ryzodeg) for treatment of type 1 or 2 diabetes | Patients with type 1 or 2 diabetes mellitus who require insulin or insulin and oral medication | 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.<br><br>Novo Nordisk a/s, Bagsværd, Denmark<br><br>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<br>Exenatide<br>Insulin<br>Insulin sensitizers (pioglitazone, rosiglitazone)<br>Metformin<br>Sitagliptin<br>Sodium glucose co-transporter 1 and/or 2 inhibitors (in development)<br>Sulfonylurea drugs (glimepiride) | Achieved target glycated hemoglobin ($HbA_{1c}$) levels<br>Reduced progression of complications<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Exenatide extended-release (Bydureon) for treatment of diabetes | Patients with type 2 diabetes mellitus (T2DM) who take oral agents for control | Despite available treatments and blood glucose monitoring devices for T2DM, achieving adequate glycemic control remains a prominent issue for patients. Extended-release exenatide (Bydureon™), a version of Byetta (approved in 2005) is taken by injection, once a week. Bydureon™ is intended to improve glycemic control in patients with T2DM. It is indicated for use in the adjunct setting along with diet and exercise.<br><br>Amylin Pharmaceuticals subsidiary of Bristol-Myers Squibb, New York, NY<br>Alkermes, Inc., Waltham, MA<br><br>FDA approved Jan 2012 with black box warning; FDA requested several studies to examine C-cell hyperplasia and compare glucagon-like peptide-1 receptor expression on human, rat, and mouse thyroid C-cells; the company must also maintain a 15-year case series registry to monitor the incidence of medullary thyroid carcinoma and its association, if any, to Bydureon; FDA also required company to conduct a double-blind, placebo-controlled trial to evaluate the effects of Bydureon on the incidence of major adverse cardiovascular events in patients with T2DM, medullary thyroid carcinoma biomarkers, and long-term effects on specific disorders of the thyroid and pancreas; the approval also required the company to create a risk evaluation and mitigation strategy plan | Diet and lifestyle changes<br>Insulin<br>Insulin sensitizers (pioglitazone, rosiglitazone)<br>Metformin<br>Sitagliptin<br>Sodium glucose co-transporter 1 and/or 2 inhibitors (in development)<br>Sulfonylurea drugs (glimepiride) | Improved target glycated hemoglobin ($HbA_{1c}$) levels<br>Reduced glycemic excursions related to meals<br>Delayed insulin dependence in T2DM<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Fasiglifam (G-protein coupled receptor 40 agonist) for treatment of type 2 diabetes mellitus | Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed | Many treatments for T2DM help control glucose levels but can be associated with significant side effects, including nausea, diarrhea, weight gain, hypoglycemia, and edema. Additionally, many patients have difficulty achieving blood-glucose control with current treatments. Fasiglifam (TAK-875) is a selective G-protein coupled receptor 40 (GPR40) agonist, a specific receptor located and expressed in pancreatic islet cells. GPR40 agonists purportedly mediate fatty acid potentiation, which could acutely increase insulin secretion and, therefore, improve glucose tolerance. The developer purports the selectivity of this G-protein-coupled receptor could potentially reduce hypoglycemia risk. In trials, the drug is administered orally as a tablet at 25 or 50 mg doses daily.<br><br>Takeda Pharmaceutical Co., Ltd., Osaka, Japan<br><br>Phase III trial completed; results reported May 2013 | Diet and lifestyle changes<br>Various approved drugs for treating T2DM<br>Other GPR40 agonists in development<br>Sitagliptin<br>Sodium glucose co-transporter 1 and/or 2 inhibitors (in development)<br>Sulfonylurea drugs (glimepiride) | Halted or delayed acute and secondary diabetes complications<br>Improved glycated hemoglobin ($HbA_{1c}$) levels |
| 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.<br><br>Alimera Sciences, Inc., Alpharetta, GA<br><br>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 to the 2nd complete response letter from FDA; Iluvien has received marketing approval in several European nations; 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 on Jan 27, 2014 | Intravitreal triamcinolone acetonide with or without laser photocoagulation<br>Laser photocoagulation<br>Pharmacotherapy (e.g., VEGF antagonists) | Increased visual acuity<br>Increased contrast sensitivity<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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 | 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, 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 both English and Spanish. This intervention could be especially useful for reaching underserved communities with limited access to health care providers. The company offered this service to health care providers and health insurance plans for free until the end of 2012.<br><br>Vovixa, Inc., Washington, DC (manufacturer)<br>HealthInsight, Salt Lake City, UT (investigator)<br><br>Pilot trial ongoing; program launched Oct 2012 | Diabetes behavior and lifestyle support groups<br>Hardcopy patient education<br>Internet-based patient education | Improved glycated hemoglobin ($HbA_{1c}$) levels<br>Reduced secondary complications<br>Reduced health disparities and improved access to diabetes program<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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 | 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.<br><br>Amylin Pharmaceuticals subsidiary of Bristol-Myers Squibb, New York, NY (drug)<br>Intarcia Therapeutics, Inc., Hayward, CA (device)<br><br>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 Lily and Co. (Indianapolis, IN) returned all development rights of exenatide to Amylin | Diet and lifestyle changes<br>Insulin<br>Insulin sensitizers (pioglitazone, rosiglitazone)<br>Metformin<br>Sitagliptin<br>Sodium glucose co-transporter 1 and/or 2 inhibitors (in development)<br>Sulfonylurea drugs (glimepiride) | Improved target glycated hemoglobin ($HbA_{1c}$) levels<br>Reduced glycemic excursions<br>Delayed insulin dependence in T2DM<br>Improved quality of life |
| 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 | 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 overweight or obese as well as not obese—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<br><br>Multiple U.S. academic research centers<br><br>Mid-to-late phase trials completed and ongoing | Behavior and lifestyle modifications<br>Various approved drugs for treating T2DM<br>G-protein coupled receptor 40 agonists (in development)<br>Sitagliptin<br>Sodium glucose co-transporter 1 and/or 2 inhibitors (in development)<br>Sulfonylurea drugs (glimepiride) | Improved quality of life<br>Reduced use of diabetes medications Reduced secondary complications<br>Resolution of diabetes |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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) | 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 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.<br><br>DiagnOptics, B.V., Groningen, the Netherlands<br><br>Unphased trials completed; has Conformité Européene (CE) mark and Health Canada License approval | Noninvasive glucose screening test in development (i.e., SCOUT DS)<br>Standard blood glucose testing | Delayed or prevented secondary complications<br>Increased screening adherence<br>Increased rate of early diagnosis<br>Improved quality of life |
| Peptide immune modulator (DiaPep277) for treatment of type 1 diabetes | Patients in whom type 1 diabetes mellitus (T1DM) has recently been diagnosed | No current treatments for T1DM are curative or address the underlying cause and dysfunction. 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).<br><br>Andromeda Biotech, Ltd., Yavne, Israel<br><br>Phase III trials ongoing (open label extensions and international multicenter DIA-AID 2); phase I/II trial ongoing in Israel; FDA granted orphan drug status | Insulin modifications<br>Islet cell transplantation<br>Pancreas transplantation | Improved beta-cell function (measured as change from baseline in stimulated C-peptide secretion during a mixed-meal tolerance test)<br>Increased glycemic control |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| 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.<br><br>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland<br>Novartis International AG, Basel, Switzerland<br><br>FDA approved Aug 2012 for treating DME | Intravitreal triamcinolone acetonide with or without laser photocoagulation<br>Laser photocoagulation<br>Pharmacotherapy (e.g., vascular endothelial growth factor antagonists) | Improved vision<br>Stabilized vision<br>Reduced side effects of existing treatment<br>Improved quality of life |
| Topical antimicrobial peptide (pexiganan acetate cream 1%, Locilex) for treatment of diabetic foot ulcer infections | Patients in whom mild diabetic foot ulcer infection (DFI) has been diagnosed | An estimated that 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.<br><br>Dipexium Pharmaceuticals, LLC, New York, NY<br><br>Phase III trial registered; not yet recruiting | Carbapenems<br>Cephalosporins<br>Clindamycin<br>Fluoroquinolones<br>Linezolid<br>Lipopeptides<br>Metronidazole<br>Penicillins<br>Topical antibiotics<br>Topical antiseptics<br>Vancomycin | Decreased systemic therapy–related side effects<br>Decreased antibiotic resistance<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Ultra-rapid-acting inhaled insulin (Technosphere Insulin Inhalation System with Afrezza) for treating diabetes | Patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) who require insulin injections | Many patients with diabetes require exogenous insulin through daily injections or a subcutaneous insulin pump. Alternatives that are less invasive and have fewer side effects could improve patients' willingness to adhere to insulin therapy. 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.<br><br>MannKind Corp., Valencia, CA<br><br>Phase III trials ongoing; Aug 2013, company announced completion of 2 pivotal clinical trials (AFFINITY 1 and 2) with results favorable enough to secure additional investor funding; Oct 2013, company announced the resubmission of a new drug application to FDA; FDA has scheduled a decision regarding approval for Apr 2014 | Diet and lifestyle changes<br>Exenatide<br>Insulin modifications<br>Insulin sensitizers (pioglitazone, rosiglitazone)<br>Metformin<br>Sitagliptin<br>Sodium glucose co-transporter 1 and/or 2 inhibitors (in development)<br>Sulfonylurea drugs (glimepiride) | Improved target glycated hemoglobin ($HbA_{1c}$) levels<br>Reduced glycemic excursions related to meals<br>Delayed insulin dependence in T2DM<br>Improved quality of life |

**Table 8. AHRQ Priority Condition: 08 Functional Limitations and Disability: 73 Interventions**

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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. Alemtuzumab is a humanized monoclonal antibody targeted to the CD52 antigen (expressed on both 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 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.<br><br>Genzyme subsidiary of Sanofi, Paris, France<br><br>FDA advisory panel gave mixed votes in Nov 2013 on the evidence: voted voted voted 12-6 that substantial evidence was provided of the drug's effectiveness; voted 11 to 6 (with 1 abstention) that the 2 pivotal trials were not adequate or well controlled; voted 14 to 2 (with 2 abstentions) that evidence was insufficient to show reduction of disability; voted 17 to 0 (1 abstention) that safety results would not preclude recommending approval; voted 16 to 0 (2 abstentions) that if approved, the drug should not be indicated as a first-line agent; FDA decision expected end of Dec 2013 | Dimethyl fumarate (Tecfidera)<br>Fingolimod<br>Glatiramer acetate<br>Interferon beta-1a<br>Interferon beta-1b<br>Mitoxantrone<br>Natalizumab | Reduced frequency of relapse<br>Slowed disease progression<br>Improved quality of life |
| Amitriptyline/ketamine analgesic cream (AmiKet) for the 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 result in significant pain and reduce quality of life. This condition often responds poorly to standard pain-treatment approaches. AmiKet (4% amitriptyline/2% ketamine topical cream) is a novel approach to the treatment of neuropathic pain, combining the tricyclic antidepressant amitriptyline and the NMDA receptor antagonist ketamine into a topical analgesic. In clinical trials, this topical agent is applied to the affected areas twice daily.<br><br>Immune Pharmaceuticals (formerly EpiCept Corp.), Tarrytown, NY<br>University of Rochester, Rochester, NY<br><br>1 phase III trial ongoing, 1 phase III trial completed; parallel development by separate institutions; FDA granted fast-track status Apr 2012 | Antiepileptic agents<br>Interventions for treating the primary cause of nerve damage<br>Opioid analgesics<br>Oral tricyclic antidepressants<br>Over-the-counter analgesics | Decreased pain frequency and intensity<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Amygdala retraining program for treatment of chronic fatigue syndrome | Patients in whom chronic fatigue syndrome (CFS) has been diagnosed | CFS has no cure, and no single therapy provides symptom relief in all patients; new therapies are needed. The amygdala retraining program (ARP) is based on the hypothesis that after a traumatic event involving acute psychological stress, the brain's amygdala may become conditioned to be chronically sensitized to signals arising in the body (i.e., physiological, chemical, dietary stressors). This conditioned response leads to overstimulation of the sympathetic nervous system eventually resulting in chronic fatigue; it is purported that the development of neuronal pathways from the medial prefrontal cortex to the amygdala in the brain can extinguish this fear response. The ARP attempts to develop these "safety neurons" by a program tailored to the patient consisting of holistic diet, lifestyle, stress management, and self-awareness treatments. Stress tools and techniques are performed for a minimum of 30 minutes a day in a single sitting (meditation, "soften and flow," alternate nostril breathing), along with some neurolinguistic-programming, 30-second tools used throughout the day when required. The intent of these techniques is to recognize and interrupt fearful responses, replacing them with a relaxation response.<br><br>Ashok Gupta, holistic medicine practitioner, London, UK<br>Ann Vincent, M.D., Mayo Clinic, Rochester, MN<br><br>Trial completed (unphased); sold as a proprietary program; clinically implementable | Behavior and lifestyle changes<br>Pharmacotherapy (e.g., antidepressants, sleeping aids)<br>Psychotherapy | Improved ability to perform daily activities<br>Reduced symptoms<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Amygdala retraining program for treatment of fibromyalgia | Patients in whom fibromyalgia has been diagnosed | Fibromyalgia is poorly understood and lacking effective treatment options for many patients. The amygdala retraining program (ARP) is based on the hypothesis that after a traumatic event involving acute psychological stress, the brain's amygdala may become conditioned to be chronically sensitized to signals arising in the body (i.e., physiological, chemical, dietary stressors). This conditioned response leads to overstimulation of the sympathetic nervous system eventually resulting in neurologic disorders such as fibromyalgia; it is purported that the development of neuronal pathways from the medial prefrontal cortex to the amygdala in the brain can extinguish this fear response. The ARP attempts to develop these "safety neurons" by a program tailored to the patient consisting of holistic dietary, lifestyle, stress management, and self-awareness treatments. Stress tools and techniques are performed for a minimum of 30 minutes a day in a single sitting (meditation, "soften and flow," alternate nostril breathing), along with some neurolinguistic-programming, 30-second tools used throughout the day when required. The intent of these techniques is to recognize and interrupt fearful responses, replacing them with a relaxation response.<br><br>Ashok Gupta, holistic medicine practitioner, London, UK<br>Ann Vincent, M.D., Mayo Clinic, Rochester, MN<br><br>Trial completed (unphased); sold as a proprietary program; clinically implementable | Pharmacotherapy (e.g., duloxetine, fluoxetine, gabapentin, lorazepam, milnacipran, pregabalin, tricyclic antidepressants)<br>Behavior and lifestyle modification | Improved ability to perform daily activities<br>Reduced symptoms<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Asfotase alfa (ENB-0040) for treatment of hypophosphatasia in infants and children | Infants and children receiving a diagnosis of hypophosphatasia | Hypophosphatasia is a rare metabolic disorder caused by deficiency of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP). No other pharmacologic therapy is available. TNSALP is a phosphomonoesterase that plays a key role in regulation of bone mineralization. Alterations in the *TNSALP* gene results 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 is an enzyme that is 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 trials, asfotase alfa is administered as daily subcutaneous injection of 0.3 or 0.5 mg/kg.<br><br>Alexion Pharmaceuticals, Inc., Cheshire, CT<br><br>Phase II/III trials ongoing; 2 phase II trials completed; FDA granted fast-track and orphan drug statuses | Pharmacotherapy (e.g., cortisone)<br>Vitamin supplementation (e.g., magnesium, vitamin $B_6$, zinc) | Restored bone mineralization<br>Decreased risk of rickets and osteomalacia<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>BrainStorm Cell Therapeutics, Inc., New York, NY<br><br>Phase IIa trial recruiting in Israel; FDA granted orphan drug status Feb 2011; U.S.-based phase II multicenter trial planned to begin by end of 2013 | Riluzole<br>Physical therapy and assistive technology (speaking tubes, motored chairs, etc.) | Slowed disease progression<br>Improved quality of life<br>Maintained independence and activities of daily living |
| 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) | No effective treatments for MS exist; therapies providing relief of symptoms are needed. CCSVI, in particular stenotic and occlusive lesions in the azygos and internal jugular veins, is hypothesized to play a role in the etiology, 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/reduce hypoperfusion of brain parenchyma to relieve MS symptoms.<br><br>Procedure uses existing technologies and is in early diffusion in Europe and the U.S.; 1st reported by University of Ferrara, Italy<br>University of British Columbia, Canada<br><br>Phase I/II trials ongoing; FDA issued safety warning in May 2012 about performing procedure outside of clinical trial settings | Dimethyl fumarate (Tecfidera)<br>Fingolimod<br>Glatiramer acetate<br>Interferon beta-1a<br>Interferon beta-1b<br>Mitoxantrone<br>Natalizumab | Improved cognitive and motor function<br>Reduced relapse<br>Reduced lesions on imaging<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 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.<br><br>Vital Therapies, Inc., San Diego, CA<br><br>Phase III trials ongoing for various types of liver failure (alcohol induced liver decompensation; acute alcoholic hepatitis; fulminant hepatic failure) | Pharmacotherapy (e.g., antibiotics and lactulose)<br>Liver transplantation | Improved rate of 30-day transplant-free survival |
| BioErodible MucoAdhesive (BEMA) delivery of buprenorphine for treatment of moderate to severe chronic pain | Patients in whom moderate to severe chronic pain has been diagnosed | 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 treating opioid maintenance therapy or management of moderate pain. BEMA™ (BioErodible MucoAdhesive) is 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 is applied to the buccal mucosa, twice daily.<br><br>BioDelivery Sciences International, Raleigh, NC, in collaboration with Endo Health Solutions, Inc., Malvern, PA<br><br>2 phase III trials completed, 1 phase III trial ongoing; BEMA delivery system has FDA approval for use with fentanyl; under development for delivery of buprenorphine and buprenorphine/naloxone combinations | Alternative long-acting opioid formulations<br>Other analgesic pharmacotherapy (e.g., COX-2 inhibitors, nonsteroidal anti-inflammatory drugs) | Reduced pain<br>Reduced risk of addiction |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| BreathID methacetin breath test to monitor liver function in acute liver failure | Patients in acute liver failure | This breath test (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 theory is that breath test could give additional liver function assessment information not available with blood tests. The company purports to provide a novel diagnostic option in patients with impaired liver function. The test requires a patient to breathe into a device and is administered in the physician's office.<br><br>Exalenz Bioscience, Inc., Modi'in, Israel<br><br>Phase II 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. In Aug 2013, Exalenz obtained a patent for BreathID use in detecting liver function | Liver function blood tests | Improved patient comfort<br>Increased adherence with liver function testing<br>Earlier detection of liver function problems |
| COR-003 (NormoCort) for treatment of 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 surgical or radiotherapy treatment 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.<br><br>Cortendo AB, Partille, Sweden<br><br>Phase III trial planned; FDA granted orphan drug status Mar 2012 | Mifepristone (Korlym)<br>Off-label pharmacotherapy agents (ketoconazole, metyrapone, mitotane)<br>Radiation therapy<br>Surgical therapy | Reduced ACTH levels<br>Reduced morbidity from excess cortisol<br>Improved symptoms of Cushing's syndrome<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 the formation of chemical bonds between and within the corneal collagen fibrils, making them stiffer.<br><br>Avedro, Inc., Waltham, MA<br><br>2 phase III trials ongoing; 1 phase III trial completed; Conformité Européene (CE) marked; FDA granted orphan drug status; manufacturer submitted new drug application to FDA in Mar 2012 | Corneal ring segment inserts<br>Surgical therapy | Improved corneal structure<br>Improved vision<br>Improved quality of life |
| Daclizumab (Zenapax) for treatment of multiple sclerosis | 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. Effective treatments are needed. Daclizumab (Zenapax®) is a humanized monoclonal antibody against the CD25 alpha subunit of the high affinity interleukin-2 receptor. Daclizumab is intended to bind the receptor and inhibit T-cell activation, thus slowing disease progression and degradation of the axon-protecting myelin sheath. Administered by subcutaneous injection, 150 mg, once every 4 weeks.<br><br>Biogen Idec International GmbH, Zug, Switzerland<br>AbbVie, North Chicago, IL<br><br>Phase III trials ongoing; data expected in 2014, not yet reported; FDA granted fast-track status | Dimethyl fumarate (Tecfidera)<br>Fingolimod<br>Glatiramer acetate<br>Interferon beta-1a<br>Interferon beta-1b<br>Mitoxantrone<br>Natalizumab | Delayed disease progression<br>Decreased demyelination<br>Fewer relapses<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Deferiprone (Ferriprox) for treatment of pantothenate kinase–associated neurodegeneration | Patients in whom pantothenate kinase–associated neurodegeneration (PKAN) has been diagnosed | Investigators have not found a cure for PKAN, a life-threatening, progressive, and degenerative disease. Deferiprone (Ferriprox®) is purported to be an iron chelator that could reduce the accumulation of iron in patients' brains that is suspected of causing pathogenesis. In a clinical trial, deferiprone will be administered as oral solution, twice daily, for 18 months at a dosage of 5–15 mg/kg.<br><br>ApoPharma, Inc., Toronto, Ontario, Canada<br><br>1 phase II and 1 phase III trial ongoing | Iron chelators | Improved motor skill functions and movement control<br>Slowed disease progression<br>Improved quality of life |
| Dimethyl fumarate (Tecfidera) for treatment of relapsing multiple sclerosis | Patients in whom relapsing forms of multiple sclerosis (MS) have been diagnosed | Available treatments provide unsatisfactory efficacy for many patients with MS. 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, Safety profile may allow combination dosing. Administered orally, 120 mg twice daily for 7 days followed by a maintenance dosage of 240 mg, twice daily.<br><br>Biogen Idec International GmbH, Zug, Switzerland<br><br>FDA approved Mar 2013 for treating relapsing forms of MS | Fingolimod<br>Glatiramer acetate<br>Interferon beta-1a<br>Interferon beta-1b<br>Mitoxantrone<br>Natalizumab | Reduced frequency of relapse<br>Reduced symptom severity<br>Slowed disease progression<br>Improved quality of life |
| Drisapersen (GSK-2402968, PRO-051) 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) | 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. Drisapersen 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 sequences of genetic code that codes for sections of protein) to correct the reading frame and allow a normal protein to be produced. This RNA therapeutic is given by injection.<br><br>GlaxoSmithKline, Middlesex, UK, in partnership with Prosensa, Leiden, the Netherlands<br><br>3 phase III trials ongoing; FDA granted orphan drug status; Sept 2013, manufacturer announced its phase III trial failed to meet its primary endpoint; investigators reviewing data to see if a subset can benefit | Orthotic devices<br>Pharmacotherapy (e.g., corticosteroids, beta-2 agonists)<br>Physical therapy<br>Respiratory support (respirator/ ventilators) | Decreased muscle degeneration<br>Improved symptoms<br>Decreased need for supportive devices<br>Increased survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Eliglustat tartrate for treatment of Gaucher's disease | Patients in whom Gaucher's disease 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. No oral drugs are approved as for 1st-line treatment of Gaucher's disease, only intravenous therapy. Eliglustat tartrate is an orally active 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 eliglustat 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.<br><br>Sanofi, Paris, France<br><br>Positive phase III data announced from 2 trials in Feb 2013, ENGAGE and ENCORE; phase III study (EDGE) ongoing | Blood transfusions<br>Bone marrow transplant<br>Enzyme replacement therapy (e.g., imiglucerase, taliglucerase alfa)<br>Joint replacement surgery<br>Miglustat (Zavesca)<br>Splenectomy | Decreased spleen volume<br>Decreased liver volume<br>Improved quality of life |
| 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 resulting from a deficiency in N-acetylgalactosamine-6-sulfate sulfatase activity, which 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. In a pivotal phase III trial, the biologic is being administered at a dose of 2 mg/kg over a period of approximately 4 hours once a week or once every other week.<br><br>BioMarin Pharmaceutical, Inc., Novato, CA<br><br>Pivotal phase III trial preliminary data completed; company announced FDA accepted biologics license application May 2013; decision date set for Feb 28, 2014 | No current treatments are available to resolve the underlying disease. | Disease regression<br>Improved bone growth as measured by radiograph<br>Improved activities of daily living<br>Increased physical endurance (6-minute walk test)<br>Improved respiratory function<br>Reduced urine keratan sulfate levels |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 current treatments provide only partial relief of symptoms, so better treatments are needed. 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.<br><br>UCB, S.A., Brussels, Belgium<br><br>Phase III trials (EMBODY™ 1 and EMBODY™ 2) ongoing; FDA granted fast-track status | Belimumab<br>Rituximab<br>Rontalizumab | Delayed disease progression<br>Reduced symptoms<br>Reduced flares<br>Improved quality of life |
| Eprodisate disodium (Kiacta) for treatment of amyloid A amyloidosis | Patients at risk of amyloid A (AA) amyloidosis, especially those in whom rheumatoid arthritis or chronic infection is present | 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. Orally administered capsules.<br><br>Bellus Health, Inc. (formerly Neurochem), Laval, Quebec, Canada<br>Celtic Therapeutics Management LLP, St. Thomas, U.S. Virgin Islands<br><br>Phase III trial ongoing; new drug application submitted to FDA in 2006, but FDA requested more data before approval; company initiated phase III confirmatory trial in 2010 to address this concern | Biologics<br>Immunosuppressants<br>Supportive care<br>Surgical excision of infected tissue and antibiotics for chronic infection<br>Kidney transplantation for kidney failure<br>Colchicine for familial Mediterranean fever | Reduced risk of organ failure (especially kidneys, liver, spleen)<br>Reduced mortality |
| Eteplirsen (AVI-4658) 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 is intended for patients in whom DMD has been diagnosed and who have a mutation in the dystrophin gene; Eteplirsen splice-switching oligomer is intended to skip exon 51 of the dystrophin (a protein that plays a key structural role in muscle fiber function) gene 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.<br><br>Sarepta Therapeutics, Inc., Cambridge, MA (formerly AVI BioPharma, Inc., Bothell, WA)<br><br>Phase IIb trial complete 2013; in 2007, FDA granted orphan drug status | Beta-2 agonists<br>Corticosteroids<br>Orthotic devices<br>Physical therapy<br>Respiratory support devices | Delayed or halted muscle degeneration<br>Reduced symptoms<br>Increased survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Raptor Pharmaceutical Corp., Novato, CA<br><br>FDA approved Apr 2013 for management of nephropathic cystinosis in adults and children older than age 6 years | Growth hormone therapy<br>Pharmacotherapy (e.g., Cystagon®, indomethacin)<br>Renal transplantation<br>Urinary loss supplementation | Improved glomerular function<br>Reduced morbidity and mortality<br>Improved quality of life |
| Glybera gene therapy for 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. Currently no treatments are available that address the underlying cause of the disease (loss of function of the lipoprotein lipase [*LPL*] gene). 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 in a single series of intramuscular injections.<br><br>uniQure, Amsterdam, the Netherlands<br><br>Phase III trial completed; Glybera has been granted orphan drug status in the U.S. and Europe; in Nov 2012, it became the 1st approved gene therapy drug in EU | Standard of care, including low fat diet | Improved plasma triglyceride levels<br>Improved chylomicron (lipoprotein particle) levels |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Handheld intracranial scanner (Infrascanner) for detection of intracranial hematomas | Patients at risk of intracranial hematoma | About 1.7 million people sustain a traumatic brain injury (TBI) each year with direct costs and indirect costs such as lost productivity attributed to TBI reaching about $76.5 billion in the U.S. in 2000. An increase in improvised explosive device use in war has increased blast-induced TBI among U.S. soldiers, and intracranial hematomas can be particularly life threatening. These traumatic injuries can have occult signs, making them difficult to diagnose, particularly without the use of expensive, sophisticated equipment. The Infrascanner™ models 1000 and 2000 are handheld spectroscopy devices that direct near-infrared light into the skull, where it is absorbed by the blood from the intracranial hematoma. Because the blood from a hematoma absorbs light differently from vascular blood, the scanner can detect differences in optical density; it wirelessly transmits the results to a handheld computer.<br><br>InfraScan Inc., Philadelphia, PA, in collaboration with Office of Naval Research, Arlington, VA<br><br>FDA cleared Dec 2011 under 510(k) de novo process; updated Model 2000 FDA cleared Jan 2013 | Automated Neuropsychological Assessment Metrics (computerized cognitive test)<br>Computed tomography scans<br>MRI studies<br>Onsite neurophysical exam | Reduced morbidity<br>Reduced mortality<br>Improved quality of life |
| High-intensity focused ultrasound (EyeOP1 HIFU-system) for treatment-refractory glaucoma | Patients in whom 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 EyeOP1 is a device that uses high-intensity focused ultrasound (HIFU) and suction to deliver concentrated energy to the ciliary body of the eye. The goal of treatment is to reduce the production of aqueous humor, thus reducing intraocular pressure (IOP). EyeOP1 system contains a command center that works with a touch screen interface and a foot pedal for control. During the procedure, generators located in the command center power the ultrasound while the clinician controls a pressurized suction system. The pressure reduction system is designed to ensure fixation of the therapy device to the eye during the ultrasound treatment. This noninvasive procedure is performed in an outpatient setting while the patient is placed under general anesthesia.<br><br>EyeTechCare, S.A., Rillieux la Pape, France<br><br>Multicenter unphased and phase IV studies ongoing in European Union; manufacturer indicated it plans to notify FDA by end of 2013 of intentions to bring to U.S. market | Microbypass implant (I-stent)<br>Pharmacotherapy (e.g., eye drops)<br>Surgical therapy<br>Trabectome (device) | Preserved vision<br>Reduced IOP |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 degeneration is a genetic eye disorder affecting the retina that causes progressive vision loss. The macular degeneration affects a small area near the center of the retina called the macula. 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 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.<br><br>Advanced Cell Technology, Inc., Santa Monica, CA<br><br>Phase I/II trials ongoing; FDA and EU granted orphan drug status | No treatment is available | Improved vision<br>Reversed loss of central vision<br>Improved functional status<br>Improved quality of life |
| Idebenone (Catena) 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. Idebenone (Catena®/Raxone®) 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.<br><br>Santhera Pharmaceuticals Holding AG, Liestal, Switzerland<br>Takeda Pharmaceutical Co., Ltd., Osaka, Japan<br><br>Phase III trial ongoing; FDA granted orphan drug status | Eteplirsen, AVI-4658 (in development)<br>Orthotic devices<br>Physical therapy<br>Respiratory support (respirator/ ventilators)<br>Symptom control using corticosteroids and beta-2 agonists | Delayed or halted muscle degeneration<br>Improved quality of life<br>Increased survival<br>Reduced symptoms |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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, 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 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.<br><br>Neuraltus Pharmaceuticals, Inc., Palo Alto, CA<br><br>Phase III trial planned to start by end of 2013; FDA granted fast-track and orphan drug statuses Aug 2011 | Riluzole<br>Supportive care | Improved biomarker levels<br>Restoration of macrophages to their neuroprotective state<br>Improved activities of daily living<br>Delayed disease progression<br>Improved quality of life |
| Masitinib for treatment of multiple sclerosis | 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. 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.<br><br>AB Science S.A., Paris, France<br><br>Phase IIb/III trial ongoing | Dimethyl fumarate (Tecfidera)<br>Fingolimod<br>Glatiramer acetate<br>Interferon beta-1a<br>Interferon beta-1b<br>Mitoxantrone<br>Natalizumab | Delayed disease progression<br>Reduced symptoms<br>Improved quality of life |

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| Micro-bypass implant (iStent Trabecular Micro-Bypass Stent System) for treatment of glaucoma | Patients undergoing cataract surgery who are also at risk of developing glaucoma because of uncontrolled, elevated intraocular pressure (IOP) | 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.<br><br>Glaukos Corp., Laguna Hills, CA<br><br>FDA approved Jul 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)<br>Surgical therapy<br>Trabectome (device) | Preserved vision<br>Reduced elevated or uncontrolled IOP |
| Mifepristone (Korlym) for treatment of endogenous Cushing's syndrome | Patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed or are not candidates for surgery | Cushing's syndrome is caused by chronic exposure to elevated levels of the hormone cortisol. Endogenous Cushing's syndrome is caused by the body's production of high levels of cortisol or a cortisol precursor (adrenocorticotrophic hormone) typically by pituitary, adrenal, or ectopic endocrine tumors. Although some tumors can be successfully treated by surgery and/or radiation therapy, patients who are ineligible for these treatments or who have persistent elevation of cortisol after treatment have no FDA-approved medical options for treatment. Mifepristone (Korlym®) acts to block the cortisol receptor, potentially ameliorating the effects of elevated cortisol levels. Mifepristone is an oral medication that in clinical trials was taken once daily.<br><br>Corcept Therapeutics, Inc., Menlo Park, CA<br><br>FDA approved Feb 2012; ongoing phase III trial of mifepristone in pediatric Cushing's Disease; ongoing phase III trial of mifepristone in pediatric Cushing's Disease | Ketoconazole (off label)<br>Metyrapone (off label)<br>Mitotane (off label) | Improved symptoms of Cushing's syndrome (e.g., diabetes, glucose intolerance, hypertension) |

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| Migalastat hydrochloride (AT1001) for treatment of Fabry disease | Patients with Fabry disease who have either migalastat-responsive mutations in alpha-galactosidase A or are receiving enzyme replacement therapy | Current enzyme replacement therapies for Fabry disease are expensive and have been subject to recent shortages. 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 used 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. Oral pill taken daily; dose not specified in trial information.<br><br>Amicus Therapeutics, Inc., Cranbury, NJ<br>GlaxoSmithKline (Middlesex, UK)<br><br>2 phase III trials ongoing (FACETS and ATTRACT) in patients who have alpha-galactosidase mutations; manufacturer announced an additional trial will be required before filing a new drug application because ongoing phase III trial failed to meet primary endpoints; FDA granted orphan drug status | Enzyme replacement therapy<br>Palliative treatment | Increased GL-3 levels (urine, kidney biopsy)<br>Improved renal function (e.g., glomerular filtration rate)<br>Improved quality of life |
| Mobile phone monitoring application (MyVision Track) 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. The 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. The results may be sent to a physician's office or a central monitoring service when a statistically significant change occurs.<br><br>Vital Art and Science, Inc., Richardson, TX<br><br>Pilot study completed; In Apr 2013, FDA cleared device for marketing; manufacturer indicated MyVision Track will be commercially available in 4th quarter of 2013 | Complete eye exam with Amsler grid test<br>Optical coherence tomography | Earlier intervention for vision decline<br>Slowed vision decline<br>Improved quality of life |

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| Monarch external trigeminal nerve stimulation (eTNS) 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. eTNS is a noninvasive therapy in which mild electrical signals pass through electrodes placed on the patient's forehead. It 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 and worn by patient during sleep.<br><br>NeuroSigma, Inc., Los Angeles, CA<br><br>Phase II study completed; Jul 2013, FDA approved start of phase III trial | Pharmacotherapy (e.g., ezogabine, lamotrigine, levetiracetam, perampanel, tiagabine, tricyclics, valproate) | Reduced frequency of seizure<br>Improved quality of life |
| MRI-guided laser interstitial thermal therapy (MRgLITT) 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. If accepted, laser ablation therapy would provide a minimally invasive, potentially curative therapy for patients receiving a diagnosis of epilepsy. Laser ablation surgery involves use of 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. Laser therapy is for patients in whom definable lesions causing epilepsy have been detected by MRI.<br><br>Texas Children’s Hospital, Houston, TX<br><br>Pilot trial completed. Surgical technique being performed at additional institutions. | Pharmacotherapy (e.g., lamotrigine, levetiracetam, tiagabine, tricyclics, valproate) | Reduced or eliminated seizures |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 have abuse liability and 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. The pegylation of NKTR-181 is intended to reduce the rate at which the drug crosses the blood-brain barrier, thereby limiting the high CNS concentrations that could lead to respiratory distress or feelings of euphoria. In clinical trials, NKTR is an oral medication administered at a dose of 100–400 mg, twice daily.<br><br>Nektar Therapeutics, San Francisco, CA<br><br>Phase II trial ongoing, FDA granted fast-track status for treating moderate to severe chronic pain; phase II trial missed primary endpoint due to unexpectedly large placebo effect in control group; manufacturer indicated additional trials in future | Conventional mu-opioid agonists<br>Opioids with abuse-deterrent properties (i.e., crush resistant or agonist-antagonist combined formulations)<br>Opioids with abuse deterrent formulations (in development) | Improved pain relief<br>Reduced adverse effects<br>Reduced abuse liability<br>Improved quality of life |
| Nabiximols oromucosal spray (Sativex) for treatment of multiple sclerosis spasticity and neuropathic pain | Patients in whom multiple sclerosis (MS) has been diagnosed | Current treatments for MS may slow disease progression, but they are not effective in all patients, and the disease has no cure. Sativex® is a whole-plant medicinal cannabis extract that contains Tetranabinex® and Nabidiolex® (cannabidiol) as its main components. Delta-9-tetrahydrocannabinol (THC) in the extract acts as a partial agonist at both cannabinoid receptors, CB1 and CB2, mimicking the effects of the endocannabinoids, which may modulate the effects of neurotransmitters (e.g., reduce effects of excitatory neurotransmitters such as glutamate) to improve symptoms. Sativex is sprayed under the tongue, 100 mcL/dose, which contains 2.5 mg cannabidiol and 2.7 mg THC. Sativex is intended to be an add-on treatment to current MS therapies.<br><br>GW Pharmaceuticals, plc, Salisbury, UK<br>Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan<br><br>1 phase III trial completed; 1 phase III trial ongoing; approved in U.K., 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<br>Reduced spasticity<br>Improved quality of life |

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| Noninvasive vagus nerve stimulation (gammaCore) for treatment-refractory migraine and cluster headaches | Patients who experience migraine or cluster headaches | Migraine and cluster headaches affect tens of millions of people each year. A variety of pharmacotherapies exists for treating headache, but many patients experience inadequate pain relief or unwanted side effects from treatments. Noninvasive neurostimulation presents a novel approach to headache prophylaxis and treatment. GammaCore is a small, portable, noninvasive vagus nerve stimulator for preventing and treating migraine and cluster headache.<br><br>ElectroCore, LLC, Morris Plains, NJ<br><br>Randomized controlled trials (unphased) ongoing; phase II trial ongoing comparing gammaCore to standard of care in cluster headache | Botox<br>GABAergic modulators<br>Opiates<br>Triptans | Decreased headache pain<br>Decreased headache symptoms<br>Decreased headache frequency<br>Improved quality of life |
| Northera (Droxidopa) 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 | Current treatment options for symptomatic neurogenic orthostatic hypotension include pharmacotherapy but do not achieve an adequate response in many patients; more effective treatment options are needed to address the underlying cause. Droxidopa (Northera™) is a norepinephrine precursor; it allows for reuptake of norepinephrine into peripheral nervous system neurons, stimulating receptors for vasoconstriction and providing physiological improvement in symptomatic neurogenic orthostatic hypotension. Administered orally, up to 3 times daily.<br><br>Chelsea Therapeutics, Inc., Charlotte, NC<br><br>Phase III trials completed; FDA granted orphan drug and fast-track statuses; Jul 2012, FDA issued a 2nd complete response letter requesting an additional trial; the company provided additional data in Dec 2012; Feb 2013, FDA responded with guidance on a new drug application (NDA) resubmission; FDA accepted NDA submission Sept 2013; FDA decision date expected Jan 2014 | Diet and lifestyle modifications<br>Pharmacotherapy (e.g., midodrine hydrochloride) | Decreased orthostatic hypotension<br>Decreased risk of falling<br>Decreased confusion from reduced cerebral circulation |

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| Ocrelizumab (RG1594) 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. Administered via infusion, once every 6 months.<br><br>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland<br>Biogen Idec International GmbH, Zug, Switzerland<br><br>Phase III trials ongoing; company expects to file new drug application in 2015 | Dimethyl fumarate (Tecfidera)<br>Fingolimod<br>Glatiramer acetate<br>Interferon beta-1a<br>Interferon beta-1b<br>Mitoxantrone<br>Natalizumab | Decreased frequency of relapse<br>Slowed disease progression<br>Improved quality of life |
| Ocriplasmin (Jetrea) treatment for 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 is thought to have potential to break 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 0.125 mg (0.1 mL) of the diluted solution, given by intravitreal injection to the affected eye once as a single injection.<br><br>ThromboGenics NV, Heverlee, Belgium<br><br>FDA approved Oct 2012 for treating symptomatic VMA | Pharmacotherapy (e.g., Macugen®)<br>Surgical therapy | Preserved vision<br>Reduced complications associated with surgical treatment<br>Improved quality of life |

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| Off-label bevacizumab for treatment of retinopathy of prematurity | Infants weighing 1,500 g or less at birth and at 30 weeks' or less gestation 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. Current 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.<br><br>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland (manufacturer)<br>BEAT-ROP cooperative (trial sponsor)<br><br>Several small retrospective and prospective case series; postmarket trial of off-label use completed; manufacturer is not pursuing a labeled indication; 2013 published clinical literature indicates high interest but as yet unanswered questions of safety and efficacy | Peripheral retinal ablation with lasers (e.g., xenon, argon, diode) | Prevented recurrence of neovascularization arising from the retinal vessels<br>Improved visual acuity |
| Off-label etanercept (Enbrel) 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.<br><br>Amgen, Inc., Thousand Oaks, CA<br><br>Phase II trial ongoing; FDA approved in 1998 for moderate to severe rheumatoid arthritis and other inflammatory conditions | Corticosteroids<br>High-dose aspirin<br>IVIG | Improved survival<br>Prevented increase in coronary artery diameter<br>Prevented new coronary artery dilation/cardiac dysfunction<br>Reduced fever |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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, 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 purportedly 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.<br><br>ALS Therapy Development Institute, Cambridge, MA<br>Georgia Regents University, Augusta<br>Massachusetts General Hospital, Boston<br>Methodist Neurological Institute, Houston, TX<br>University of California, Irvine, Orange, CA<br><br>Phase II trial begun; FDA approved for treating relapsing-remitting multiple sclerosis | Physical and speech therapy<br>Medications for symptom management (muscle cramps, constipation, fatigue, excessive salivation, excessive phlegm, pain, depression)<br>Riluzole (Rilutek®) | Reduced symptoms<br>Slowed or halted disease progression<br>Increased survival<br>Improved quality of life |
| Off-label mexiletine (Mexitil) for treatment of nondystrophic myotonia | Patients in whom nondystrophic myotonia (NDM) has been diagnosed | NDMs are rare diseases caused by mutations in skeletal muscle ion channels. NDM causes delayed muscle relaxation leading to limited functionally, stiffness, and pain. No effective treatments are available. Mexiletine (Mexitil®) is a class 1b antiarrhythmic medication that purportedly has high affinity for muscle sodium channels. In clinical models, it purportedly reduced muscle fiber excitability caused by common NDM mutations. Mexiletine is administered orally, 200 mg, 3 times daily.<br><br>University of Kansas Medical Center, Kansas City, KS<br><br>Phase II international trial completed; positive results published in JAMA Oct 2012 | Supportive care | Improved clinical myotonia assessment<br>Improved handgrip<br>Reduced stiffness, pain, weakness, and tiredness<br>Improved quality of life |

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| Off-label naltrexone for treatment of fibromyalgia | Patients in whom fibromyalgia has been diagnosed | Fibromyalgia 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 the investigators to be involved in pain felt by patients with fibromyalgia. Administered orally, 3.0–4.5 mg, once daily.<br><br>Stanford University, Stanford, CA<br><br>Pilot study completed; results published | Behavior and lifestyle modification<br>Pharmacotherapy (e.g., duloxetine, fluoxetine, gabapentin, lorazepam, milnacipran, pregabalin, tricyclic antidepressants) | Improved ability to perform daily activities<br>Reduced symptoms<br>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. Current FM treatments target only centrally acting pain pathways and neglect the potential for immunologic involvement on FM symptoms. Ketotifen is purportedly an antihistamine and mast cell stabilizer, which prevents mast cell degranulation (release of inflammatory meditators), which might improve FM symptoms. Administered orally as a 1 mg tablet, once or twice daily.<br><br>Indiana University-Perdue University, Indianapolis<br><br>Phase III trial ongoing (KetoforFMS); currently approved for preventing asthma attacks and as eye drops for allergic pinkeye | Behavior and lifestyle modification<br>Pharmacotherapy (e.g., duloxetine, fluoxetine, gabapentin, lorazepam, milnacipran, pregabalin, tricyclic antidepressants) | Improved ability to perform daily activities<br>Reduced pain symptoms<br>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. Orally administered, 80 mg, daily.<br><br>AstraZeneca, London, UK<br><br>Phase II trial complete | Interferon beta-1a<br>Interferon beta-1b<br>Mitoxantrone<br>Natalizumab | Delayed disease progression<br>Reduced symptoms<br>Improved quality of life |

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| Oral short-chain fatty acid derivative compound (HQK-1001) 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. An increased prevalence of disease is seen in people of African and Mediterranean descent; about 1 in 500 African-American children born have sickle cell anemia. Despite advancements in managing complications of SCD (i.e., pain crises), the only drug FDA approved for treatment is hydroxyurea. HQK-1001 is a short chain fatty acid derivative (SCFAD) compound that purportedly reduces the frequency of pain crises and hospitalizations related to SCD. SCFAD has been shown to stimulate expression of fetal hemoglobin and production of red blood cells. HQK-1001 is administered orally at 10, 20 or 30 mg/kg, once a day (on dosing days).<br><br>HemaQuest Pharmaceuticals, Inc., San Diego, CA<br><br>Phase II/IIb trials ongoing; FDA granted orphan drug status | Allogeneic hematopoietic stem cell transplantation<br>Antioxidant therapy<br>Azacitidine<br>Decitabine butyrate<br>Gardos channel inhibition<br>Gene therapy<br>Hydroxyurea<br>Lenalidomide<br>Nitrous oxide and vasodilators<br>Statins | Reduced severity and duration of vaso-occlusive crises<br>Reduced health disparities (African Americans)<br>Improved quality of life |
| Pasireotide (Signifor) for treatment of Cushing's disease | Patients who have Cushing's disease caused by an adreno-corticotropic hormone (ACTH)-secreting pituitary tumor | The majority of Cushing's disease cases are caused by benign pituitary tumors that generate elevated levels of 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. No medical treatments directly targeting ACTH-secreting pituitary tumors were available, and not all patients respond to surgical or radiotherapy treatment. Pasireotide (Signifor®) is a subcutaneously administered somatostatin analog that activates a wide range of somatostatin receptors 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.<br><br>Novartis International AG, Basel, Switzerland<br><br>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 | Pharmacotherapy (e.g., ketoconazole, metyrapone, mitotane)<br>Radiation therapy<br>Surgical therapy | Reduced ACTH levels<br>Reduced morbidity from excess cortisol<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Pasireotide (Signifor) for treatment of gastrointestinal injuries from acute radiation exposure | 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.<br><br>Novartis International AG, Basel, Switzerland (manufacturer)<br>University of Arkansas for Medical Sciences, Little Rock (investigator)<br><br>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; Signifor is FDA approved for Cushing's disease | Pharmacotherapy (e.g., antibiotics, hematopoiesis-stimulating agents)<br>Stem cell therapy | Prevented or reduced GI flora<br>Decreased mortality |
| Pediatric Vision Scanner screening for strabismus or amblyopia | Pediatric patients who need screening for amblyopia or strabismus | 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. As many as half of affected children are not identified until school age. If found early, amblyopia and strabismus are fully treatable. 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 to screen for amblyopia and strabismus.<br><br>REBIScan, Inc., Cambridge, MA<br><br>Unphased trials completed; additional unphased trial ongoing | Standard vision examination<br>Photoscreening | More appropriate referrals to ophthalmologists<br>Reduced vision loss<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Pegylated recombinant phenylalanine ammonia lyase (PEG-PAL) enzyme replacement therapy for treatment of phenylketonuria | Individuals in whom phenylketonuria has been diagnosed | Phenylketonuria is an inherited disorder in which an enzyme that is needed to break down essential amino acid phenylalanine is missing. Pegylated recombinant phenylalanine ammonia lyase (PEG-PAL) might offer a new treatment; the drug is intended to reduce levels of phenylalanine in patients whose disease is unresponsive to Kuvan®. Administered by injection, 1–3 times a week.<br><br>BioMarin Pharma, Inc., Novato, CA<br><br>Phase II and III trials ongoing; FDA granted orphan drug status | Kuvan (tetrahydrobiopterin or BH4) | Decreased phenylalanine levels<br>Fewer diet restrictions<br>Improved quality of life |
| Personal activity monitors for post-stroke patient rehabilitation | Patients who are undergoing inpatient 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. Monitoring patient compliance to standard physical and occupational therapies has been a challenge for health care providers and measuring the effectiveness of treatment for patients who perform home-based therapies has been difficult. Stroke Inpatient Rehabilitation Reinforcement of Activity (SIRRACT) is a program that uses simple accelerometers in conjunction with Medical Daily Activity Wireless Network (MDAWN) wireless monitoring system to measure the patient's movement in the home 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.<br><br>University of California, Los Angeles<br><br>Phase II trial completed; additional unphased trial registered in Jun 2013, not yet open for recruitment | Robot-assisted rehabilitative therapy<br>Standard occupational therapy<br>Standard physical therapy | Improved care monitoring<br>Improved patient self-care motivation |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Pimavanserin for treatment of Parkinson's disease psychosis | Patients in whom Parkinson's disease psychosis has been diagnosed | Parkinson's disease psychosis is a debilitating disorder associated with increased caregiver distress and burden, nursing home placement, and increased mortality. No therapies have been FDA approved to treat Parkinson's disease psychosis. Antipsychotic drugs may be used off label to treat the psychosis; however, antipsychotic drugs block dopamine receptors, which can negate dopamine replacement therapy, leading to worsening of Parkinsonian motor symptoms. Additionally, antipsychotic drugs currently used are associated with a number of problematic adverse events in elderly patients with Parkinson's disease, especially elderly patients with dementia-related psychosis. Pimavanserin is a small molecule purported to selectively block the activity of the serotonin family 5-$HT_{2A}$ receptor, which is thought to play an important role in Parkinson's disease psychosis. Pimavanserin is intended to selectively target the 5-$HT_{2A}$ receptor without compromising motor control or while maintaining acceptable tolerability. In a clinical trial, pimavanserin has been administered orally, 10–40 mg, once daily.<br><br>ACADIA Pharmaceuticals, Inc., San Diego, CA<br><br>Phase III trial completed; additional trials ongoing; Apr 2013 company met with FDA and stated plans to complete new drug application filing requirements | Antipsychotics (off label) | Reduced symptoms<br>Reduced side effects compared with other drugs<br>Improved quality of life |
| 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. Administered orally, at doses of 45 or 67.5 mg, twice daily.<br><br>Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel<br><br>Phase III trials completed; FDA granted orphan drug status | Pharmacotherapy (e.g., tetrabenazine, antidepressants, antipsychotics) | Improved clinical global impression of change, cognitive function, behavior, and symptoms of depression and anxiety<br>Improved voluntary motor function |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Prosthetic arm to restore natural arm functions | Patients with trauma-induced amputations of the upper limbs | This advanced prosthetic arm technology comprises 2 major components, a prosthetic arm and body-machine interfaces. 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. Body-machine interfaces are designed to improve the number of control sites available to manipulate the arms. Techniques under clinical evaluation include implantable myoelectric sensors, peripheral nerve interface electrodes, and targeted muscle reinnervation (surgery).<br><br>U.S. Defense Advanced Research Projects Agency, Arlington, VA (commissioned and funded research)<br>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<br><br>Early phase trials ongoing; FDA is piloting a new regulatory pathway for this technology, the innovative device pathway, which is intended to move innovative devices to market within 4 years of start of trials | Conventional prosthetic arms | Significant restoration of limb function compared with function of current prosthetic devices |
| Recombinant porcine factor VIII (OBI-1) for treatment of acquired hemophilia | Individuals with acquired hemophilia A who develop immune reaction to human 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. Administered as intravenous infusion every 2–3 hours for the 1st 24 hours of treatment.<br><br>Baxter International, Deerfield, IL<br><br>Phase II/III trial ongoing; FDA granted orphan and fast-track status Nov 2012 | Human coagulation factor VIIa | Adequate control of bleeding episodes |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| RenalGuard for prevention of contrast-induced nephropathy | Patients at risk of contrast-induced nephropathy (CIN) | 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.<br><br>PLC Systems, Inc., Milford, MA<br><br>Pivotal trial completed; phase III and phase IV trials ongoing; in Jun 2013, manufacturer announced receipt of expanded coverage for RenalGuard patent to include more toxic agents in additional settings. In Oct 2013, RenalGuard was used following a kidney transplant, prompting further expansion of its investigated indication. | Pharmacotherapy (e.g. deferoxamine)<br>Hydration | Reduced occurrence and complications of CIN<br>Reduced incidence of CIN in high-risk patients with CKD<br>Improved quality of life |
| Responsive Neurostimulation system for treatment-refractory partial epilepsy | Patients in whom refractory 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 leave the brain susceptible to unintended injury and resultant neurological complications. The Responsive Neurostimulation system (RNS®) is a device that uses electrical stimulation to suppress the incidence of seizure before symptoms occur. It is surgically implanted underneath the patient's scalp by a surgeon. The neurostimulating portion of the device is then connected to the surface of the brain by 1 or 2 wires which contain electrodes. The RNS system continuously monitors electrical activity of the brain and delivers brief electrical stimulation when "signatures" of onset are detected. The manufacturer purports that the device suppresses seizure activity by delivering responsive stimulation.<br><br>NeuroPace, Inc., Mountain View, CA<br><br>Phase III trial completed; in Feb 2013, FDA advisory panel voted unanimously to recommend approval of RNS | Pharmacotherapy (e.g., ezogabine, lamotrigine, levetiracetam, perampanel, tiagabine, tricyclics, valproate) | Reduced frequency of seizures<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 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.<br><br>Retina Implant AG, Reutlingen, Germany<br><br>Pilot trial completed; received Conformité Européene (CE) mark Jul 2013 | Argus II retinal prosthesis system | Improved visual acuity<br>Improved quality of life and independence |
| Retinal prosthesis system (Argus II) for treatment of retinitis pigmentosa | Patients with retinitis pigmentosa (RP) and 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 persons 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.<br><br>Second Sight® Medical Products, Inc., Sylmar, CA<br><br>FDA approved Feb 2013; Conformité Européene (CE) marked in 2011 | Standard of care<br>Alpha IMS system (in development) | Improved visual acuity<br>Improved quality of life and independence |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Rituximab for the 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. 1st-line treatment for pediatric nephrotic syndrome includes corticosteroids, and other treatment options include diuretic therapy and antihypertensive therapy. Rituximab is a monoclonal antibody indicated for treating patients with non-Hodgkin's lymphoma and rheumatoid arthritis. This drug therapy purports to reduce the frequency of refractory cases of pediatric nephrotic syndrome.<br><br>University of Tokyo, Japan<br><br>2 phase II/III trials ongoing | Antihypertensives<br>Corticosteroids<br>Diuretics | Improved quality of life<br>Reduced frequency of refractory nephrotic syndrome |
| Sebelipase alpha (SBC-102) 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. The early onset form is also known as Wolman disease, and is rapidly fatal, usually within the 1st year. Late-onset LAL is also known as cholesteryl ester storage disease (CESD), and can lead to liver fibrosis, cirrhosis, liver failure, cardiovascular events, and premature death. Sebelipase alpha is a recombinant protein intended to be used as enzyme replacement therapy for this disease. 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.<br><br>Synageva BioPharma, Lexington, MA<br><br>Phase III trials ongoing in infants, children, adults; FDA granted orphan drug and breakthrough therapy status | Palliative treatments | Improved cholesteryl ester and triglyceride levels<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Smartpatch stimulator for treatment of poststroke pain | Patients in whom stroke has been diagnosed | Approximately 10% of stroke survivors experience mild to severe pain after the stroke. It can be acute or chronic. The Smartpatch peripheral nerve stimulation system is proposed as a minimally invasive therapy during which a fine wire from the patch is placed through the skin near the selected nerves to relieve pain. It purportedly differs from existing electrical stimulation modalities for treating pain because it is not an implanted stimulator device and is placed near nerves rather than touching them.<br><br>SPR Therapeutics, LLC, Cleveland, OH<br><br>Pivotal unphased trial currently recruiting participants; Conformité Européene (CE) marked Jan 2013 | Anticonvulsants<br>Antidepressants<br>Corticosteroids<br>Nonsteroidal anti-inflammatory drugs | Reduced pain<br>Improved quality of life |
| 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-shaped 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.<br><br>SOLX, Inc., Waltham, MA<br><br>Phase III trials ongoing; approved in Canada and parts of Europe | Pharmacotherapy (e.g., eye drops)<br>Surgical therapy<br>Trabectome (device) | Reduced IOP<br>Preserved vision |
| 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.<br><br>Bruin Biometrics, LLC, Los Angeles, CA<br><br>Pilot trial completed; other trials ongoing | Electronic pressure sensing mat (in development)<br>Visual assessment | Prevention or early treatment of decubitus ulcers<br>Reduced morbidity and mortality from complications |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Tafamidis (Vyndaqel) 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 within a decade in the absence of a liver transplant. 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. Tafamidis (Vyndaqel®) purportedly is a transthyretin stabilizer intended to treat TTR-FAP. Tafamidis purportedly binds to the TTR protein to promote the stabilization of functional tetrameric molecules, slowing the formation of misfolded amyloid fibrils.<br><br>Pfizer, Inc., New York, NY<br><br>Phase III trials ongoing; FDA granted orphan drug status; new drug application submitted to FDA Apr 2011; FDA issued a refusal to accept letter in Jun 2012 and asked the company to conduct another trial | Supportive therapy | Improved Neuropathy Impairment Score<br>TTR stabilization |
| 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, 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 is purported to selectively activate the fast skeletal muscle troponin complex by increasing its sensitivity to calcium, leading to an increase in skeletal muscle force.<br><br>Cytokinetics, Inc., South San Francisco, CA<br><br>Phase II trial (BENEFIT-ALS) ongoing; FDA granted orphan drug status | Riluzole (Rilutek®) | Improved patient/investigator global assessment of symptoms |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Tozadenant (SYN115) for treatment of Parkinson's disease | Patients in whom Parkinson's disease (PD) has been diagnosed | 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.<br><br>Biotie Therapies Corp., Turku, Finland<br>UCB, Brussels, Belgium (licensed worldwide rights from Biotie)<br><br>Phase II/III trial completed; phase III trial planned | Adenosine A2A receptor antagonist (in development)<br>Dopamine agonists<br>Glutamate receptor 5 modulators (in development)<br>Levodopa/carbidopa<br>Monoamine oxidase-B inhibitors<br>Nicotinic receptor agonist (in development) | Improved motor skills<br>Improved symptoms<br>Reduced disease progression<br>Reduced incidence/severity of levodopa-induced dyskinesia<br>Improved quality of life |
| Vesicular monoamine transporter type 2 inhibitor (NBI-98854) for treatment of tardive dyskinesia | Patients with schizophrenia who have been given a diagnosis of tardive dyskinesia | 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 the 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.<br><br>Neurocrine Biosciences, Inc., San Diego, CA<br><br>2 phase II trials completed, 1 phase II trial ongoing. FDA granted fast-track status Jan 2012. Phase IIb failed to meet primary endpoints in 50 mg dose; however 100 mg dose showed clinically meaningful reduction in reducing the symptoms after 2 weeks of treatment | Pharmacotherapy (e.g., benzodiazepines, Cogentin®, omega-3 fatty acids, Mirapex®, Tarvil®, tetrabenazine) | Reduced abnormal involuntary movements |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Wearable artificial kidney (WAK) for end-stage kidney failure | Patients with advanced kidney failure | In current peritoneal dialysis (dialysate) is infused into the abdomen through a permanent indwelling catheter to remove toxins. Peritoneal lining acts as a filter. Spent dialysate solution is drained from peritoneal cavity. With 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.<br><br>AWAK Technologies, Inc., Burbank, CA<br>Fresenius Medical Care Holdings AG & Co. KGaA (acquired developer Xcorporeal, Inc.)<br><br>FDA selected this technology in Apr 2012 as 1 of 3 technologies to be piloted for its new innovation pathway designation. Phase I study completed by developers Royal Free London NHS Foundation Trust (formerly Royal Free Hampstead NHS Trust) and Xcorporeal, Inc. in the United Kingdom; 5 randomized controlled trials planned, 1 pilot trial completed | Conventional home dialysis systems<br>Kidney transplantation | Adequate filtration of toxins from kidneys<br>Improved mobility<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Wearable battery powered exoskeletons (ReWalk and Ekso systems) to enable walking after spinal cord injury | Patients with spinal cord injury resulting in paraplegia and need for wheelchair use | Conventional manual and powered wheelchairs are the primary assistive devices to restore some degree of mobility in people with paraplegia. However, these devices do not help users walk or climb stairs. Wearable powered exoskeletons in development, the ReWalk-I™ (institutional) and ReWalk-P™ (personal use), and Ekso systems could provide greater mobility and freedom to persons with paraplegia from spinal cord injury. The ReWalk 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 to walk with crutches and who have good bone density and cardiovascular health. The Ekso system is a described by the manufacturer as a ready-to-wear, battery-powered exoskeleton worn over the user's clothing. The device weighs 45 lb, but purportedly transfers its load to the ground so the patient doesn't bear the weight. The system is adjustable to fit people weighing 220 pounds or less with a height between 5 feet, 2 inches, and 6 feet, 2 inches, and with partial upper body strength. The system has 3 walk modes. The patient provides the balance and proper body positioning.<br><br>Argo Medical Technologies, Ltd., Yokneam Illit, Israel (ReWalk system) distributed in the U.S. by Bionics Research, Inc., Mt. Laurel, NJ<br>Ekso Bionics, Richmond, CA (Ekso system)<br><br>The ReWalk-I system is FDA-listed for institutional use only; the company registered the ReWalk-P system for personal use with FDA for routine use outside of institutions and it became available in late 2012; the Ekso system is available in 21 U.S. rehabilitation centers; Conformité Européene (CE) marked in May 2012 | Wheelchairs | Improved mobility<br>Improved independence<br>Improved quality of life |

**Table 9. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 39 Interventions**

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| ABT-450/ritonavir 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. ABT-450/r is an NS3/4A HCV protease inhibitor co-administered with ritonavir and is under study in many clinical trials in combination with other HCV treatments. It is administered as ABT-450 (tablets) dosed 150 mg once daily with ritonavir (capsules) dosed 100 mg once daily.<br><br>AbbVie Inc., North Chicago, IL<br>Enanta Pharmaceuticals, Inc., Watertown, MA<br><br>Phase III trials ongoing; FDA granted breakthrough therapy status for treating HCV genotype 1 in combination with ABT-333, ABT-267, with and without ribavirin | Boceprevir<br>Pegylated interferon plus ribavirin<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks)<br>Decreased need for liver transplant<br>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 | Current HCV treatment options are not effective in all patients, even with the newly approved agents of telaprevir and boceprevir. 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 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 an oral 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.<br><br>Debiopharm, S.A., Lausanne, Switzerland<br>Novartis International AG, Basel, Switzerland<br><br>Phase III trials completed; FDA granted fast-track status | Boceprevir<br>Pegylated interferon plus ribavirin<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks<br>Decreased need for liver transplant<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Human Genome Sciences, Rockville, MD<br><br>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<br>Antibiotics | Protection against inhalation anthrax<br>Rapid resolution of symptoms |
| 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.<br><br>Asahi Kasei Corp., Tokyo, Japan<br><br>Phase IV trial ongoing | Coagulation factor concentrates or cryoprecipitate<br>Plasma | Reduced episodes of life-threatening bleeding<br>Reduced mortality |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Asunaprevir for treatment of chronic hepatitis C virus infection | Patients in whom chronic infection with hepatitis C virus (HCV) 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 NS5A inhibitor BMS-914143 with or without the standard-of-care pegylated interferon plus ribavirin (IFN/RBV).<br><br>Bristol-Myers Squibb, New York, NY<br><br>Phase III trials ongoing; FDA granted breakthrough therapy status for asunaprevir in combination with daclatasvir (NS5A inhibitor) BMS-791325 (non-nucleoside polymerase inhibitor) | Boceprevir<br>IFN/RBV<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks)<br>Decreased need for liver transplant<br>Improved quality of life |
| Brincidofovir (CMX001) for prevention of cytomegalovirus after hematopoietic stem cell transplant | Patients who 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, oral antiviral for treating or preventing life-threatening double-stranded DNA (dsDNA) viral diseases. Brincidofovir combines Chimerix'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.<br><br>Chimerix, Inc., Durham, NC<br><br>Phase III trial recruiting; FDA granted fast-track status | Cidofovir (off label)<br>Ganciclovir | Decreased rate of organ rejection<br>Increased time to organ rejection<br>Reduced CMV load |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>International Copper Association, New York, NY<br>Various manufacturers<br><br>Commercially available; studies at hospitals ongoing | Terminal cleaning of standard surfaces | Reduced costs associated with HAIs<br>Reduced infection rates<br>Reduced bacteria isolated from surfaces<br>Reduced morbidity and mortality from HAIs |
| Daclatasvir for treatment of chronic hepatitis C virus infection | Patients in whom chronic hepatitis C infection (HCV) 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 and BMS-791325. Administered orally, 60 mg, once daily.<br><br>Bristol-Myers Squibb, New York, NY<br><br>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<br>Sofosbuvir (investigational)<br>Pegylated IFN plus ribavirin<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks)<br>Decreased need for liver transplant<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Delamanid 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 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, or 200 mg, once daily, in addition to standard TB regimens.<br><br>Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan<br><br>Phase III trial recruiting | Bedaquiline (Sirturo™)<br>Ethionamide (Trecator®)<br>Kanamycin<br>Ofloxacin (Floxin®)<br>PA-824, a nitroimidazole (in development)<br>Pyrazinamide | Improved patient adherence with therapy<br>Reduced spread of infection<br>Reduced time to clinical response<br>Resolution of active TB infection<br>Improved quality of life |
| Deleobuvir for treatment of chronic hepatitis C infection | Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed | Current standard of care for HCV infection is ineffective in more than half of infected patients; 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).<br><br>Boehringer Ingelheim GmbH, Ingelheim, Germany<br><br>Phase III trials ongoing; FDA granted fast-track status in combination with faldaprevir in an INF-free combination | Boceprevir<br>IFN/RBV<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks)<br>Decreased need for liver transplant<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Extracorporeal membrane oxygenation for treatment of serious influenza infections | Patients in whom serious influenza infection has been diagnosed | Influenza continues to cause significant morbidity and mortality in susceptible patients; better treatments are needed. Extracorporeal membrane oxygenation (ECMO) is intended to give continuous cardiopulmonary support for several days to weeks, as an adjunctive treatment for severe respiratory and cardiac failure. The therapeutic goal is to minimize ventilator-induced lung injury and allow more time to treat the underlying disease process and to enable recovery. ECMO had historically been contraindicated in patients with serious infections; however, recent trials in patients (infants, children, and adults) with H1N1 influenza suggested some utility for the procedure in improving survival. ECMO is a complicated technology that requires a dedicated, experienced team; it is typically used only in clinical cases where the patient is at significant risk of death from respiratory and cardiac failure. It involves cannulas placed in large blood vessels to provide access to the patient's blood. An ECMO machine continuously pumps blood from the patient through a membrane oxygenator that imitates the gas exchange process of the lungs, and oxygenated blood is then returned to circulation.<br><br>Various U.S. hospitals<br>Various European, Asian, Australian hospitals<br><br>Several clinical trials completed; case series published; can be implemented readily in centers with ECMO experience | Standard care for influenza | Reduced morbidity<br>Reduced mortality |
| Faldaprevir for treatment of chronic hepatitis C virus infection | Patients in whom chronic infection with hepatitis C virus (HCV) has been diagnosed | HCV treatment options are not effective in all patients, 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); may also be administered in an IFN-free regimen with the polymerase inhibitor deleobuvir and RBV.<br><br>Boehringer Ingelheim GmbH, Ingelheim, Germany<br><br>Phase III trials ongoing; FDA granted fast-track status in combination with standard of care and in IFN-free combination with deleobuvir | Boceprevir<br>IFN/RBV<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks)<br>Decreased need for liver transplant<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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. 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) with the intended purpose of introducing healthy flora to the intestinal tract to prevent recurrence of CDI.<br><br>Multiple trials ongoing at various U.S. medical centers<br><br>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 to use fecal microbiota transplantation for treating CDI not responding to standard therapies provided physicians obtains adequate informed consent | Fidaxomicin<br>Metronidazole<br>Vancomycin | Reduced diarrhea<br>Reduced dehydration<br>Reduced reinfection |
| 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.<br><br>BIOVIGIL Hygiene Technologies, LLC, Ann Arbor, MI<br><br>System is available for use | Patient-centered signage<br>Radiofrequency identification hand-washing systems<br>Standard hand-washing practices | Increase hand hygiene compliance<br>Reduced HAI incidence<br>Reduced HAI morbidity and mortality<br>Reduced health care costs associated with HAIs |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Ledipasvir for treating chronic hepatitis C infection | Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed | Current HCV treatment options are not effective in all patients, even with the newly approved agents of telaprevir and boceprevir. 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. Ledipasvir is an oral 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 viral particles. Ledipasvir could inhibit the activity of all HCV genotypes. Administered orally 30 mg, once daily. Intended to be used in combination with sofosbuvir in a single pill.<br><br>Gilead Sciences, Inc., Foster City, CA<br><br>Phase III trial ongoing | Boceprevir<br>Pegylated interferon plus ribavirin<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks)<br>Decreased need for liver transplant<br>Improved quality of life |
| Letermovir (AIC246) 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 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.<br><br>AiCuris GmbH & Co. KG, Wuppertal, Germany<br>Merck & Co Inc., Whitehouse Station, NJ<br><br>Phase II trial complete; FDA granted orphan drug and fast-track statuses | Cidofovir (off label)<br>Ganciclovir | Decreased rate of organ rejection<br>Increased time to organ rejection<br>Reduced HCMV load |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Bruker Corp., Billerica, MA<br><br>Manufacturer plans to file for regulatory approval in 2013 | Culture methods<br>Microscopy<br>Polymerase chain reaction | Rapid disease detection<br>Fewer cases of antibacterial resistance<br>Improved treatment outcomes |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Nitazoxanide (NT-300) for treatment of influenza | Patients in whom viral influenza has been diagnosed | New influenza treatments are needed because of the development of resistance to existing agents. Nitazoxanide 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, 300 mg, twice a day.<br><br>Romark Laboratories, L.C., Tampa, FL<br><br>Phase III trial recruiting | Oseltamivir (Tamiflu®)<br>Zanamivir (Relenza®) | Reduced complications of influenza infection<br>Shorter duration of symptoms |
| Nonnucleoside polymerase inhibitor (ABT-333) 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, 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. ABT-333 is a nonnucleoside NS5B polymerase inhibitor intended to bind HCV RNA-dependent RNA polymerase and inhibit replication of the viral genome. It is administered orally 250 mg twice daily.<br><br>AbbVie Inc., North Chicago, IL<br><br>Phase III trials ongoing; FDA granted breakthrough therapy status for HCV genotype 1 in combination with ABT-450/r, ABT-267, with and without ribavirin | Boceprevir<br>Pegylated interferon plus ribavirin<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks)<br>Decreased need for liver transplant<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| NS5A inhibitor (ABT-267) for treating chronic hepatitis C virus infection | Patients in whom chronic hepatitis C virus infection has been diagnosed | Current HCV treatment options are not effective in all patients, even with the newly approved agents of telaprevir and boceprevir. 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. ABT-267 is an oral 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 viral particles. ABT-267 could inhibit the activity of all HCV genotypes. Administered orally 25 mg, once daily.<br><br>AbbVie Inc., North Chicago, IL<br><br>Phase III trials ongoing; FDA granted breakthrough therapy status for HCV genotype 1 in combination with ABT-450/r, ABT-333, with and without ribavirin | Boceprevir<br>Pegylated interferon plus ribavirin<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks)<br>Decreased need for liver transplant<br>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 receptor-5 antagonist (CCR-5) that is approved for treating CCR-5-tropic HIV-1 in combination with other antiretroviral agents. 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. It is intended to be administered daily as preexposure prophylaxis for people at high risk of HIV infection. Administered orally, 300 mg, once daily.<br><br>ViiV Healthcare, Middlesex, UK<br><br>Phase II trial recruiting | Condoms<br>Harm-reduction campaigns<br>Preexposure prophylaxis (tenofovir/emtricitabine)<br>Prophylactic vaccines (investigational)<br>Vaginal microbicide gels (investigational) | Reduced transmission and incidence of HIV<br>Reduced morbidity and mortality |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| OraQuick in-home rapid test for detection of HIV infection | Patients 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.<br><br>OraSure Technologies, Inc., Bethlehem, PA<br><br>FDA approved Jul 2012 | Home-based blood tests (mail-in)<br>Clinic-based rapid test (OraQuick) | Reduced HIV transmission<br>Earlier intervention to control viral load<br>Increased HIV screening rate |
| 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.<br><br>Windsor Regional Hospital, Windsor, Ontario, Canada<br>Medizone International, Inc., Sausalito, CA<br><br>Manufacturer is in discussions with the U.S. Environmental Protection Agency for marketing clearance as a disinfection system | Antimicrobial copper touch surfaces<br>Terminal cleaning procedures using bleach and cleaning of visibly soiled surfaces as necessary<br>Ultraviolet light | Reduced costs associated with HAIs<br>Reduced bacteria isolated from surfaces<br>Reduced infection rates<br>Reduced HAI morbidity and mortality |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Novartis International AG, Basel, Switzerland<br>Bayer AG, Leverkusen, Germany<br><br>Phase II trials ongoing; FDA granted orphan drug and fast-track statuses | Ethambutol<br>Ethionamide<br>Isoniazid<br>Kanamycin<br>Ofloxacin<br>Pyrazinamide<br>Rifampicin | Shorter duration of therapy<br>Simpler dosing<br>Improved adherence<br>Safer method of action<br>Lower cost of overall treatment |
| Pegylated interferon lambda (BMS-914143) for treatment of chronic hepatitis C infection | Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed | Current standard of care for HCV infection is ineffective in more than half of infected patients and the presence of pegylated interferon (IFN)a-2a results in poor treatment tolerability in many patients; 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.<br><br>Bristol-Myers Squibb, New York, NY<br><br>Phase III trials ongoing | IFNa-2a<br>IFN-free HCV drug combinations | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks)<br>Decreased need for liver transplant<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Point-of-care testing systems for methicillin-resistant *Staphylococcus aureus* screening | Patients who may be infected by methicillin-resistant *Staphylococcus aureus* (MRSA) | Current MRSA screening tests are time-intensive and typically require highly trained laboratory workers to perform the test. Testing systems and assays are being developed that could be used by nonclinical laboratory staff in the point-of-care setting and provide results in 10–15 minutes.<br><br>Multiple manufacturers:<br>Blaze Venture Technologies, Ltd., Ware, UK<br>Enigma Diagnostics, Ltd., Salisbury, UK<br>InstantLabs Medical Diagnostics Corp., Reston, VA<br>QuantaLife, Inc., Pleasantville, CA<br>Smiths Group, plc, London, UK<br>TwistDx, Ltd., Cambridge, UK<br><br>Unphased trials ongoing; devices and test kits expected to be cleared through 510(k) pathway with no requirement for clinical evidence of efficacy | MRSA culture<br>Conventional 1st-generation polymerase chain reaction (PCR) assay<br>2nd-generation quantitative PCR | Reduced transmission of MRSA<br>Increased sensitivity and specificity of MRSA detection<br>Faster MRSA detection |
| 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. Private ICU rooms may help to better isolate patients and contain their infections or prevent them from contracting a new infection.<br><br>McGill University Health Centre, Montreal, Quebec, Canada<br><br>Early adoption ongoing | Antimicrobial copper touch surfaces<br>Standard infection control practices<br>Portable pulsed xenon ultraviolet light added to terminal cleaning | Reduced hospital-acquired infection rates |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 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.<br><br>Cepheid, Sunnyvale, CA<br><br>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<br>Tuberculin skin test (Mantoux test)<br>Ziehl-Neelsen microscopy | Less lab staff training time<br>Rapid detection<br>Improved treatment<br>Better control of antibacterial resistance |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>GlaxoSmithKline, Middlesex, UK<br>PATH Malaria Vaccine Initiative, Washington, DC<br><br>Phase III trials completed; phase II trials ongoing | Chloroquine phosphate<br>Mosquito nets | Reduced incidence of malaria infection<br>Increased overall survival |
| Silicone-based condom (ORIGAMI Anal Condom) to prevent HIV infection during receptive anal intercourse | Persons 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.<br><br>Origami Condoms of California, Culver City, CA<br><br>Trial expected to be completed Oct 2013; larger trials planned for 2014 | Latex condoms<br>Harm reduction campaigns<br>Preexposure prophylaxis (tenofovir/emtricitabine)<br>Prophylactic vaccines (investigational) | Reduced transmission and incidence of HIV<br>Patient satisfaction<br>Increased use of condoms during receptive anal intercourse |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Simeprevir 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. Simeprevir in an oral NS3/4a HCV protease inhibitor that may be used to limit viral replication in combination with pegylated interferon plus ribavirin (IFN/RBV). Simeprevir is also being investigated in combination with sofosbuvir and daclatasvir as an IFN-free regimen. Administered 150 mg, once daily.<br><br>Janssen Research & Development unit of Johnson & Johnson, New Brunswick, NJ<br><br>Phase III trials ongoing; FDA granted fast-track status; FDA accepted new drug application for priority review May 2013; FDA advisory committee voted to recommend approval Oct 2013; expected decision date Nov 2013 | Boceprevir<br>IFN/RBV<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks)<br>Decreased need for liver transplant<br>Improved quality of life |
| Sofosbuvir 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 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, simeprevir, and other agents. Administered orally 400 mg, once daily.<br><br>Gilead Sciences, Inc., Foster City, CA<br><br>Phase III trials ongoing; FDA granted fast-track status; new drug application submitted Apr 2013; FDA granted priority review Jun 2013; FDA decision date set for Dec 2013 | Boceprevir<br>IFN/RBV<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks)<br>Decreased need for liver transplant<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Sovaprevir (NS3 protease inhibitor) for treatment of chronic hepatitis C virus infection | Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed | Current standard of care for HCV infection is not effective in all patients seeking treatment and is poorly tolerated in many patients; 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. It is intended to be used in combination with standard-of-care pegylated interferon plus ribavirin (IFN/RBV), and is taken orally, 200–800 mg, once daily. Sovaprevir could be taken in combination with ACH-3102 (NS5A inhibitor) and ribavirin as an IFN-free regimen.<br><br>Achillion Pharmaceuticals, Inc., New Haven, CT<br><br>Phase II trial ongoing; FDA granted fast-track status for chronic HCV infection; FDA placed sovaprevir on clinical hold Jul 1, 2013, due to safety concerns when the drug was administered with ritonavir-boosted atazanavir | Boceprevir<br>IFN/RBV<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks)<br>Decreased need for liver transplant<br>Improved quality of life |
| Streaming weekly educational soap opera episodes to smartphones for people at high risk of contracting HIV | Patients who are at high risk of contracting HIV infection | Despite HIV prevention and education efforts, the epidemic continues to spread. New methods to educate patients about how to better avoid activities associated with elevated risk of contracting HIV are needed. A 12-episode soap opera video series called “Love, Sex, and Choices” was designed to educate women about HIV risk reduction methods. Women were given a secure cell phone that streamed weekly episodes incorporating HIV risk-reduction messages. Delivering risk-reduction messages in this format could lead to better awareness.<br><br>Rutgers College of Nursing, Newark, NJ<br><br>Study completed | Standard risk-reduction programs<br>Text messaging risk reduction programs | Reduced HIV incidence in women at risk of contracting the infection<br>Increased knowledge and identification of high-risk behavior |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Surotomycin (CB-183,315) 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 is a novel cyclic lipopeptide, which purportedly disrupts bacterial membrane potential, inhibiting bacterial metabolism. Administered orally, 125–250 mg, twice daily, for 10 days.<br><br>Cubist Pharmaceuticals, Inc., Lexington, MA<br><br>Phase III trials recruiting participants; FDA granted qualified infectious disease product and fast-track statuses | Fidaxomicin<br>Metronidazole<br>Vancomycin | Reduced CDI recurrence rate<br>Shorter hospitalization time<br>Faster time to resolution of diarrhea |
| Tenofovir and emtricitabine (Truvada) for prevention of HIV infection | People at risk of HIV infection | Although behavior-change programs have resulted in dramatic reductions in HIV transmission in the U.S., there remains no truly effective means to prevent HIV infection among populations at high risk of contracting HIV infection. Truvada® is a combination of 2 reverse transcriptase inhibitors, tenofovir disoproxil fumarate (Viread®) and emtricitabine (Emtriva®) given as preexposure prophylaxis for people at high risk of HIV infection. Daily prophylactic use of tenofovir and emtricitabine could reduce the risk of contracting HIV during homosexual or heterosexual sex. The 2 drugs are combined into 1 oral tablet, taken daily.<br><br>Gilead Sciences, Inc., Foster City, CA<br><br>FDA approved Jul 2012 to reduce the risk of HIV infection in high-risk, uninfected individuals who may engage in sexual activity with infected partners; as a condition of approval, FDA also directed Gilead to develop a risk evaluation and mitigation strategy to help ensure safe use as part of a comprehensive prevention strategy for the disease; the company will also provide vouchers for free HIV testing and condoms, an opt-in service for reminders about HIV testing, and subsidized HIV resistance testing for any person who becomes HIV-positive while taking the drug as prescribed for prevention | Condoms<br>Harm reduction campaigns<br>Prophylactic vaccines (investigational)<br>Vaginal microbicide gels (investigational) | Reduced transmission and incidence of HIV |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Terlipressin (Lucassin) for reversal of hepatorenal syndrome type 1 | Patients in whom hepatorenal syndrome (HRS) type 1 has been diagnosed | HRS 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. No U.S.-approved drugs for HRS are available. Given intravenously, in combination with albumin.<br><br>Ikaria, Inc., Clinton, NJ<br><br>Phase III completed; FDA granted orphan drug status | Liver transplantation<br>Pharmacotherapy (e.g., dopamine, misoprostol, vasoconstrictors) | Confirmed HRS reversal<br>Increased survival to time of transplantation<br>Increased rates of transplant-free survival up to 90 days |
| TransVax (ASP0113) 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. ASP0113, TransVax™ 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.<br><br>Vical, Inc., San Diego, CA<br>Astellas Pharma, Inc., Tokyo, Japan<br><br>Phase III trial recruiting | Cidofovir (off label)<br>Ganciclovir | Decreased rate of organ rejection<br>Increased time to organ rejection<br>Reduced HCMV load |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| xTAG Gastrointestinal Pathogen Panel for detecting gastroenteritis | Patients suspected of having gastroenteritis | Traditional stool testing for gastroenteritis can take 2–3 days, during which time a severe gastrointestinal infection can kill a patient. Faster detection methods are needed. The xTAG Gastrointestinal Pathogen Panel (GPP) is a rapid molecular diagnostic test that simultaneously analyzes the DNA or RNA of 11 viral, bacterial, and parasitic causes of infectious gastroenteritis from a single stool sample using the Luminex xMAP® platform. Pathogens detected include norovirus and rotavirus A, the bacteria *Campylobacter*, *Clostridium difficile* toxin A/B, *Salmonella* and 3 strains of *Escherichia coli*, as well as the parasites *Cryptosporidium* and *Giardia*. Testing for DNA and RNA from all 11 species occurs simultaneously. The panel purportedly takes 5 hours to perform, which could improve treatment outcomes.<br><br>Luminex Corp., Austin, TX<br><br>FDA cleared via the de novo pathway (route to market for low to moderate risk classified in class III; not substantially equivalent to predicate device on market) in Jan 2013 for diagnosing gastroenteritis | Antibody-based detection methods<br>Polymerase chain reaction assay<br>Stool culture | Rapid resolution of diarrhea and symptoms<br>Reduced mortality |

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

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Aspiration system (AspireAssist) for treatment of obesity | Patients with body mass index (BMI) 35.0–55.0 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 during conscious sedation.<br><br>Aspire Bariatrics, Inc., King of Prussia, PA<br><br>Pivotal U.S. trial ongoing; Conformité Européene (CE) marked Dec 2011 | Endoluminal sleeve (EndoBarrier)<br>Gastric banding surgery<br>Gastric pacemaker (in development)<br>Intragastric balloons (in development)<br>Pharmacotherapy<br>Sleeve gastrectomy surgery | Decreased comorbidities<br>Improved quality of life<br>Total weight loss |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| 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. 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.<br><br>Vivus, Inc., Mountain View, CA<br><br>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 | Bariatric surgery<br>Behavior and lifestyle modifications<br>Combination norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (Contrave®; in development)<br>Lorcaserin (Belviq)<br>Orlistat (Xenical®) | Decreased comorbidities<br>Improved quality of life<br>Total weight loss |
| 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.<br><br>Ohio State University, Columbus<br>University of Southern California, Los Angeles<br><br>Unphased trials completed | Aspiration therapy system (in development)<br>Endoluminal sleeve (EndoBarrier)<br>Gastric banding surgery<br>Gastric pacemaker (in development)<br>Intragastric balloons (in development)<br>Pharmacotherapy<br>Roux en Y bypass surgery<br>Sleeve gastrectomy surgery | Decreased food cravings<br>Decreased obesity-associated comorbidities (e.g., prediabetes, high blood pressure)<br>Increased weight loss<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| 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.<br><br>Academic Medical Centre at the University of Amsterdam, the Netherlands<br><br>Pilot trial completed; fecal microbiota therapy has also been used to treat other conditions, such as recurrent *Clostridium difficile* infection. | Antiobesity pharmacotherapy<br>Diet and behavior changes<br>Surgical intervention (e.g., bariatric surgery) | Improved fecal flora composition<br>Weight loss<br>Resolution of metabolic syndrome |
| 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 guidewire positions the dual balloon appropriately, the dual balloon is inflated with 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.<br><br>ReShape Medical, Inc., San Clemente, CA<br><br>Pivotal U.S. trial ongoing; Conformité Européene (CE) marked in 2007; after product revisions, it was launched in UK in Mar 2012 | Endoluminal sleeve (EndoBarrier)<br>Gastric banding surgery<br>Gastric pacemaker (in development)<br>Pharmacotherapy<br>Sleeve gastrectomy surgery | Decreased comorbidities<br>Improved quality of life<br>Total weight loss |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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. 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 once-daily treatment showed potential in preclinical studies and studies in overweight patients without diabetes to reduce food intake and induce weight loss.<br><br>Novo Nordisk a/s, Bagsværd, Denmark<br><br>1 phase III trial completed and 1 phase III trial ongoing in nondiabetic obese patients. | 5-HT$_{2C}$ receptor agonist (Belviq®)<br>Behavior and lifestyle modifications<br>Combination appetite suppressant/stimulant and anticonvulsant (Qsymia®)<br>Combination norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (Contrave®; in development)<br>Pancreatic lipase inhibitor (orlistat, Xenical®)<br>Surgical therapy (e.g., bariatric surgery) | Decreased comorbidities<br>Improved quality of life<br>Total weight loss |
| Lorcaserin (Belviq) for treatment of obesity | Overweight adults (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 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. 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.<br><br>Arena Pharmaceuticals, Inc., San Diego, CA (manufacturer)<br>Eisai, Inc., U.S., a subsidiary of Eisai Co., Ltd., Tokyo, Japan (U.S. distributor)<br><br>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<br>Combination appetite suppressant/stimulant and anticonvulsant (Qsymia®)<br>Combination norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (Contrave®; in development)<br>Pancreatic lipase inhibitor (orlistat, Xenical®)<br>Surgical therapy (e.g., bariatric surgery) | Decreased comorbidities<br>Improved quality of life<br>Total weight loss |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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, the 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. Bupropion purportedly acts on weight control by stimulating the POMC neuron. Naltrexone purportedly prevents inhibition of POMC neurons by blocking the action of beta-endorphin. Naltrexone and bupropion extended release (Contrave SR®) is taken orally, once a day.<br><br>Orexigen Therapeutics, Inc., La Jolla, CA<br><br>FDA rejected new drug application Feb 2011; requested additional trial on cardiovascular effects; enrollment began Jun 2012 and company announced it had enrolled more quickly than anticipated; expects to complete data collection by end of 2013; company anticipates resubmission of data in early 2014; Jan 2013, company announced it made progress with FDA on faster path to resubmission | Bariatric surgery<br>Behavior and lifestyle modifications<br>Combination appetite suppressant/stimulant and anticonvulsant (Qsymia®)<br>Lorcaserin (Belviq®)<br>Orlistat (Xenical®) | Decreased comorbidities<br>Improved quality of life<br>Total weight loss |
| 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.<br><br>University of Minnesota, Minneapolis<br><br>Pilot trial completed; phase II trial completed | Bariatric surgery<br>Behavior and lifestyle modifications<br>Pancreatic lipase inhibitor (orlistat, Xenical®)<br>Surgical therapy (e.g., bariatric surgery) | Decreased comorbidities<br>Improved quality of life<br>Total weight loss |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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.<br><br>EnteroMedics, Inc., St. Paul, MN<br><br>Pivotal ReCharge trial ongoing; phase III EMPOWER™ trial ongoing, with expected completion in 2013; Jun 2013, the company announced that it had submitted a premarket approval application to FDA for the Maestro RC System | Bariatric surgery<br>Behavior and lifestyle modifications<br>Combination appetite suppressant/stimulant and anticonvulsant (Qsymia®)<br>Combination norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (Contrave®; in development)<br>Lorcaserin (Belviq®)<br>Pancreatic lipase inhibitor (orlistat, Xenical®) | Decreased comorbidities<br>Improved quality of life<br>Total weight loss |

**Table 11. AHRQ Priority Condition: 11 Peptic Ulcer Disease and Dyspepsia: 10 Interventions**

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Allogeneic precultured adult bone marrow–derived mesenchymal stem cells remestemcel-L (Prochymal) for treatment of Crohn's disease | Patients in whom Crohn's disease has been diagnosed | 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.<br><br>Osiris Therapeutics, Inc., Columbia, MD<br><br>Phase III trials ongoing; FDA granted fast-track status | Autologous bone marrow–derived MSC stromal cells (in development)<br>Teduglutide | Increased disease remission<br>Improved disease symptoms<br>Improved quality of life |
| 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 to prevent periodic disease flares besides surgery. 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, leading 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.<br><br>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<br><br>Phase II/III trial ongoing; procedure may be adopted by gastroenterologists who are using the procedure for treating recurrent *Clostridium difficile* infection | Aminosalicylates (mesalazine)<br>Antibiotics (for acute flares)<br>Corticosteroids (e.g., prednisone)<br>Immunomodulators (e.g., azathioprine)<br>Monoclonal antibodies (e.g., natalizumab, infliximab) | Reduced relapse frequency<br>Reduced use of medications<br>Reduced symptoms<br>Reduced or postponed need for surgery<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Linx Reflux Management System for treatment-refractory gastroesophageal reflux disease | Patients in whom treatment-refractory gastroesophageal reflux disease (GERD) has been diagnosed | GERD is a progressive disease that is not always managed by pharmacologic treatments, and many patients undergoing surgical treatment remain on pharmacologic therapy. The Linx® Reflux Management System purportedly augments the activity of the weak lower esophageal sphincter of patients with GERD, which may restore the body's natural barrier to reflux. The system comprises a small flexible band of interlinked titanium beads with magnetic cores. The magnetic attraction between the beads is intended to help the lower esophageal sphincter remain closed in response to gastric pressures to prevent reflux from the stomach into the esophagus. Swallowing force temporarily breaks the magnetic bond of the beads, allowing food and liquid to pass normally into the stomach; after swallowing, the lower esophageal sphincter closes. The system is implanted via laparoscopic surgery.<br><br>Torax Medical, Inc., Shoreview, MN<br><br>FDA approved Mar 2012 for patients with treatment-refractory GERD despite use of optimal medical therapy | Antacid medications<br>Fundoplication<br>$H_2$ antagonists<br>Proton pump inhibitors | Reduced GERD symptoms<br>Reduced risk of GERD-related cancer<br>Improved quality of life |
| MuDelta (JNJ-27018966) for treatment of diarrhea-predominant irritable bowel syndrome | Patients in whom diarrhea-predominant irritable bowel syndrome (IBS-d) has been diagnosed | MuDelta 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 MuDelta acts locally in the digestive tract, thus having a low potential for systemic side effects.<br><br>Furiex Pharmaceuticals, Inc., Morrisville, NC<br><br>Phase III trials ongoing; FDA granted fast-track status Jan 2011 | Antispasmodic drugs<br>Opioids<br>Serotonin agonists<br>Tricyclic antidepressants | Reduced abdominal pain and bloating symptoms<br>Long-term relief |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| PerOral endoscopic myotomy (POEM procedure) for treatment of esophageal achalasia | Patients in whom esophageal achalasia has been diagnosed | Current 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.<br><br>Northwestern Memorial Hospital, Chicago, IL<br><br>Phase IV trial ongoing | Heller myotomy | Improved Esophageal Function Tests (upper endoscopy, barium swallow, esophageal manometry, pH test) scores<br>Improved quality of life |
| Rifaximin (Xifaxan) for treatment of nonconstipating irritable bowel syndrome | Patients in whom nonconstipating irritable bowel syndrome has been diagnosed | Rifaximin (Xifaxan®) is a nonabsorbable oral antibiotic approved for treating traveler's diarrhea and under study for irritable bowel syndrome with diarrhea. 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, 3 times a day.<br><br>Salix Pharmaceuticals, Inc., Morrisville, NC<br><br>Phase III trial began recruiting Sept 2013 | Antispasmodic drugs<br>Opioids<br>Serotonin agonists<br>Tricyclic antidepressants | Reduced abdominal pain and bloating symptoms<br>Long-term relief |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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. Current treatments supplement and stabilize nutritional needs; however, parenteral support does not improve absorption and is associated with infections, blood clots, liver damage, poor quality of life, and high costs. Teduglutide (Gattex™) is a recombinant analog of human glucagon-like peptide 2 that purportedly increases nutrient absorption and intestinal cell growth in patients with SBS.<br><br>NPS Pharmaceuticals, Inc., Bedminster, NJ<br><br>FDA approved Dec 2012 for treating SBS | Intravenous fluids<br>Parenteral nutrition | Improved hydration<br>Improved nutritional status<br>Weight gain<br>Reduced diarrhea<br>Improved quality of life |
| Tofacitinib (JAK 3 kinase inhibitor) for treatment of ulcerative colitis | Patients in whom ulcerative colitis (UC) has been diagnosed | Current therapies for UC temporarily control symptoms and are poorly tolerated in some patients; the only cure is surgery. Tofacitinib is an oral 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. Tofacitinib has been administered twice daily (0.5, 1, 3, 5, 10, and 15 mg) doses.<br><br>Pfizer, Inc., New York, NY<br><br>Phase III trials ongoing | Aminosalicylates (mesalazine)<br>Antibiotics (for acute flares)<br>Corticosteroids (e.g., prednisone)<br>Immunomodulators (e.g., azathioprine)<br>Monoclonal antibodies (e.g., natalizumab, infliximab) | Improved clinical response<br>Reduced flare symptoms<br>Reduced or postponed need for surgery<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Vedolizumab for treatment of moderate to severe ulcerative colitis | Patients in whom moderate to severe ulcerative colitis (UC) has been diagnosed | Current therapies for UC temporarily control symptoms and are poorly tolerated in some patients; the only cure is surgery. Vedolizumab is an infused monoclonal antibody that may provide an alternative treatment.<br><br>Millennium Pharmaceuticals unit of Takeda Pharmaceutical Co., Ltd., Osaka, Japan<br><br>Phase III trial completed (Gemini I); in Jun 2013, the manufacturer announced that it had submitted a biologics license application to FDA; in Sept 2013, FDA granted priority review status to vedolizumab | Aminosalicylates (mesalazine)<br>Antibiotics (for acute flares)<br>Corticosteroids (e.g., prednisone)<br>Immunomodulators (e.g., azathioprine)<br>Monoclonal antibodies (e.g., natalizumab, infliximab) | Reduced flare symptoms<br>Maintained remission<br>Reduced or postponed need for surgery<br>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 | 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, administered 500 mg, twice daily.<br><br>Chemocentryx, Inc., Mountain Valley, CA<br><br>1 phase III trial completed, 3 phase III trials terminated; GSK returned all rights to Chemocentryx following failed clinical trials | Aminosalicylates (mesalazine)<br>Antibiotics (for acute flares)<br>Corticosteroids (e.g., prednisone)<br>Immunomodulators (e.g., azathioprine)<br>Monoclonal antibodies (e.g., natalizumab, infliximab) | Delayed or avoided surgery<br>Reduced flares<br>Reduced side effects<br>Disease remission<br>Symptom improvement<br>Improved quality of life |

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

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Bi-directional communication for personalized body weight management (SmartMoms) for pregnant women | Pregnant women | Pregnant women in the U.S. are at increased risk of exceeding pregnancy weight goals at term as recommended by current Institute of Medicine guidelines, leaving both 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 weight management counselor via a smartphone. The patient will also be asked to submit weight data (using a provided scale) and nutritional information via smartphone.<br><br>Pennington Biomedical Research Center, Baton Rouge, LA<br><br>Phase III trial ongoing | Other perinatal weight-management strategies | Improved perinatal weight management<br>Reduced morbidity<br>Improved maternal and fetal health outcomes<br>Improved quality of life |
| Blood test (ProNid) to predict spontaneous preterm birth | Pregnant women | 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; having results of such a test would allow clinicians and their patients to plan preterm birth prevention strategies. ProNid™ 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.<br><br>Sera Prognostics, Salt Lake City, UT<br><br>Validation study ongoing; completed enrollment of 5,500 women in Aug 2013 | Assessment of cervical length<br>Detection of bacterial vaginosis<br>Fetal fibronectin levels<br>Home uterine activity monitoring<br>Salivary estriol testing | Earlier intervention for women at risk of preterm birth<br>Reduced incidence of preterm birth<br>Reduced neonatal complications<br>Reduced use of neonatal intensive care services |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Bucelipase-alfa (Kiobrina) for low-birthweight preterm infants | Patients 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 the growth of preterm infants is the need for improvement in 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. For formula-fed infants, 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.<br><br>Swedish Orphan Biovitrum AB, Stockholm, Sweden<br><br>Phase III trial ongoing | Donor human breast milk<br>Infant formula<br>Maternal breast milk | Improved neonate growth<br>Reduced health care costs<br>Improved quality of life |
| Elagolix (gonadotropin-releasing hormone antagonist) for treatment of endometriosis | Patients in whom endometriosis has been diagnosed | Elagolix is the 1st oral nonpeptide gonadotropin-releasing hormone (GnRH) antagonist that, unlike available injectable GnRH agonists (which take up to several weeks to work), has a rapid onset in suppressing hormones (stops ovulation and endometriosis symptoms) without a hormonal flare or injection site reactions; 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.<br><br>AbbVie Inc., North Chicago, IL<br><br>Phase III trials ongoing | Pharmacotherapy (e.g., hormonal contraceptives, steroids)<br>Surgical intervention (e.g., endometrial growth and scar tissue excision, hysterectomy) | Improved composite pelvic signs and symptoms score (measures dysmenorrhea, nonmenstrual pelvic pain, dyspareunia, pelvic tenderness and induration)<br>Maintained bone mineral density<br>Improved patient global impression of change<br>Less pain (visual analog scale) |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| In utero fetal catheterization procedure for treatment of hypoplastic left heart syndrome | Pregnant women receiving a diagnosis of fetal hypoplastic left heart syndrome (HLHS) | 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, treatment protocol involves admitting the patient to the neonatal intensive care unit, placing the neonate on a ventilator, and giving prostaglandin E1 to keep the ductus arteriosus patent. Texas Children's Fetal Center has created a fetal in utero catheterization 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, catheterization 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 (AV 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 baby to become more oxygenated and increasing odds of postnatal survival.<br><br>Texas Children's Fetal Center of Texas Children's Hospital, Houston, TX<br><br>4-patient surgery trial completed | Neonatal surgery | Increased oxygenation to fetus<br>Increased survival to live birth<br>Increased postnatal survival |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Preconception Care System (Gabby) for improving health outcomes in pregnancy | Women of reproductive age with potential for pregnancy | Despite overall improvement in contraceptive methods and access to early prenatal care, poor maternal and infant mortality rates persist in the U.S., disproportionately affecting minority and socially disadvantaged populations. Preconception care is a concept that aims to mitigate poor reproductive health outcomes by addressing a broad range of issues, including family planning, previous health condition history, environmental or nutritional exposure to teratogens, and behavior practices. Health information technology innovations have been used to improve the preconception care model. Gabby is a virtual patient advocate (VPA), or animated computer character, that mimics the behavior of a health provider to simulate a face-to-face encounter between patient and clinician. The Gabby system delivers health educational information individually tailored to the patient's needs, based on previous medical records and information collected. In this case, this VPA is designed to engage in educational dialogue with the patient about preconception care, particularly delivering culturally competent and appropriate information to underprivileged populations. This system screens individuals for preconception risks, does an individual assessment of acceptance to behavior change, teaches individuals about preconception risks, and creates an action plan to reduce those risks. Researchers hypothesize this delivery innovation could mitigate poor birth outcomes, both for mother and child.<br><br>Boston University School of Medicine's Department of Family Medicine/Boston Medical Center, MA<br><br>Pilot trial completed; unphased trial (n=230) ongoing | Educational therapy<br>Routine care | Reduced maternal and infant mortality rates<br>Improved health outcomes |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Vending machine dispensers for emergency oral contraceptives (Plan B One Step) to prevent pregnancy | Women at risk of 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.<br><br>Shippensburg University, Shippensburg, PA<br><br>Dispensers not subject to FDA approval; FDA approved; FDA announced in Jun 2013 that Plan B One Step became available for purchase without age restrictions | Over-the-counter access to emergency contraceptives | Decreased risk of pregnancy<br>Increased emergency contraceptive use<br>Increased risk of adverse events associated with emergency contraception |

**Table 13. AHRQ Priority Condition: 13 Pulmonary Disease, Asthma: 17 Interventions**

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Aeris Therapeutics, LLC, Woburn, MA<br><br>8 phase III and IV trials and postmarket registry registered, recruiting, or ongoing; Conformité Européene (CE) marked Sept 2010 | Antibiotics<br>Bronchodilators<br>Corticosteroids<br>Oxygen<br>Pulmonary rehabilitation program<br>Surgery: lung-reduction volume surgery, bullectomy, lung transplantation | Improved lung function<br>Improved activities of daily living<br>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 treatments are available that address the cause of CF rather than only the symptoms. 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 is given orally 3 times daily in clinical trials.<br><br>PTC Therapeutics, Inc., South Plainfield, NJ<br><br>1 phase III trial completed, 1 phase III trial ongoing; FDA granted orphan drug status | Antibiotics<br>Bi-level positive airway pressure ventilators<br>Bronchodilators<br>Chest physiotherapy<br>DNase (such as Pulmozyme®)<br>Gene therapies (viral vector or liposome delivery of normal CFTR; investigational)<br>Hypertonic saline<br>Mucolytics (acetylcysteine) | Improved lung function<br>Increased survival<br>Reduced need for additional therapies<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Endobronchial valve system (Zephyr) for treatment of heterogeneous emphysema | Patients in whom heterogeneous emphysema has been diagnosed | This implanted endobronchial valve system (Zephyr®) is intended as a minimally invasive method to treat hyperinflation in the lungs. The device is intended to 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.<br><br>Pulmonx, Inc. (formerly Emphasys), Redwood City, CA<br><br>Multicenter pivotal investigational device exemption clinical trial ongoing | Antibiotics<br>Bronchodilators<br>Corticosteroids<br>Oxygen<br>Pulmonary rehabilitation program<br>Surgery: lung-reduction volume surgery, bullectomy, lung transplantation | Improved lung function<br>Improved activities of daily living<br>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, 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 current formulations of amikacin while also minimizing systemic exposure to the drug. Administration is via inhalation, once daily.<br><br>Insmed, Inc., Monmouth Junction, NJ<br><br>Phase II trial ongoing; FDA granted orphan drug and fast-track statuses. Arikace is approved for other indications; 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)<br>Other antibiotics such as:<br>Amoxicillin/clavulanate<br>Capreomycin<br>Clarithromycin<br>Clofazimine<br>Ethionamide<br>Fluoroquinolones<br>Imipenem/cilastatin<br>Isoniazid<br>Kanamycin<br>Linezolid<br>Pyrazinamide<br>Streptomycin<br>Terizidone<br>Thioacetazone | Resolved abnormalities as seen on computed tomographic scan<br>Higher rate of culture conversion to negative<br>Improved 6-minute walk distance and oxygen saturation<br>Extended time before need for rescue antimycobacterial drugs |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Ivacaftor (Kalydeco) for treatment of cystic fibrosis in patients with G551D-CFTR mutation | Patients 6 years of age or older with cystic fibrosis (CF) who have the *G551D-CFTR* gene mutation (10% to 15% of patients with CF) | Ivacaftor (Kalydeco™) is intended to improve lung function by improving function of mutant cystic fibrosis transmembrane conductance regulator (CFTR) protein; regulator protein is an epithelial ion channel involved in salt and fluid transport. Administered orally, 150 mg, twice daily, with fat-containing food.<br><br>Vertex Pharmaceuticals, Inc., Cambridge, MA<br><br>Phase III trials ongoing for patients who are aged 2–5 years; FDA approved Jan 2012 for patients with CF who are aged 6 years or older with the G551D mutation | No treatment available for the cause of the gene mutation | Reduced lung damage<br>Improved lung function<br>Slowed disease progression |
| Lumacaftor (VX-809) 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. VX-809 is considered a corrector of the cystic fibrosis transmembrane regulator (*CFTR*) gene mutation; intended to increase regulator's function by increasing its movement to the cell surface. Given as oral monotherapy and in combination with ivacaftor (Vertex's other CF drug).<br><br>Vertex Pharmaceuticals, Inc., Cambridge, MA<br><br>2 phase III trials and 1 phase II trial ongoing; FDA granted orphan drug and fast-track statuses | Antibiotics<br>Gene therapies (viral vector or liposome delivery of normal CFTR)<br>Transplantation (lungs)<br>Chest physiotherapy<br>Bilevel positive airway pressure ventilators | Improved lung function<br>Increased survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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, and a less invasive approach to lung volume reduction is desirable. 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; 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 (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.<br><br>PneumRx, Inc., Mountain View, CA<br><br>Pivotal phase III trial ongoing; Conformité Européene (CE) marked Oct 2010; procedure performed in 1,500 patients in European Union | Antibiotics<br>Bronchodilators<br>Corticosteroids<br>Oxygen<br>Pulmonary rehabilitation program<br>Surgery: lung-reduction volume surgery, bullectomy, lung transplantation | Improved lung function, physical endurance, and activities of daily living<br>Improved scores in St. George's Respiratory Questionnaire (which measures impaired health and perceived well-being in airways disease) |
| 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.<br><br>AB Science S.A., Paris, France<br><br>Phase III trial ongoing | Bronchial thermoplasty<br>Inhaled corticosteroids<br>Ipratropium (Atrovent)<br>Leukotriene modifiers<br>Long-acting beta agonists<br>Omalizumab (Xolair®)<br>Short-acting beta agonists<br>Theophylline | Improved asthma control<br>Improved asthma exacerbation rate<br>Reduced emergency room visits<br>Reduced hospitalization<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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, 250, or 750 mg, every 4 weeks.<br><br>GlaxoSmithKline, Middlesex, UK<br><br>Phase III trials ongoing | Bronchial thermoplasty<br>Inhaled corticosteroids<br>Ipratropium (Atrovent)<br>Leukotriene modifiers<br>Long-acting beta agonists<br>Omalizumab (Xolair®)<br>Reslizumab (in development)<br>Short-acting beta agonists<br>Theophylline | Improved asthma control<br>Improved asthma exacerbation rate<br>Reduced emergency room visits<br>Reduced hospitalization<br>Improved quality of life |
| Nintedanib (BIBF-1120) 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 regulate tumor growth and angiogenesis. Nintedanib is under study for treating IPF and slowing of disease progression and symptoms.<br><br>Boehringer Ingelheim GmbH, Ingelheim, Germany<br><br>2 phase III trials completed. 1 phase III extension trial currently recruiting | Azathioprine<br>Bosentan<br>Corticosteroids<br>Cyclophosphamide<br>Cyclosporine<br>Methotrexate<br>Penicillamine<br>Pirfenidone (investigational)<br>Pulmonary rehabilitation<br>Supplemental oxygen | Improved lung function measured by forced vital capacity<br>Improved ability to perform activities of daily living<br>Slowed disease progression<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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, for 1 year to prevent COPD exacerbations.<br><br>University of Colorado, Denver, Health Sciences Center<br><br>Phase III trials completed; FDA approved in 1992 for treating community-acquired respiratory infections and skin infections | Glucocorticoids<br>Long-acting anticholinergic agents<br>Long-acting beta-2 agonists<br>Roflumilast | Reduced cost due to exacerbations<br>Reduced incidence of exacerbations<br>Increased survival<br>Improved quality of life |
| Off-label thalidomide for treating cough associated with idiopathic pulmonary fibrosis | Patients in whom idiopathic pulmonary fibrosis (IPF) with persistent cough 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; 80% of patients have a dry nagging cough, for which no approved treatments are available. Thalidomide is considered to be a potent anti-inflammatory drug and is thought to suppress excessive tumor necrosis factor alpha production and down-modulate adhesion molecules involved in leukocyte migration. Thalidomide is also purported to suppress prostaglandin synthesis by macrophages, and modulate interleukin-10 and interleukin-12 production by peripheral blood mononuclear cells. These immunomodulatory effects could improve cough symptoms. Administered orally, 50–100 mg, daily.<br><br>Celgene Corp., Summit, NJ<br><br>Phase III trial completed | Azathioprine<br>Bosentan<br>Corticosteroids<br>Cyclophosphamide<br>Cyclosporine<br>Intedanib (investigational)<br>Methotrexate<br>Penicillamine<br>Pirfenidone (investigational) | Improved ability to perform activities of daily living<br>Improved lung function measured by forced vital capacity<br>Slowed disease progression<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Pirfenidone (Esbriet) for treatment of idiopathic pulmonary fibrosis | Patients in whom idiopathic pulmonary fibrosis (IPF) has been diagnosed | IPF is a progressive, debilitating disease characterized by inflammation and scarring (fibrosis) in the lungs, with a median survival time from diagnosis of 2–5 years; 5-year survival rate is about 20%. 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.<br><br>InterMune, Inc., Brisbane, CA<br><br>2 phase III trials completed and 2 phase III trials ongoing; FDA advisory panel voted 9-3 in Mar 2013 to recommend; FDA granted fast-track and orphan drug statuses | Azathioprine<br>Bosentan<br>Corticosteroids<br>Cyclophosphamide<br>Cyclosporine<br>Intedanib (investigational)<br>Methotrexate<br>Penicillamine<br>Pulmonary rehabilitation<br>Supplemental oxygen | Improved ability to perform activities of daily living<br>Improved lung function measured by forced vital capacity<br>Slowed disease progression<br>Improved quality of life |
| 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.<br><br>TransMedics, Inc., Andover, MA<br><br>Phase III FDA-approved investigational device status trial ongoing | Cold-storage preservation | Increased graft survival<br>Decreased graft dysfunction<br>Increased utilization of available organs<br>Reduced total cost of care<br>Improved patient outcomes |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| 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.<br><br>Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel (acquired developer Cephalon, Inc., Oct 2011)<br><br>Phase III trials ongoing | Bronchial thermoplasty<br>Inhaled corticosteroids<br>Ipratropium (Atrovent)<br>Leukotriene modifiers<br>Long-acting beta agonists<br>Mepolizumab (in development)<br>Omalizumab (Xolair®)<br>Short-acting beta agonists Theophylline | Improved asthma control<br>Improved asthma exacerbation rate<br>Reduced emergency room visits<br>Reduced hospitalization<br>Improved quality of life |
| 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.<br><br>University of Rochester School of Medicine and Dentistry, Rochester, NY<br><br>Pilot study completed; program developers received National Institutes of Health grant funding in Feb 2013 | Standard care | Fewer days missed from school<br>Increased symptom- free days<br>Reduced symptoms at night<br>Reduced rescue medication use<br>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.<br><br>Airsonett AB, Ängelholm, Sweden<br><br>Phase III trials completed; received U.S. patent approval Jun 2013 | Air purifiers<br>Antiallergenic pillow/mattress encasements<br>Home heating, ventilation, and air conditioning systems | Reduced asthma symptoms<br>Improved peak nasal inspiratory flow<br>Improved sleep quality<br>Improved quality of life |

**Table 14. AHRQ Priority Condition: 14 Substance Abuse: 8 Interventions**

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Buprenorphine implants (Probuphine) for treatment of opioid dependence | Patients in whom opioid dependence has been diagnosed | Many patients with opioid dependence attempt abstinence, but relapse rates remain high. This intervention uses sublingual buprenorphine-naloxone tablet induction followed by buprenorphine implants. Buprenorphine is a partial agonist of opioid receptors and binds more strongly to receptors in the brain than other opioids and may reduce reaction of opioids when in system.<br><br>Titan Pharmaceuticals, Inc., South San Francisco, CA (manufacturer) Braeburn Pharmaceuticals subsidiary of Apple Tree Partners, New York, NY (licensee)<br><br>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)<br>Psychotherapy (e.g., cognitive behavior therapy) | Resolution of problems with adherence, diversion<br>Reduced illicit use of opioids<br>Improved health outcomes associated with abstinence<br>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 problematic 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, North Carolina, 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 for reversing overdoses by community members, and evaluating project components. Primary care physicians receive an educational tool kit on chronic pain management and safe opioid prescribing practices.<br><br>Project Lazarus in collaboration with the Community Care of North Carolina's Chronic Pain Initiative<br><br>After success in Wilkes County, ongoing expansion efforts are bringing this program and care model statewide. Program site reports this program has been implemented in over 30 counties to date. | Other substance abuse prevention and treatment programs; various combinations of opioid replacement therapy and detoxification treatment | Decreased incidence of overdose and overdose-related death<br>Improved chronic pain management<br>Improved opioid prescribing practices |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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).<br><br>SmartStart, Inc., Irving, TX, with Intelligent Fingerprinting, Norwich, UK<br><br>U.S. launch planned for 2013 | Other body fluid testing (urine, saliva, blood)<br>Field sobriety tests | Improved detection of illicit substances<br>Reduced invasiveness of drug testing<br>Reduced turnaround time for drug testing<br>Reduced biohazard risk<br>Reduced risk of cross reactivity<br>Improved health outcomes |
| Off-label aprepitant (Emend) for treatment of alcohol dependence in patients with posttraumatic stress disorder | Patients in whom alcoholism secondary to posttraumatic stress disorder (PTSD) has been diagnosed | No therapies are indicated specifically for alcoholism 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.<br><br>Merck & Co., Inc., Whitehouse Station, NJ (manufacturer)<br>National Institute on Alcohol Abuse and Alcoholism (investigator)<br><br>Phase II trial ongoing | Off-label pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone)<br>Psychotherapy (e.g., cognitive behavior therapy) | Reduced alcohol consumption<br>Reduced relapse<br>Improved health outcomes associated with abstinence<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Off-label deep brain stimulation for treatment of alcohol dependence | Patients in whom treatment-refractory alcohol dependence has been diagnosed | Only 36% of patients with alcohol dependence experience full remission when using available pharmacotherapy. Deep brain stimulation (DBS) uses permanently implanted electrodes to electrically interfere with activity in targeted parts of the brain. DBS is approved for use in conditions such as Parkinson's disease and obsessive-compulsive disorder. 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.<br><br>Medtronic, Inc., Minneapolis, MN (manufacturer)<br>University of Cologne, Cologne, Germany (investigator)<br>Tangdu Hospital, Xi'an, China (investigator)<br>National Institute on Alcohol Abuse and Alcoholism (investigator)<br><br>Several small pilot studies completed and ongoing internationally; it does not appear that the manufacturer of the equipment used in these studies is seeking a labeled indication change for this product | Pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone)<br>Psychotherapy (e.g., cognitive behavior therapy) | Reduced alcohol craving<br>Reduced alcohol consumption<br>Reduced relapse<br>Improved health outcomes associated with abstinence<br>Improved quality of life |
| Off-label mifepristone for treatment of alcohol dependence | Patients in whom alcohol dependence has been diagnosed | Only 36% of patients with alcohol dependence experience full remission when using available pharmacotherapy. Research has suggested that pharmacotherapy efficacy is linked to the protracted abstinence phase, a phase where 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 the glucocorticoid receptor has 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.<br><br>The Scripps Research Institute, La Jolla, CA<br><br>Phase II trial ongoing; preliminary results available | Pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone)<br>Psychotherapy (e.g., cognitive behavior therapy) | Reduced alcohol consumption<br>Reduced relapse<br>Improved health outcomes associated with abstinence<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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 | No agents are approved for treating cocaine dependence. Mifepristone 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.<br><br>New York State Psychiatric Institute, New York<br>The Scripps Research Institute, La Jolla, CA<br><br>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); the manufacturer does not appear to be seeking a labeled indication for cocaine dependence; thus, it would be used off label for this indication | Off-label pharmacotherapy (e.g., disulfiram)<br>Psychotherapy (e.g., cognitive behavior therapy) | Reduced reward associated with cocaine use<br>Reduced cocaine consumption<br>Reduced relapse<br>Improved health outcomes associated with abstinence<br>Improved quality of life |
| Off-label ondansetron for treatment of alcohol dependence | Patients in whom alcohol dependence has been diagnosed | Only 36% of patients with alcohol dependence fully recover when using available pharmacotherapy; serotonin 5-$HT_3$ receptors are a novel therapeutic target for this population. Ondansetron is a serotonin 5-$HT_3$ receptor antagonist, approved for treating chemotherapy-induced nausea and vomiting and 1st marketed by GlaxoSmithKline (Middlesex, UK) as Zofran®. The drug 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 the severity of alcohol consumption, which underpins the hypothesis that medications that affect the function of the 5-HT transporter may be viable treatments for this population.<br><br>Under study at 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<br>No ondansetron manufacturers are sponsoring these studies<br><br>Phase III trials completed; several phase II and III trials ongoing | Pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone)<br>Psychotherapy (e.g., cognitive behavior therapy) | Reduced alcohol craving<br>Reduced alcohol consumption<br>Reduced relapse<br>Improved health outcomes associated with abstinence<br>Improved quality of life |

**Table 15. AHRQ Priority Condition: 15 Cross-Cutting: 8 Interventions**

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Diffusion tensor imaging–brain mapping for guidance of neurosurgical procedures | Patients undergoing neurosurgical procedures that involve resection of brain tissue | Many complicated neurosurgical procedures (i.e., tumor resection, epilepsy surgery) pose the risk of damaging critical brain structures and fiber tracts, resulting in loss of function and impairment. Standard MRI imaging and intraoperative electrophysiology allow basic anatomical and functional brain mapping, but these approaches fail to provide information about white matter connectivity within the brain. Diffusion tensor imaging (DTI) tracks water molecules as they travel along axonal fibers in the brain. DTI enables neurosurgeons to build a 3-dimensional, directional map of the fiber pathways connecting critical brain structures. This information can be overlaid with structural and functional MRI to provide enhanced brain-mapping guidance for neurosurgery.<br><br>Imaging modality available through multiple device manufacturers<br>Examined by multiple academic research institutions, including Memorial Sloan-Kettering Cancer Center, New York, NY; University of Pennsylvania, Philadelphia; and UT Southwestern Medical Center, Dallas, TX<br><br>Clinical trials ongoing | Intraoperative electrophysiology<br>Functional MRI<br>Structural MRI | Improved surgical outcomes |
| 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 various 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 being treated for chronic diseases and requiring ongoing medication, such as tuberculosis, diabetes, heart failure, AIDS, hepatitis C virus infection, and mental health disorders. This is an edible microchip affixed to oral drugs (tablets) to monitor patient adherence; wearable data recorder in the form of a patch adhered to the skin captures actual drug consumption and vital statistics, reminds patients of missed doses, and transmits patient data to clinicians through a mobile device.<br><br>Proteus Digital Health, Inc., Redwood City, CA<br><br>FDA granted marketing clearance for the monitoring device Mar 2010; Jul 2012, the company also received marketing clearance for the ingestible sensor | Conventional oral drug therapy<br>Patient medication reminders via telephone, text message, and/or email | Improved disease management by maintaining consistent oral drug dosing and reducing missed doses |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Internet-based clinic electronic visits for diagnosis and treatment of simple conditions | Patients who require diagnosis and treatment of minor conditions | Accessing health care can present a problem for patients who live prohibitive distances from providers or do not have transportation. Patients may also have social, cultural, linguistic, or financial barriers that make it difficult to seek or obtain care, and a shortage of health care providers has increased the waiting period for appointments. Thus, a large unmet need exists for care delivery models that can extend health care to these populations. Virtuwell™ is an example of an online health care delivery innovation that uses rigorous clinical protocols and sophisticated interview algorithms combined with available patient and clinician-initiated telephone interactions to provide diagnoses, treatment plans, and prescriptions for patients. A patient can log on to the Virtuwell Web site, complete the interview questions, and receive either a diagnosis from a nurse practitioner or a recommendation to see a provider in person. The nurse practitioner can also send prescriptions. The entire process takes about 15 minutes to complete. Virtuwell is for diagnosing and treating simple conditions. Additional programs include Zipnosis and NowClinic.<br><br>Several programs across the U.S.<br><br>Available to residents in Arizona, California, Connecticut, Illinois, Kansas, Kentucky, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Nebraska, New Mexico, New York, North Dakota, Ohio, Pennsylvania, South Dakota, Utah, Wisconsin, and Wyoming. | Telehealth programs<br>Nonurgent-care clinics | Improved access to care<br>Reduced cost of care<br>Improved patient outcomes |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| 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 in close proximity to 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 only intended to be used for a short amount of time (although times vary from clinic to clinic) until the patient can get care from a primary care physician.<br><br>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<br><br>Several clinics have been launched in the U.S. | Outpatient followup care (e.g., with primary care physician) | Improved patient outcomes<br>Reduced hospital readmissions |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>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 are not senior-specific and can be uncomfortable or unsafe for elderly patients. Additionally, risk of hospital readmission and drug interactions are high in this population. Finally, 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).<br><br>Senior-specific EDs have been opened across the U.S.<br><br>1st senior-specific ED launched in 2008; approximately 50 senior-specific EDs in U.S. as of 2013 | General EDs | Improved health outcomes for seniors<br>Improved quality of life |
| Sublingual patient-controlled analgesia system (Zalviso) for treatment of pain following major surgery | Patients who have undergone major abdominal or orthopedic surgery | Patient-controlled analgesia (PCA) systems have led to significant improvements in postoperative pain management, but many approaches rely on intravenous (IV) medication delivery. Limitations associated with IV delivery of analgesic medications include IV-related analgesic gaps, pump programming or system errors, limited patient mobility, and catheter-related infections. Zalviso is a preprogrammed, sublingual, patient-controlled sufentanil delivery device (15 mcg/dose) that is intended to address many of these issues.<br><br>AcelRx Pharmaceuticals, Inc., Redwood City, CA<br><br>Phase III trials completed (major abdominal or orthopedic surgery). In May 2013, the manufacturer announced that it planned to file a new drug application with FDA in 3rd quarter 2013 | Intravenous opiates<br>Intravenous PCA systems<br>Nonopiate analgesics | Improved pain control<br>Increased ease-of-use for patients and providers<br>Reduced dosing frequency |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| 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, systems that 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, and Triggering" links and synthesizes data from these systems and presents the information on a single screen. 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.<br><br>Boston Children's Hospital, Boston, MA, working with software developer Arcadia Solutions, Burlington, MA<br><br>Implemented in 2 hospitals | Multiple monitoring platforms | Improved decisionmaking<br>Improved care-plan adjustment<br>Improved patient outcomes |
| 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 | 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.<br><br>Flagstaff Medical Center, Flagstaff, AZ<br><br>50-patient trial ongoing; the program is a National Institutes of Health Public-Private Partnership | In-person patient-monitoring visits<br>Kiosk monitoring programs<br>Other rural health programs in development (e.g., Project ECHO) | Fewer office visits and hospital readmissions<br>Improved patient monitoring<br>Improved patient outcomes<br>Reduced costs |

# Section 2. Interventions Added Since Last Update: 35 Interventions

**Table 16. AHRQ Priority Condition: 01 Arthritis and Nontraumatic Joint Disease: 3 Interventions**

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| 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 years have a particularly high incidence. No pharmacologic treatment exists for treating lumbar disc herniation. The disease 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. Degrading glycosaminoglycans is assumed to reduce 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 as a single local injection.<br><br>Seikagaku Corp., Tokyo, Japan<br><br>Phase III trial ongoing | Lumbar disc replacement surgery<br>Physical therapy | Improvements in leg pain |
| 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 the patient's life. The KineSpring® System purportedly fills an unmet need in knee OA treatment by providing a minimally invasive and reversible option between conservative care and joint-modifying surgery. The KineSpring System is intended to treat pain and restore knee function in patients with OA of the medial knee joint 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 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 motions. The absorber is implanted in the extracapsular space along the medial side of the joint through 2 incisions. The procedure is purportedly joint sparing and reversible; the device is extracapsular and extra-articular; no bone, ligament, or cartilage is removed.<br><br>Moximed, Inc., Hayward, CA<br><br>Pivotal trial ongoing | High tibial osteotomy<br>Joint distraction<br>Mesenchymal stem-cell therapy<br>Nonsteroidal anti-inflammatory drugs<br>Physical therapy<br>Platelet-rich plasma<br>Special orthotic devices<br>Unloading braces<br>Weight loss | Reduced pain<br>Improved mobility<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Oral phosphodiesterase type 4 inhibitor (apremilast) 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 is purported to inhibit phosphodiesterase type 4 (PDE-4). By inhibiting the PDE-4 enzyme, apremilast purportedly increases intracellular cAMP, which modulates multiple inflammatory mediators. In a clinical trial, the drug was administered orally, 20 or 30 mg, twice daily.<br><br>Celgene Corp., Summit, NJ<br><br>Phase III trial ongoing | Corticosteroids<br>Disease-modifying antirheumatic drugs<br>Nonsteroidal anti-inflammatory drugs<br>Physical therapy<br>Sulfasalazine (Azulfidine)<br>Tumor necrosis factor inhibitors | Reduced signs and symptoms<br>Improved mobility<br>Improved quality of life |

**Table 17. AHRQ Priority Condition: 02 Cancer: 14 Interventions**

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Dinaciclib for treatment of chronic lymphocytic leukemia | Patients in whom chronic lymphocytic leukemia (CLL) has been diagnosed and who have undergone prior chemotherapy and/or chemoimmunotherapy 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.<br><br>Merck & Co., Inc., Whitehouse Station, NJ<br><br>Phase III trial ongoing | Alemtuzumab, bendamustine, chlorambucil, or lenalidomide with or without rituximab<br>Ofatumumab | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Entinostat (SNDX-275) for treatment of breast cancer | Patients with locally advanced/unresectable or metastatic estrogen receptor–positive breast cancer whose disease has progressed following treatment with nonsteroidal aromatase inhibitor | Few effective treatment options exist for recurrent, advanced breast cancers that have become resistant to endocrine therapy or are hormone receptor negative. Entinostat (SNDX275) 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, entinostat is administered orally, at dose of 5 mg, once weekly.<br><br>Syndax Pharmaceuticals, Inc., Waltham, MA<br><br>Phase II trials ongoing; received FDA breakthrough therapy designation Sept 2013 for treating estrogen receptor–positive breast cancer in combination with exemestane | Everolimus plus exemestane<br>Targeted therapies (in development; e.g., bevacizumab)<br>Various single-agent or combination chemotherapy regimens | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Erismodegib (LDE225) 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.<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase III trial ongoing | Combination chemotherapy<br>Radiation therapy | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 who are at high risk of disease recurrence based on International Prognostic Index score at time of diagnosis | 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, everolimus was administered orally, 10 mg, once daily.<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase III trial ongoing | High-dose chemotherapy with autologous stem cell transplant<br>Observation | Increased disease-free survival<br>Increased overall survival<br>Improved quality of life |
| Ex vivo expanded cord blood as allogeneic bone marrow transplant for treatment of hematologic malignancies | Patients with 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.<br><br>Mesoblast, Ltd., New York, NY<br><br>Phase III trial ongoing | Pooled unexpanded cord blood transplant<br>Unexpanded cord blood transplant | Improved bone marrow engraftment rate<br>Improved rate of neutrophil recovery<br>Improved rate of platelet recovery |

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Bristol-Myers Squibb, New York, NY<br><br>Phase III trial ongoing | Etoposide and platinum therapy (cisplatin or carboplatin)<br>Radiation therapy | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Lambrolizumab (MK-3475) 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. Lambrolizumab (MK-3475) is a monoclonal antibody that targets a novel immune-checkpoint pathway distinct from that of ipilimumab. Lambrolizumab 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. Lambrolizumab is administered by intravenous infusion at a dose of 10 mg, once every 2 weeks.<br><br>Merck & Co., Inc., Whitehouse Station, NJ<br><br>Phase III trial ongoing; FDA granted breakthrough therapy status Apr 2013 | Dacarbazine<br>Ipilimumab<br>Vemurafenib | Increased progression-free survival<br>Increased overall survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Lambrolizumab (MK-3475) 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. One of the hallmarks of cancer is its ability to evade an immune response. Lambrolizumab (MK-3475) is a monoclonal antibody that targets a novel immune-checkpoint pathway. Lambrolizumab 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. Lambrolizumab is administered by intravenous infusion at a low or high dose (to be established based on maximum tolerated dose), once every 3 weeks.<br><br>Merck & Co., Inc., Whitehouse Station, NJ<br><br>Phase II/III trial ongoing; FDA granted breakthrough therapy status Apr 2013 for treating melanoma | Erlotinib<br>Single-agent chemotherapy (e.g., docetaxel, pemetrexed) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |
| Lestaurtinib for treatment of acute infantile 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.<br><br>National Cancer Institute, Bethesda, MD<br><br>Phase III trial ongoing | Multiagent chemotherapy regimens lacking lestaurtinib | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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 are often overlooked in standard care approaches. 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.<br><br>HopeLabs, Redwood City, CA, in collaboration with CIGNA Corp., Bloomfield, CT<br><br>Unphased, randomized, controlled trial completed; freely available | Standard education programs and resources (e.g., patient counseling and education) | Improved health outcomes<br>Improved treatment adherence<br>Improved self-efficacy<br>Improved quality of life |
| Selumetinib (AZD6244, ARRY-142886) for treatment of KRAS-positive nonsmall cell lung cancer | Patients in whom locally advanced or metastatic, KRAS mutation–positive nonsmall cell lung cancer (NSCLC) has been diagnosed and 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 current 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, inhibition of MEK activity could inhibit cancer cell growth and/or survival. However, no MEK inhibitor is currently 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 dose of 25 mg, twice daily, in combination with docetaxel and pegylated granulocyte colony stimulating factor.<br><br>AstraZeneca, London, UK<br><br>Phase III trial ongoing | Crizotinib (if *alk* mutation–positive)<br>Erlotinib<br>Cytotoxic chemotherapy (e.g., docetaxel, pemetrexed) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Siltuximab for treatment of multicentric Castleman disease | Patients in whom multicentric Castleman disease has been diagnosed | Castleman 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 disease frequently experience relapses following treatment with cytotoxic chemotherapy. Castleman disease purportedly develops through an autoinflammatory process involving elevated levels of interleukin-6 (IL-6). Siltuximab is an IL-6 monoclonal antibody that has the potential to limit the activity of IL-6. In clinical trials, siltuximab was administered by intravenous infusion once every 3 weeks at a dose of 11 mg/kg.<br><br>Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ<br><br>Phase II trial ongoing; in Sept 2013, biologic license application submitted to FDA | Various chemotherapy regimens including 1 or more of the following: carmustine, cladribine, chlorambucil, cyclophosphamide, doxorubicin, etoposide, melphalan, vinblastine, and vincristine | Increased remission rate<br>Increased remission duration<br>Improved quality of life |
| 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.<br><br>Bayer AG, Leverkusen, Germany, and Onyx Pharmaceuticals, Inc., South San Francisco, CA<br><br>Phase III trial ongoing; enrollment complete | Single-agent or combined chemotherapy regimens (e.g., capecitabine, cyclophosphamide, gemcitabine, nab-paclitaxel, platinum agents, vinorelbine)<br>Various targeted therapies (under development; e.g., bevacizumab) | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Trans sodium crocetinate for treatment of glioblastoma | Patients in whom glioblastoma multiforme (GBM) has been diagnosed | Glioblastoma multiforme 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 for treating GBM; 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.<br><br>Diffusion Pharmaceuticals LLC, Charlottesville, VA<br><br>Phase II trial ongoing; FDA granted orphan drug status | Immunotherapeutics (in development, e.g., HSPPC-95, ICT107)<br>Radiation therapy<br>Surgical resection (with or without carmustine wafer)<br>Temozolomide | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life |

**Table 18. AHRQ Priority Condition: 03 Cardiovascular Disease: 0 Interventions**

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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**Table 19. 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 |
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**Table 20. AHRQ Priority Condition: 05 Depression and Other Mental Health Disorders: 1 Intervention**

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| Video games for cognitive behavior therapy for major depressive disorder | Adolescent and young adult (AYA) patients with mild to moderate severity depression | Many AYA patients with symptoms of depression do not have the condition diagnosed or it is resistant 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-dimentional, interactive gaming program designed to provide cognitive behavior therapy (CBT) to AYAs experiencing clinically significant symptoms of depression. SPARX guides the user through a number a 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.<br><br>University of Auckland in partnership with Metia International, both of Auckland, New Zealand; published by Linked Wellness, Baltimore, MD<br><br>Unphased trials completed | Antidepressants<br>Psychotherapy | Reduced severity of depression symptoms<br>Increased remission rates<br>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 |
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**Table 22. AHRQ Priority Condition: 07 Diabetes Mellitus: 2 Interventions**

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Grafix 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® 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 membrane. The growth factors and proteins of Grafix purportedly aid cell proliferation, maturation, and mitigation. MSCs, neonatal fibroblasts, and epithelial cells purportedly coordinate the tissue repair process. In clinical trials, Grafix is being administered weekly. FDA regulates Grafix as a Human Cellular and Tissue Based Product.<br><br>Osiris Therapeutics, Inc., Columbia, MD<br><br>Phase IV trial ongoing | Apligraf<br>Dermagraft<br>EndoForm™ Dermal Template<br>Lipopeptides<br>Oasis Wound Matrix<br>TheraSkin ®<br>Topical antibiotics<br>Topical antiseptics | Improved wound closure<br>Improved quality of life |
| 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 | T1DM accounts for about 5% of all diagnosed cases of diabetes mellitus, whereas T2DM makes up 95%. Currently, 25.8 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. Diabetes mellitus treatment requires a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and, in some cases, taking insulin. An artificial pancreas device system 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. The MiniMed®530G system with Enlite® sensor may be the 1st step towards a fully automated artificial pancreas. 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.<br><br>Medtronic, Inc., Minneapolis, MN<br><br>Multiple ongoing trials of various phases; FDA placed on innovation pathway; FDA approved Sept 2013 | Insulin modifications<br>Islet cell transplantation<br>Pancreas transplantation | Halted or delayed progression of secondary complications<br>Reliable glycemic control at desired levels<br>Reduced risk of acute and nighttime hypoglycemia<br>Reduction in postprandial (after meal) hyperglycemia<br>Improved quality of life |

**Table 23. AHRQ Priority Condition: 08 Functional Limitations and Disability: 5 Interventions**

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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. It is administered orally, once daily.<br><br>Lumena Pharmaceuticals, San Diego, CA<br><br>Phase II trials ongoing; FDA granted orphan drug status Sept 2013 | Antipruritics<br>Bile duct surgery<br>Dietary changes<br>Liver transplant<br>Ursodeoxycholic acid | Improved liver function<br>Reduced symptoms<br>Improved health outcomes<br>Improved quality of life |
| Bimagrumab (BYM338) 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. Investigators have not found a definitive treatment. Bimagrumab 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.<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase II/III trial ongoing; FDA granted breakthrough therapy status Aug 2013 | None | Improved motor function symptoms<br>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 current methods and the lack of a quantitative diagnostic test hampers 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.<br><br>Banyan Biomarkers, Inc., Alachua, FL, with support from the U.S. Department of Defense<br><br>2,000-patient ALERT-TBI trial ongoing | Clinical neurologic evaluation<br>Computed tomography<br>Magnetic resonance imaging | Improved sensitivity for traumatic brain injury<br>Improved specificity for traumatic brain injury |

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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. 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.<br><br>Enhanced Surface Dynamics, Inc., Nashville, TN, parent company of Wellsense<br><br>Phase II trial complete. FDA classified as Class I exempt device; available for marketing; Conformité Européene (CE) marked | Visual assessment<br>Subepidermal moisture scanner (investigational) | Prevention or early treatment of decubitus ulcers<br>Reduced hospital stay from complications of decubitus ulcers<br>Reduced morbidity and mortality from decubitus ulcer complications |
| Focused ultrasound 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. A study evaluating focused ultrasound efficacy for ET treatment uses the ExAblate device, which consists of a unique helmet-like apparatus containing phased array focused ultrasound transducers. CT 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<br><br>University of Virginia (UVA) Focused Ultrasound Center, Charlottesville, VA (partnership of UVA, Charlottesville; Commonwealth of Virginia; Focused Ultrasound Foundation, Charlottesville; and InSightec, Ltd., Tirat Carmel, Israel)<br><br>Phase I trial ongoing | Antiepileptics<br>Beta blockers<br>Deep brain stimulation<br>Stereotactic thalamotomy | Improvement in contralateral tremor as assessed on the Clinical Rating Scale for Tremor (CRST)<br>Improved functional activities score as assessed on disabilities section of CRST<br>Improved quality of life |

**Table 24. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 8 Interventions**

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| 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.<br><br>Merck & Co., Inc., Whitehouse Station, NJ<br><br>Phase III trials ongoing | Fecal microbiota transplant<br>Fidaxomicin<br>Metronidazole<br>Vancomycin | Increased clinical cure rates<br>Reduced CDI recurrence |
| 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.<br><br>Merck & Co., Inc., Whitehouse Station, NJ<br><br>Phase III trial ongoing | Fecal microbiota transplant<br>Fidaxomicin<br>Metronidazole<br>Vancomycin | Increased clinical cure rates<br>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.<br><br>Merck & Co., Inc., Whitehouse Station, NJ<br><br>Phase III trial ongoing | Fecal microbiota transplant<br>Fidaxomicin<br>Metronidazole<br>Vancomycin | Increased clinical cure rates<br>Reduced CDI recurrence |

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
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| *Clostridium difficile* vaccine (ACAM-CDIFF) for prophylaxis in patients expecting 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.<br><br>Sanofi, Paris, France<br><br>Phase III trial ongoing | Hospital infection control programs | Reduced *C. difficile* infection rates<br>Reduced use of antibacterial drugs<br>Reduced hospitalization time<br>Reduced isolation |
| NS5A inhibitor (MK-8742) for treating chronic hepatitis C infection | Patients in whom chronic hepatitis C infection (HCV) has been diagnosed | Current HCV treatment options are not effective in all patients, even with the newly approved agents of telaprevir and boceprevir. 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. MK-8742 inhibits HCV NS5A; 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; 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.<br><br>Merck & Co., Inc., Whitehouse Station, NJ<br><br>Phase II trials recruiting; FDA granted breakthrough designation for treating HCV genotype 1 in combination with MK-5172 | Boceprevir<br>Pegylated interferon alfa plus ribavirin<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks)<br>Decreased need for liver transplant<br>Improved quality of life |

| 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.<br><br>Rebiotix, Inc., Roseville, MN<br><br>Phase II trial ongoing; FDA granted fast-track status for treating recurrent CDI | Fecal microbiota transplant<br>Fidaxomicin<br>Metronidazole<br>Vancomycin | Increased clinical cure rates<br>Reduced CDI recurrence |
| Protease inhibitor MK-5172 for treatment of chronic hepatitis C | Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed | Current HCV treatment options are not effective in all patients, even with the newly approved agents of telaprevir and boceprevir. 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. 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.<br><br>Merck & Co., Inc., Whitehouse Station, NJ<br><br>Phase II trials recruiting; FDA granted breakthrough designation for treating HCV genotype 1 in combination with MK-8742 | Boceprevir<br>Pegylated interferon alfa plus ribavirin<br>Telaprevir | Rapid virologic response (HCV RNA undetectable at week 4)<br>Slowed or halted disease progression (fibrosis and cirrhosis)<br>Sustained virologic response (defined as undetectable virus at 24 weeks<br>Decreased need for liver transplant<br>Improved quality of life |
| 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.<br><br>PaxVax, Inc., Menlo Park, CA<br><br>Phase III trial ongoing | Improved hygiene | Protection against challenge<br>Reduced severity of disease |

**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 |
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| | | | | |

**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: 0 Interventions**

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

**Table 29. AHRQ Priority Condition: 14 Substance Abuse: 1 Intervention**

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts |
|---|---|---|---|---|
| Off-label baclofen for treatment of alcohol dependence | Patients in whom alcohol dependence has been diagnosed | Only 36% of patients with alcohol dependence experience full remission when using available therapy options. Improved therapy 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; this agent is approved for treating muscle spasticity associated with multiple sclerosis. 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 doses of 5–200 mg, daily.<br><br>Numerous investigators, including the National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, as well as Ethypharm, Saint-Cloud, France<br><br>Multiple phase II and III trials ongoing | Acomprosate<br>Benzodiazepines<br>Disulfiram<br>Gabapentin<br>Naltrexone<br>Psychotherapy | Reduced alcohol consumption<br>Increased abstinence rates<br>Decreased alcohol craving<br>Decreased alcohol withdrawal symptoms |

**Table 30. 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 |
|---|---|---|---|---|
| 3-D printing for creating bioresorbable implants | Patients requiring medical implants, skin grafts, or prosthetics | Implants have limited ability to be customized to each specific patient's needs. Furthermore the implant is made with synthetic material foreign to the body. 3-dimensional (3-D) printing creates an implantable, customized, bioresorbable splint, created with a computer-aided design based on a computed tomographic image of the patient's specific needs. The implant is then fabricated using laser-based 3-D printing, which allows health care providers to create prosthetics and implants that are specifically tailored to the individual patient.<br><br>University of Michigan, Ann Arbor<br><br>1 case reported. FDA granted emergency use exemption for this instance. | Traditional implants | Increased survival<br>Improved health outcomes<br>Improved quality of life |

# Section 3. Interventions Tracked but Archived Since Last Update: 28 Interventions

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

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
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**Table 32. AHRQ Priority Condition: 02 Cancer: 8 Interventions**

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| CD34-positive cell selection system (CliniMACS) for treatment of acute myeloid leukemia | Patients with acute myeloid leukemia (AML) who are undergoing allogeneic stem cell transplantation (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 donor immune cells 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. Methods to prevent GVHD include pretransplant depletion of the donor T cells thought to be the cause of GVHD. However, no FDA-approved device is available to perform T-cell depletion, and its use has been hampered by the potential for poor engraftment and/or AML relapse in patients treated with processed grafts. The CliniMACS® CD34 reagent system is intended to prepare T-cell depleted stem cell grafts. The system uses CD34 monoclonal antibodies coupled to magnetic particles to isolate CD34-positive hematopoietic stem cells while simultaneously passively removing differentiated T cells.<br><br>Miltenyi Biotec GmbH, Bergisch Gladbach, Germany<br><br>Phase II trial complete; company filed for humanitarian use device exemption with FDA, so phase III trials may not be required for clinical use | Noncommercial, manual methods of T-cell depletion | Improved engraftment rate<br>Increased duration of disease-free survival<br>Improved rates of acute and chronic GVHD | Development has not progressed for 2 or more years. |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Cilengitide (EMD 121974) for treatment of glioblastoma | Patients in whom glioblastoma has been diagnosed | Median survival of patients with glioblastoma is only about 14 months with current therapies. Integrins are transmembrane proteins that are widely expressed in both glioblastomas and tumor vasculature and mediate cell processes such as cell survival and migration and tumor angiogenesis. Cilengitide is a 1st-in-class, small-molecule antagonist of integrins (specifically alpha-v-beta3 and alpha-v-beta5), which may have antiglioblastoma activity. Treatment is intended for use against newly diagnosed glioblastoma that exhibits methylation of the methylguanine-DNA methyltransferase gene (a marker of temozolomide sensitivity). In clinical trials, cilengitide is administered in a twice-weekly, intravenous dose of 2,000 mg in combination with standard therapy using temozolomide and radiation therapy.<br><br>EMD Serono, Inc., Rockland, MA, subsidiary of Merck KGaA, Darmstadt, Germany<br><br>Phase III trial ongoing, trial failed to meet endpoints; several phase II trial in newly diagnosed GBM ongoing; also in trials for nonsmall cell lung cancer | Temozolomide plus radiation therapy | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life | U.S. development halted because phase III trial did not meet primary endpoint of improved progression-free survival or overall survival |
| Diphtheria toxin expression vector (BC-819) for treatment of pancreatic cancer | Patients with locally advanced, unresectable pancreatic adenocarcinoma that is amenable to intratumoral injection under ultrasound guidance and expresses high levels of H19 | Patients in whom pancreatic cancer has been diagnosed have a 5-year survival rate of only 5%, and effective treatment options are not available. H19 is a noncoding RNA that is expressed in a wide variety of cancers, including many pancreatic cancers, but is not actively transcribed in the majority of adult tissues. BC-819 is a DNA plasmid that encodes the highly cytotoxic diphtheria toxin under the control of the H19 promoter and is intended to induce the expression of diphtheria toxin exclusively in H19-expressing cancer cells. In current clinical trials, BC-819 is administered by intratumoral injection as an addition to the standard systemic chemotherapy drug gemcitabine.<br><br>BioCancell Therapeutics, Inc., Jerusalem, Israel<br><br>Phase IIb trial ongoing; FDA granted fast-track status | 5-Fluorouracil/ leucovorin monotherapy<br>Gemcitabine monotherapy<br>Gemcitabine plus nab-paclitaxel | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life | Company announced Aug 2013 that it halted talks to find a partner to fund further study of BC-819 in bladder and pancreatic cancer. |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Dovitinib (TKI258) for treatment of metastatic renal cell carcinoma | Patients in whom metastatic renal cell carcinoma (RCC) has been diagnosed | Metastatic RCC that has progressed after vascular endothelial growth factor (VEGF)-targeted and mTOR inhibitor therapies has not been treatable, and patients have a poor prognosis. Dovitinib is a novel multikinase inhibitor that inhibits multiple tyrosine kinases including VEGF receptors, platelet-derived growth factor receptors, and fibroblast growth factor receptors (FGFRs). Dovitinib's activity against FGFR differentiates it from multikinase inhibitors available for treating RCC. Research has demonstrated that signaling through FGFR may be a mechanism by which resistance to VEGF-targeted therapy occurs; therefore, simultaneous inhibition of the VEGF and FGF pathways may generate responses in disease that is refractory to VEGF-targeted therapy. In clinical trials, dovitinib is an oral medication administered at a dose of 500 mg per day, for 5 out of 7 days each week to patients previously treated with both VEGF-targeted therapy (e.g., axitinib, bevacizumab, pazopanib, sunitinib, tivozanib) and mTOR inhibitor therapy (e.g., everolimus, ridaforolimus, temsirolimus).<br><br>Novartis International AG, Basel, Switzerland<br><br>Phase III trial ongoing, enrollment complete; phase III trial failed to meet primary endpoint of progression-free survival but remains listed in company pipeline for RCC; development also ongoing for other studies for several other solid tumors | Sorafenib | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life | U.S. development halted because phase III trial did not meet primary endpoint of improved progression-free survival compared to progression-free survival with sorafenib |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Duloxetine (Cymbalta) for treatment of chemotherapy-induced peripheral neuropathy | Patients experiencing chemotherapy-induced peripheral neuropathy | Up to 40% of patients who receive neurotoxic chemotherapy treatment develop painful peripheral neuropathy that can persist for long periods of time beyond chemotherapy treatment completion. Effective, nonnarcotic treatment options are needed to manage chemotherapy-induced neuropathic pain. Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor that effectively reduced symptoms in patients with chemotherapy-induced neuropathy. In a clinical trial, duloxetine was administered as an oral dose of 30–60 mg for 5 weeks.<br><br>Cancer and Leukemia Group B (CALGB), Chicago, IL, in collaboration with the National Cancer Institute, Rockville, MD (investigators)<br>Eli Lilly and Co., Indianapolis, IN (manufacturer)<br><br>Phase III trial completed, positive results published Apr 2013; drug may be prescribed off label | Antidepressants (i.e., SNRIs)<br>Anticonvulsants<br>Opiates | Decreased pain<br>Decreased analgesic intake<br>Improved neuropathy-related functional status<br>Improved non-painful symptoms (i.e., numbness and tingling)<br>Improved quality of life | After initial tracking, horizon scanning team subsequently determined that intervention has small, incremental potential only; trial results appear marginally incremental with <1 point pain reduction on 10-point pain scale |
| Pacritinib for treatment of myelofibrosis | Patients in whom myelofibrosis has been diagnosed | Few treatment options are available for myelofibrosis. The kinase JAK2 appears to play a central role in the majority of myelofibrosis pathophysiology; therefore, inhibition of JAK2 is seen as a promising intervention for myelofibrosis, as demonstrated by the marketing approval of a dual JAK1/JAK2 inhibitor (ruxolitinib, Jakafi™) for this indication. Pacritinib is a novel JAK kinase inhibitor that is selective for JAK2, potentially altering the drug's efficacy and/or side effect profile. Pacritinib is administered orally at a dose of 400 mg, once daily.<br><br>Cell Therapeutics, Inc., Seattle, WA<br><br>Phase III trial ongoing; company has reached agreement with FDA on a special protocol assessment for a 2nd phase III trial | Ruxolitinib | Increased overall survival<br>Increased progression-free survival<br>Reduced spleen size<br>Improved quality of life | Similar to ruxolitinib, a JAK inhibitor that received FDA approval as 1st in class; pacritinib is now an agent with modestly incremental benefit |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Ramucirumab (IMC-1121B) for treatment of metastatic breast cancer | Patients with metastatic or nonresectable locally advanced HER2-negative breast cancer who have received no prior chemotherapy for metastatic disease | Patients with metastatic or nonresectable locally advanced HER2-negative breast cancer have a poor prognosis with current treatment options. 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. Treatment is intended to be used in the 1st-line setting for metastatic or nonresectable disease in combination with docetaxel. In clinical trials for breast cancer, ramucirumab is administered intravenously, 10 mg/kg, once every 3 weeks.<br><br>ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN<br><br>Phase III trial ongoing, trial failed to achieve primary endpoint in progression-free survival | Taxane-based (e.g., docetaxel, paclitaxel) therapy with or without capecitabine or gemcitabine or bevacizumab or anthracycline-based therapy | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life | U.S. development halted because phase III trial for 1st line treatment in this patient population failed to meet progression-free-survival endpoint |
| Ruxolitinib (Jakafi) for treatment of myelofibrosis | Patients who have myelofibrosis (primary myelofibrosis, post-polycythemia vera myelofibrosis, or post essential thrombocythemia myelofibrosis) | Ruxolitinib (Jakafi®) is a Janus kinase (JAK) inhibitor that inhibits the activity of both JAK 2 and JAK 1. Half of myelofibrosis cases bear an activating mutation in JAK 2; therefore, its inhibition is thought to be a key target. Ruxolitinib labeling indicates that the drug should be given as follows: At a starting dosage of 20 mg, twice daily, for patients with a platelet count greater than 200 × 10^9/L; at a dosage of 15 mg, twice daily, for patients with a platelet count between 100 × 10^9/L and 200 × 10^9/L; At a dosage of 5 mg, twice daily, for patients with a platelet count between 50 × 10^9/L and 100 × 10^9/L. As platelet counts allow, the dose may be increased up to 25 mg, twice daily, for patients with initial platelet counts greater than 100 × 10^9/L and up to 10 mg, twice daily, for patients with initial platelet counts between 50 × 10^9/L and 100 × 10^9/L.<br><br>Incyte Corp., Wilmington, DE, in collaboration with Novartis International AG, Basel, Switzerland<br><br>FDA approved Nov 2011 | None<br>Off-label treatments are only palliative | Increased overall survival<br>Increased progression-free survival<br>Improved quality of life | Tracked 2 years after FDA approval; no longer meets horizon scanning criteria for tracking. |

**Table 33. AHRQ Priority Condition: 03 Cardiovascular Disease: 8 Interventions**

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Early warning system (Health Recovery Solutions) to reduce hospital readmission for heart failure | Patients in whom heart failure (HF) has been diagnosed | About 1/3 of all patients hospitalized for HF are readmitted within 30 days of discharge. Although recommended practices exist for preventing hospital readmission in patients with HF, implementation varies widely among hospitals, and fewer than 3% of all hospitals implement all the recommended practices. Health Recovery Solutions is a system that uses readmission risk algorithms integrated into electronic medical records, taking into account patient wellness and activity. The system uses a research-based platform that guides patients' behavior using software loaded on tablets given to them (PatientConnect). Additionally, the system makes patient clinical data instantly accessible for care providers through electronic medical record integration, Web monitoring portal, and smartphone applications (i.e., ClinicianConnect, CaregiverConnect), allowing care providers to take action when necessary to reinforce healthy lifestyles.<br><br>Health Recovery Solutions, Inc., New York, NY<br><br>Health Recovery Solutions is conducting pilot programs with providers | Current hospital discharge practices | Decreased hospital readmission<br>Improved health outcomes<br>Improved quality of life | After initial tracking, horizon scanning team subsequently determined that intervention has small, incremental potential only over existing telehealth/remote monitoring programs. |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Off-label minocycline as a neuroprotectant for ischemic or hemorrhagic stroke | Patients in whom ischemic or hemorrhagic stroke has been diagnosed | Thrombolysis using tissue plasminogen activator (tPA) during ischemic stroke has been associated with hemorrhage about 7% of the time, and continued bleeding is believed to contribute to poor outcomes in up to 40% of cases. Plasma levels of matrix metalloproteinase (MMP)-9 are known to be amplified by tPA, and elevated MMP-9 levels are associated with neurological severity. MMP-9 also is known to predict the risk of tPA-related hemorrhage. Minocycline is known to be a potent MMP inhibitor; thus, researchers are investigating whether concomitant administration of minocycline for treating stroke is neuroprotective. It is being researched for use in both ischemic and hemorrhagic stroke.<br><br>Various research institutions<br><br>Several trials completed and others ongoing | Standard of care | Reduced bleeding in stroke<br>Improved neurologic outcomes after treating acute ischemic stroke | Trial halted for futility; interim analysis showed no benefit |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Pediatric ventricular assist device (Excor) for pediatric end-stage heart failure | Pediatric patients in whom heart failure (HF) has been diagnosed who are in need of mechanical support as a bridge to cardiac transplantation | Adult heart-assist devices are too large to be used in children with end-stage HF. While awaiting transplant, the standard of care in this population is extracorporeal membrane oxygenation (ECMO), in which a pump circulates blood through an artificial lung back into the bloodstream. This technique is not approved and is associated with many limitations, including high incidence of complications when used for long-term support, high risk of stroke, and need for anticoagulation therapy. ECMO also requires immobilization of the patient, limiting rehabilitation. The Excor® Pediatric Ventricular Assist Device (VAD) is designed to support pediatric patients (newborns to teenagers) and to bridge patients awaiting heart transplantation for days to several months, until a donor heart becomes available. The device is a paracorporeal, pulsatile VAD, with blood pumps located outside the body and connected to the heart and blood vessels via cannulas. The device can be used for single- or double-ventricle assistance.<br><br>Berlin Heart GmbH, Berlin, Germany<br><br>FDA approved Dec 2011 under humanitarian device exemption process | ECMO | Increased recovery of native heart (when used as destination therapy)<br>Increased overall survival<br>Reduced adverse events compared with ECMO | Tracked 2 years after FDA approval; no longer meets horizon scanning criteria for tracking |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Pneumatic abdominal aortic tourniquet (AAT) for treatment of inguinal hemorrhage on the battlefield | Soldiers on the battlefield with inguinal hemorrhage | For soldiers on the battlefield with inguinal bleeding, no products are available that can effectively stop the blood flow but also remain stable and in place during patient transport. The Institute of Surgical Research has identified this unmet need (uncompressible hemorrhage that is not treatable by a tourniquet in the leg, groin and inguinal region) as its priority for battlefield care because of the extremely high morbidity and mortality of this condition. The Abdominal Aortic Tourniquet (AAT™) is a pneumatic circumferential tourniquet that is placed around the body at the navel level, tightened, and inflated into the abdomen until it occludes the aorta and stops the bleeding. The product differs from available options (conventional tourniquets, knee pressing, clamps) because they aren't designed to tighten around a person's midsection, and the aortic artery is located under several inches of flesh, next to the spine.<br><br>Compression Works, LLC., Birmingham, AL (manufacturer)<br>Speer Operational Technologies, LLC, Greenville, SC (distributor)<br><br>FDA granted 510(k) clearance Oct 2011, after expedited review | Clamps<br>Conventional tourniquet<br>Knee pressing | Improved bleeding control<br>Reduced morbidity<br>Reduced mortality | Tracked 2 years after FDA approval; no longer meets horizon scanning criteria for tracking |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Point-of-care genetic testing to determine antiplatelet regimen after percutaneous coronary intervention | Patients undergoing percutaneous coronary intervention (PCI) who will be placed on dual antiplatelet (DAP) therapy | DAP therapy is the standard of care for patients who undergo PCI. The standard regimen consists of aspirin plus the P2Y12 inhibitor clopidogrel. However, a subset of patients who carry a loss-of-function allele of CYP2C19 (CYP2C19*2) are at increased risk of major adverse cardiovascular events when treated with this regimen. Investigators think the increase is caused by the failure of CYP2C19*2 to convert clopidogrel (Plavix®) to its active metabolite, lowering the therapeutic concentration of the drug. Prasugrel (Effient®) is an alternative P2Y12 inhibitor that is unaffected by the CYP2C19*2 polymorphism; however, its routine use is precluded by its association with an increased rate of bleeding. Therefore, prasugrel is typically reserved for patients who have been shown to harbor the CYP2C19*2 polymorphism. Because many of the adverse cardiovascular events after PCI occur within the 1st few hours of treatment, a need exists for highly accessible, rapid, genetic tests for the CYP2C19 genotype. The Spartan RX CYP2C19 test is a genetic test that could potentially be performed rapidly (about 1 hour), at the bedside, by clinical staff who lack formal clinical laboratory training.<br><br>Spartan Bioscience, Inc., Ottawa, Ontario, Canada<br><br>Phase IV trial registered Dec 2012; Conformité Européene (CE) marked; FDA 510(k) clearance granted in Aug 2013 | No genetic testing<br>Genetic testing performed in a clinical laboratory | Decreased cardiovascular death<br>Decreased stent thrombosis<br>Decreased nonfatal myocardial infarction<br>Decreased high reactivity on DAP | Expert comments indicated no potential for high impact because it has low potential to improve patient health |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Serotonin receptor antagonist (terguride) for treatment of pulmonary arterial hypertension | Patients in whom pulmonary arterial hypertension (PAH) has been diagnosed | PAH has no cure and can result in heart failure and death. Terguride is an oral antagonist of the 5-$HT_{2B}$ and 5-$HT_{2A}$ (serotonin) receptors. Serotonin purportedly stimulates proliferation of smooth muscle cells in the pulmonary artery, and can induce fibrosis in pulmonary arteries, which can lead narrowing. By inhibiting the activity of serotonin on pulmonary arteries, terguride could improve the signs and symptoms of PAH. Administered orally.<br><br>Pfizer, Inc., New York, NY<br><br>Phase II trial completed; FDA granted orphan drug status for treating PAH | Calcium channel blockers<br>Endothelin receptor antagonists<br>Phosphodiesterase type 5 inhibitors<br>Prostanoids | Improved exercise capacity<br>Reduced mortality<br>Reduced hospitalization | Development appears to be halted; no ongoing clinical trials registered; no longer listed in company pipeline |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Standardized protocol and integrated system (RACE Project) for treatment and transfer of patients with ST-elevated myocardial infarction | Patients in whom an ST-elevated myocardial infarction (STEMI) has been diagnosed | Current guidelines recommend that patients with STEMI receive fibrinolysis within 30 minutes of symptom onset, and primary percutaneous coronary intervention (PCI) within 90 minutes, yet fewer than half of patients receive this care within the recommended time frame. Additionally, only 4% of patients who are transferred to a 2nd (PCI-capable) hospital are treated within the 90-minute time frame. Reperfusion of Acute Myocardial Infarction in North Carolina Emergency Departments (RACE) Project is a statewide initiative to identify and overcome barriers to recommended rapid reperfusion times by establishing optimal regional systems of care (with parallels to existing trauma systems). The goal is to improve both the rate and speed of STEMI care through specific interventions with a systemic approach. PCI and non-PCI hospitals are assessed to determine barriers to rapid reperfusion, and customized plans for improvement are developed. Interventions include the following: educational symposia (on topics such as electrocardiogram [ECG] interpretation, STEMI recognition, treatment options), placing ECG and transmittal equipment on EMS transport vehicles, and establishing a single telephone number to access transfer to a PCI hospital. Transfer-specific interventions include the following: leaving the patient on the original stretcher, creating system-compatible intravenous tubing and pumps, and eliminating the need for IV pumps (e.g., by administering intravenous bolus of unfractionated heparin).<br><br>Sponsored by North Carolina Chapter of the American College of Cardiology<br><br>Initial RACE project completed, with data available; current phase of this project is called RACE CARS (Cardiac Arrest Resuscitation System) focusing on out-of-hospital cardiac arrest. The RACE project is being used as a national model for STEMI care; a RACE Operations Manual is available on the program's Web site | Current STEMI practices (vary between hospitals) | Reduced door-in-to-door-out time<br>Reduced time to treatment<br>Improved cardiovascular morbidity<br>Improved mortality outcomes | Tracked more than 2 years in horizon scanning system; program has diffused |

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Transcatheter aortic valve (Sapien) implantation for treatment of severe aortic stenosis | Patients with severe calcific aortic stenosis (AS) who are considered to be high-risk or nonoperable for conventional open-heart valve replacement surgery | AS 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 AS 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 AS are not suitable candidates for valve implantation performed as an open-heart surgery procedure. Sapien transcatheter aortic valve is a tissue valve deployed into the heart using a minimally invasive transcatheter-based procedure (transfemoral or transapical) to try to repair a severely stenotic aortic valve.<br><br>Edwards Lifesciences Corp., Irvine, CA<br><br>FDA approved Nov 2011 for "transfemoral delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis." In Oct 2012, approval expanded to include patients with symptomatic severe aortic stenosis who are at high operative risk; a next-generation transcatheter aortic valve, Sapient XT, is in phase III trials for patients who are considered inoperable or who are at high risk of operative mortality | Open surgery<br>Optimal medical management<br>Other transcatheter aortic valves | Accurate valve replacement<br>Avoided open surgery<br>Decreased rehospitalization for heart failure<br>Decreased mortality<br>Improved quality of life | Tracked 2 years after FDA approval; no longer meets horizon scanning criteria for tracking |

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

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Off-label venlafaxine (Effexor) for treatment of compulsive hoarding | Patients with compulsive hoarding habits who have no other identified psychiatric morbidity | Compulsive hoarding affects an estimated 2% to 5% of individuals in the U.S. The condition can be difficult to treat, and only a single study has been conducted to determine whether pharmacotherapy is an effective treatment. Selective serotonin reuptake inhibitors (SSRIs) have been used in this population, but they are associated with side effects and suboptimal efficacy, especially in older adults. Extended-release venlafaxine (Effexor XR®) is a selective norepinephrine reuptake inhibitor that is indicated in the U.S. for treating depression, generalized anxiety disorder, social anxiety disorder, and panic disorder. Because this agent is well tolerated and has shown efficacy in treating obsessive-compulsive disorder (often associated with hoarding), researchers hypothesize that it may have utility in patients in whom compulsive hoarding has been diagnosed. In trials, the drug was administered orally, once daily.<br><br>Pfizer, Inc., New York, NY (manufacturer)<br>University of California, San Diego (investigator)<br><br>Clinical trial completed; manufacturer does not appear to be seeking a labeled indication change | Psychotherapy<br>SSRIs | Improved scores on hoarding rating scales<br>Reduced morbidity<br>Reduced mortality<br>Improved quality of life | After initial tracking, horizon scanning team subsequently determined that intervention has small, incremental potential only; no ongoing trials are registered |

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

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

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

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Off-label salsalate for treatment of type 2 diabetes | Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed | Research has demonstrated a link between T2DM progression and inflammation. Salsalate is a widely available anti-inflammatory derivative of salicylic acid; although salicylic acid has been known for many years to aid in control of blood glucose levels, concerns regarding gastrointestinal (GI) side effects have prevented its use; salsalate may avoid these GI side effects while maintaining anti-inflammatory activity.<br><br>Joslin Diabetes Center, Boston, MA; various academic research centers<br><br>Phase II/III trial completed; other phase II/III trials ongoing | Diet and lifestyle changes<br>Exenatide<br>Insulin<br>Insulin sensitizers (pioglitazone, rosiglitazone)<br>Metformin<br>Sitagliptin<br>Sodium glucose co-transporter 1 and/or 2 inhibitors (in development)<br>Sulfonylurea drugs (glimepiride) | Achieved target glycated hemoglobin ($HbA_{1c}$) levels<br>Desired fasting glucose level control<br>Resolved insulin sensitivity | Expert comments indicated no potential for high impact because intervention has low potential to meet unmet need |

**Table 38. 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 | Reason |
|---|---|---|---|---|---|
| Davunetide for treatment of progressive supranuclear palsy | Patients in whom progressive supranuclear palsy (PSP) has been diagnosed | No treatments exist for PSP, a rare condition; anticholinergic medications for Parkinson's disease are used to control symptoms. Davunetide, also known as AL-108, is a 1st-in-class agent intended to target tau tangles—PSP is believed to have underlying tau-related pathology (abnormal clumps of tau). Davunetide is an intranasal formulation of a microtubule-interacting peptide that is intended to prevent neuronal apoptosis by repairing the microtubular network and potentially restoring both axonal transport within nerve cells and chemical transmission between them. It also is intended to promote neurite growth and restore transmission between nerve cells. The drug is derived from a naturally occurring protein called activity-dependent neuroprotective protein. Administered intranasally, 30 mg, twice daily.<br><br>Endo Health Solutions, Inc., which announced Nov 5, 2013, it would acquire Paladin Labs, Inc., Montreal, Quebec, Canada, and form a company called New Endo<br><br>Phase II/III trial completed, did not meet primary endpoints; FDA granted orphan drug status Jan 2010 | Botulinum toxin type A (Botox®) injection<br>Pharmacotherapy (e.g., anticholinergic medications, antidepressants) | Improved symptom control<br>Delayed or halted disease progression<br>Improved quality of life | Did not prove effective in phase II/III trial; company is being acquired by U.S.-based specialty pharmaceutical company, Endo Pharmaceuticals, 1st half of 2014 |
| Deferiprone (Ferriprox) for treatment of contrast-induced acute kidney injury | Patients in whom contrast-induced acute kidney injury (CI-AKI) has been diagnosed | The only current standard treatment for CI-AKI in high-risk patients with chronic kidney disease (CKD) is hydration and avoidance of nephrotoxic drugs. Deferiprone (Ferriprox®) is an orally active hydroxypyridin-4-one iron chelator that binds and removes excess iron from the body. If proven effective, deferiprone could become the 1st therapeutic drug to prevent CI-AKI in CKD. Deferiprone 900 mg is administered orally, 1 immediate release tablet and 2 extended-release tablets, 1–3 hours before angiography, and then every 12 hours for 8 days.<br><br>CorMedix, Inc., Bridgewater, NJ<br><br>FDA approved Oct 2011 for treating patients with excess iron in the body; phase III trial ongoing under FDA special protocol assessment | Pharmacotherapy (e.g., deferoxamine)<br>Hydration | Reduced occurrence and complications of CI-AKI<br>Reduced incidence of CI-AKI in high risk patients with CKD | U.S. development halted because phase II trial did not meet desired endpoints |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Intraoral tongue-drive computerized system to maneuver electrically-powered wheelchairs | Patients with spinal cord paralysis, particularly from the neck down | The Tongue Drive System (TDS) is a computerized, tongue-operated, assistive neurotechnology. It consists of a lentil-sized, magnetic, tracer-stud that is embedded in a dental retainer worn in the mouth with the tracer affixed to the tongue, most commonly by piercing. The magnetic tracer-stud creates a magnetic field around the pierced glossal area, and magnetic sensors located on a wireless headset/headphones communicate with a wheelchair. In spinal cord injuries and neuromuscular diseases, 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, designating it the target of choice for the magnetic pierced-tongue mobility aid. The change in magnetic field (prompted by tongue movement) in the mouth is detected by the magnetic sensors on the headset, transmitting information wirelessly 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. According to the registered clinical trial protocol description, the TDS requires that the patient's teeth are brushed, the oral surface sterilized with chlorhexidine mouthwash, and local anesthetics applied on the tongue before clinicians pierce it with a titanium magnetic stud. Patients must undergo computer 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.<br><br>Georgia Institute of Technology, Atlanta<br><br>Pilot trial and unphased trials completed | Comparators depend on severity of spinal cord paralysis<br>Chin control wheelchair<br>Head control wheelchair<br>"Sip and puff" wheelchair<br>Speech control wheelchair<br>Tongue keyboard controller wheelchair | Improved wheelchair function and control<br>Improved aesthetics of device<br>Improved mobility<br>Improved quality of life | Expert comments deemed this intervention to be of incremental benefit relative to other available devices |

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Tolvaptan for treatment of polycystic kidney disease | Patients in whom polycystic kidney disease (PKD) is diagnosed | According to the National Kidney Foundation, polycystic kidney disease (PKD) affects more than 600,000 patients in the U.S. Investigators have not found a cure. Treatment is aimed at slowing the loss of kidney function, managing pain, preventing infection, and controlling blood pressure. Tolvaptan is a vasopressin selector antagonist indicated for treating patients with hyponatremia. This drug therapy purports to inhibit cyst growth and slow the decline of kidney function.<br><br>Otsuka Holdings Co., Ltd., Tokyo, Japan<br><br>Phase III trial complete; FDA advisory committee voted against approval for this indication Aug 2013; drug was previously approved for “clinically significant hypervolemic and euvolemic hyponatremia” | No other therapies exist for treating PKD | Inhibited cyst growth<br>Reduced decline of kidney function<br>Improved quality of life | No potential for high impact after safety concerns emerged; FDA advisory committee voted not to recommend approval in Aug 2013 for PKD; FDA officially limited duration and usage of tolvaptan to 30 or fewer days due to risk of liver disease/failure; FDA to reevaluate PKD data before making final determination |

**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 |
|---|---|---|---|---|---|
| Crofelemer (Fulyzaq) for treatment of HIV-1-associated diarrhea | Patients on HIV antiretroviral therapy with chronic diarrhea | About 40% of patients in the U.S. with HIV-1 infections have chronic diarrhea, which can reduce adherence to antiretroviral regimens. Effective antidiarrheals that do not cause adverse reactions with antiretrovirals are needed. Crofelemer (Fulyzaq™) treats diarrhea by inhibiting the cystic fibrosis transmembrane conductance regulator ion channel, which is responsible for transporting chloride ions into the intestinal lumen, drawing water into the bowel. It is thought to work by blocking chloride secretion, thereby reducing the high volume water loss seen in HIV-associated diarrhea. The drug is a delayed release formulation, and the dosage in the approved product labeling is 125 mg, twice daily.<br><br>Salix Pharmaceuticals, Inc., Raleigh, NC (distributor)<br>Napo Pharmaceuticals, Inc., San Francisco, CA (licenser)<br><br>FDA approved Dec 2012 for "symptomatic relief of non-infectious diarrhea in adult patients with human immunodeficiency virus (HIV)/ acquired immune deficiency syndrome (AIDS) on anti-retroviral therapy (ART)." | Absorbents containing attapulgite or polycarbophil<br>Antibiotics<br>Diphenoxylate<br>Loperamide | Reduced number of watery bowel movements<br>Relief of diarrhea | After initial tracking, horizon scanning team subsequently determined that intervention has small, incremental potential only; many patients will require additional agents to treat their diarrhea |
| Patient-centered signage to improve hand washing among health care workers | Patients attending health care facilities | 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. Signage posted where hand washing should occur stating "Hand Hygiene Prevents Patients from Catching Diseases" may be more effective than "Hand Hygiene Prevents You from Catching Diseases" or a generic catchy message such as "Gel In, Wash Out." A patient-centered message may appeal to the "do no harm" precept of the Hippocratic oath.<br><br>University of North Carolina at Chapel Hill<br><br>Can be readily put in place | Standard hand-washing practices<br>Radiofrequency identification hand-washing systems | Reduced costs associated with health care-acquired infections (HAIs) Reduced HAI incidence<br>Reduced HAI morbidity and mortality | After initial tracking, horizon scanning team subsequently determined that intervention has small, incremental potential only; 1 word was changed in a handwashing sign to assign the infectious disease risk from caregivers to patients in an attempt to improve handwashing adherence. |

| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| PneumoniaCheck device for detection of pneumonia | Patients in whom pneumonia is suspected | Only 40% of suspected pneumonia cases are thought to be accurately detected because organisms from the mouth and lungs contaminate the sample, leading to inappropriate treatment and increased morbidity and mortality. The PneumoniaCheck™ device purportedly uses fluid mechanics in a simple design that separates upper and lower airway aerosols, allowing contaminating organisms from the mouth to be eliminated from the lower respiratory isolates needed for appropriate diagnosis. The device consists of a plastic tube with a mouthpiece. A patient coughs into the device to fill up a balloon-like upper airway reservoir before the lung aerosols go into a filter that can be analyzed with standard polymerase chain reaction methods.<br><br>MD Innovate, Inc., Decatur, GA<br><br>Exempt from FDA regulatory clearance processes; classified as a class I device | Sputum and culture detection methods | Improved accuracy of diagnosis<br>Improved treatment plan<br>Reduced duration of symptoms through appropriate treatment | Tracked 2 years after commercialization in Jan 2011 |
| Universal clearance (decolonization) to prevent methicillin-resistant *Staphylococcus aureus* infections in intensive care units | Patients admitted to intensive care units (ICUs) | Hospital-acquired infections such as methicillin-resistant *Staphylococcus aureus* (MRSA) are a major cause of morbidity and death; improved infection control protocols are needed. Screening patients admitted to ICUs for MRSA colonization followed by isolation or decolonization is standard practice in many facilities. Universal decolonization consists of nasal decolonization of all patients with mupirocin for 5 days and daily chlorhexidine baths for the duration of ICU stay. Universal decolonization is purportedly more effective in reducing the incidence of MRSA in the ICU and reducing the need for surveillance cultures and isolation in the ICU.<br><br>University of California Irvine School of Medicine, Orange, CA<br><br>Large trial completed | Nasal screening followed by isolation<br>Nasal screening followed by isolation and decolonization | Reduced infection rates | Tracked 2 or more years in horizon scanning system; no longer meets horizon scanning criteria for tracking; has diffused |

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

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
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**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 |
|---|---|---|---|---|---|
| Zysa (AST-120) for treatment of diarrhea-predominant irritable bowel syndrome | Patients in whom diarrhea-predominant irritable bowel syndrome (IBS-d) has been diagnosed | Current treatments for IBS-d 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. Other treatments include off-label antispasmodic agents and antidepressants and probiotics. Zysa™ (AST-120) is an oral spherical carbon adsorbent that purportedly binds to and neutralizes the activity of several compounds associated with IBS-d pathogenesis as well as ammonia, indoles (serotonin), histamine, bile acids, advanced glycation endproducts, and certain bacterial toxins. By binding and neutralizing toxins in the gut, AST-120 could relieve IBS-d symptoms.<br><br>Ocera Therapeutics, Inc., San Diego, CA<br><br>Phase II trial completed; FDA granted fast-track status May 2012; Conformité Européene (CE) mark granted in 2012 | Antispasmodic drugs<br>Opioid receptor agonist in development<br>Opioids<br>Serotonin agonists<br>Tricyclic antidepressants | Reduced abdominal pain and bloating<br>Long-term relief | No longer listed in manufacturer pipeline or on Web site; appears development has halted as no news has been reported since May 2012 |

**Table 42. AHRQ Priority Condition: 12 Pregnancy, Including Preterm Birth: 1 Intervention**

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
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| Topic Title | Potential Patient Population | Intervention<br>Developer/Manufacturer(s)<br>Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
|---|---|---|---|---|---|
| Ulipristal acetate (Emsya, PGL 4001) for treatment of uterine fibroids and excessive uterine bleeding | Premenopausal women in whom symptomatic uterine fibroids have been diagnosed | Uterine fibroids are the most common benign tumor in women, with some fibroids causing excessive pain and bleeding. Available therapies can work with limited efficacy, marking a need for more novel treatment. Ulipristal acetate (known as Emsya® for uterine fibroids and EllaOne® for pregnancy prevention) is a selective P receptor modulator with antiprogestin effects. Administered orally, 10 or 20 mg, once daily. The drug is already approved in the U.S. as an emergency contraceptive to prevent pregnancy.<br><br>PregLem, a division of Gedeon Richter, plc, Budapest, Hungary<br>Activas, Inc., Parsippany, NJ<br><br>4 non-U.S. phase III trials ongoing; approved in Canada and Europe for treatment of uterine fibroids | Cryomyolysis<br>ExAblate<br>Gonadotropin-releasing hormone agonists<br>Hysterectomy<br>Uterine artery embolization | Avoided or delayed hysterectomy<br>Reduced total fibroid volume<br>Prevention of anemia due to heavy menstrual bleeding<br>Reduced symptoms (e.g., pain)<br>Improved quality of life | No U.S.-based trials ongoing at this time, although the company, Gedeon Richter, has entered into licensing agreements with various other companies for other markets |

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

| Topic Title | Potential Patient Population | Intervention Developer/Manufacturer(s) Phase of Development | Potential Comparators | Potential Health or Other Impacts | Reason |
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**Table 45. AHRQ Priority Condition: 15 Cross-Cutting: 0 Interventions**

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