AHRQ Healthcare Horizon Scanning System – Status Updates

Horizon Scanning Status Update: October 2012

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

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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. The Status Update is a summary of data elements collected from implementation of the Horizon Scanning Identification and Monitoring Protocol. Status Updates are produced 4–6 times a year, with each new report superseding the prior version. This Status Update is organized by into four main topic-status sections and then by priority condition within each section. Topics are listed in tables pertaining to each AHRQ priority condition. The table of contents provides links directly 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," followed by "Interventions Tracked but Archived Since Last Update," and finally, "Interventions Identified and Not Tracked" during the prior tracking period of more than 2 months. Each table provides the Topic Title, Potential Patient Population, Intervention Description (including the Developer/Manufacturer[s] and Phase of Development), Potential Comparators, and Potential Health or Other Impacts.

Criteria for including topics in the Status Update are provided in detail in the "Horizon Scanning Protocol and Operations Manual," which is available on the Effective Health Care Web site (Protocol and Operations Manual). Briefly, broad scanning is performed for each priority condition to detect "leads" to interventions and innovations. Sets of questions are applied to determine whether any given intervention addresses an "unmet need" such as a 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 then entered into the System for tracking and appear in the Status Update report as "Currently Tracked Interventions" and "Interventions Added Since Last Update."

Some of the accepted topics may also be selected during the meeting for Topic Profile development. Clinical interventions (i.e., drugs, devices, procedures) that are voted for advancing to Topic Profile development must be far enough along in development (typically phase III for drugs and phase II or the equivalent for devices) to have some preliminary efficacy and safety data available for inclusion in the profile. Topics that are programs or care delivery innovations may be advanced for Topic Profile development with fewer data available if enough information is available to describe the care delivery innovation well and if demonstration projects or pilot studies are under way. The horizon scanning medical librarians and analysts proceed with more in-depth and topic-specific searching for information on the topics selected for advancement.

During the process of gathering more information, we sometimes conclude that an intervention does not, in fact, meet criteria for monitoring. Such topics are listed in the Status

Update as "Identified but Not Tracked." 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 is no longer novel, or because the intervention has diffused past early adoption.

Overall, populating the horizon scanning system has been ongoing since December 2010. During that time, more than 13,000 leads have been uploaded into the system and reviewed by analysts, from which about 1,540 topics have been initially identified and moved through the system. This Status Update report contains a total of 971 identified interventions being tracked, of which 34 are new topics entered into the system this reporting period. We archived 26 topics during this reporting period. The reason for archiving each topic is provided in the respective tables of archived topics. Three reasons account for the majority of archived topics: expert commenters saw no potential for high impact in the areas of interest to AHRQ; companies halted development; or topics that had been tracked met criteria for retiring from the system because they have diffused since tracking started or were 2 years post-approval by the U.S. Food and Drug Administration.

In this update, five priority areas comprise about 77% of the interventions (including programs) being tracked. Interventions related to cancer account for 31% (300/971) of tracked topics. The other priority areas with the most tracked topics in descending order of number of topics are as follows: functional limitations and disability (18%, 179/971), infectious diseases (12%, 117/971), cardiovascular diseases (10%, 99/971), and diabetes (6%, 55/971).

Interventions being tracked in the remaining nine priority conditions (arthritis, dementia, depression and other mental illness, developmental delays, 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 less than 4% each, or a combined total of about 23% (220/971) of topics being tracked in the system. The proportion that topics in each priority area constitute relative to the total number being tracked has changed by less than two percentage points from Update to Update since the inaugural Status Update report.

In terms of overall types of interventions, about 85% fall into one of four general categories, and the proportions of topics in these categories have changed very little since initial reporting, as well. Slightly more than 62% of topics in the system are a pharmaceutical/biotechnology (i.e., drug, vaccine, biologic); about 15% are devices—either implanted or used to deliver treatments externally; about 6% are technologies intended to screen, diagnose, identify risk, identify gene mutations, and/or monitor a disease state. About 2% are innovative programs, services, or care delivery practices. Other categories include medical procedures, alternative/complementary medicine, surgery, and assistive (i.e., rehabilitative or physical support) technologies, and information technology, which each constitute less than 3% of the interventions in the system.

Section 1. Currently Tracked Interventions: 937 Interventions

Table 1. AHRQ Priority Condition: 01 Arthritis and Nontraumatic Joint Disease: 29 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Allogeneic mesenchymal precursor cells (NeoFuse) for treatment of degenerative disc disease	Patients in whom degenerative disc disease (DDD) of the lower back has been diagnosed	Between 15% and 40% of the population will experience DDD. Although physical therapy and medication provide a solution in most cases, spinal surgery involving either total disc replacement or spinal fusion is needed by a subset of patients. Noninvasive treatments are needed to relieve the symptoms of patients who do not require surgery, would like to prevent the need for surgery, or are at risk of losing disc height following surgery. Allogeneic adult stem cells combined with hyaluronic acid (NeoFuse™) are injected into severely damaged intervertebral discs with the intention of reversing the degenerative process, stimulating regrowth of disc cartilage, and sustaining normalization of disc pathology, anatomy, and function; mesenchymal precursor cells are purported to produce the proteoglycans found in disc cartilage, so the manufacturer hypothesizes that the injection of mesenchymal stem cells into a degenerated intervertebral disc will lead to replacement of the proteoglycan of cartilage resulting in a minimally invasive, lower cost therapy for patients with moderate or severe DDD. Mesoblast, Ltd., New York, NY Phase II trials ongoing	Artificial disc replacement Discectomy Spinal fusion	Increased activities of daily living Reduced chronic lumbar back pain Reduced use of pain medications
Atacicept 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. Atacicept is a biologic that is purported to decrease the activity of autoreactive B cells, which may play a key role in the pathogenesis of SLE. Atacicept is a recombinant protein that consists of domains from the proteins B-lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL), which are involved in the maintenance, proliferation, and antibody production of B cells, fused to the constant domain of immunoglobulin. Because BLyS and APRIL bind the TACI (transmembrane activator and calcium-modulating and cyclophilin ligand [CAML] interactor) receptor, atacicept is also called TAC-Ig. Atacicept is purported to be an antagonist for the TACI receptor. Atacicept is hypothesized to selectively impair mature B cells and plasma cells more than memory B cells or progenitor cells. Atacicept is administered subcutaneously, 75 or 150 mg, once weekly. EMD Serono, Inc., Rockland, MA Phase II/III trial ongoing; estimated completion Oct 2012	Belimumab Corticosteroids Cyclophosphamide Methotrexate Tumor necrosis factor-alpha inhibitors Rituximab	Delayed disease progression Reduced symptoms Fewer flares Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) 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 is purported to have different effects from platelet-rich plasma therapy. NY Spine Medicine, Schottenstein Pain & Neurology, New York, NY Pilot studies completed; procedure currently diffusing in the U.S.	Lifestyle modification (weight loss, exercise) Mesenchymal stem-cell therapy Nonsteroidal anti-inflammatory drugs Physical therapy Platelet-rich plasma Viscosupplementation	Reduced pain Improved mobility Improved quality of life
Autologous mesenchymal stems cells for treatment of joint osteoarthritis	Patients in whom osteoarthritis (OA) has been diagnosed	Current conservative therapies for osteoarthritis (OA) target disease symptoms such as pain and inflammation; however, they do not address the underlying pathology of the disease or halt its progression. Treating osteoarthritic joints with mesenchymal stem cells has the potential to be the 1st treatment could restore the large cartilage defects found in patients with OA. Mesenchymal stem cells are adult stem cells that progenitor cells that retain the ability to differentiate into a number of cell types, including chondrocytes, which are the cells responsible for maintaining cartilage. The stem cells can be isolated from several tissues, including bone marrow, synovium, periosteum, skeletal muscle, and adipose tissue. When 1st isolated from the patient, mesenchymal stem cells constitute a small fraction of the cells present in the sample and must either be concentrated by centrifugation or be passaged multiple times in vitro to expand the mesenchymal cell population. The condition of the patient may influence the attributes of the mesenchymal stem cells that are produced, and both patient age and the presence of OA have been shown to affect the ability of isolated mesenchymal stem cells to proliferate and differentiate into chondrocytes. Regenerative Sciences, Inc., Broomfield, CO Arthritis Treatment Center, Frederick, MD Trials completed	Lifestyle modification (weight loss, exercise) Mesenchymal stem-cell therapy Nonsteroidal anti-inflammatory drugs Physical therapy Platelet-rich plasma Viscosupplementation	Reduced pain Improved mobility Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous platelet-rich plasma therapy for treatment of joint osteoarthritis	Patients in whom 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. Orthohealing Center, Los Angeles, CA Phase III trials ongoing	Lifestyle modification (weight loss, exercise) Mesenchymal stem-cell therapy Nonsteroidal anti-inflammatory drugs Physical therapy Viscosupplementation	Decreased pain Increased mobility Improved quality of life
BAFF-targeting peptibody blisibimod (A-623) for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	Current SLE treatments provide partial symptomatic relief; treatments with improved efficacy are needed. B-cell activating factor (BAFF) is a soluble and membrane-bound growth factor for B cells that has been associated with a wide range of B-cell mediated autoimmune diseases, including SLE. Blisibimod is purported to be a broad inhibitor of BAFF; it is purported to be a novel proprietary fusion protein called a peptibody. Administered weekly via subcutaneous injection. Anthera Pharmaceuticals, Inc., Hayward, CA Phase IIb trial ongoing	Belimumab Corticosteroids Cyclophosphamide Methotrexate Tumor necrosis factor-alpha inhibitors Rituximab	Delayed disease progression Symptom relief Improved quality of life
Chemokine receptor type 1 antagonist (CCX354) for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	Current RA therapies are not effective in some patients and can lead to immunosuppression and poor tolerability. Improved targeted therapies are needed. CCX354 is purported to be a potent and selective antagonist of chemokine receptor type 1, which is purported to be involved in recruiting inflammatory cells such as monocytes, macrophages, and T cells into the joints of patients with RA. By selectively blocking this receptor, CCX354 is intended to reduce the infiltration of inflammatory cells into the joints of RA patients, limiting inflammation and joint destruction, while minimizing systemic side effects. ChemoCentryx, Inc., Mountain View, CA, and GlaxoSmithKline, Middlesex, UK Phase II trials completed	Adalimumab Disease-modifying antirheumatic drugs Etanercept Infliximab Syk inhibitor prodrug in development Tocilizumab Tyrosine kinase inhibitor in development	Improved symptom scores as measured by American College of Rheumatology 20/50/70 instruments

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
C-reactive protein inhibitor (ISIS-CRP_{Rx}) for reduction of elevated C-reactive protein levels associated with rheumatoid arthritis	Patients with elevated C-reactive protein (CRP) in whom rheumatoid arthritis (RA) has been diagnosed	Elevated CRP levels have been associated with various inflammatory disorders including RA, cardiovascular disease, and diabetes. ISIS-CRP_{Rx} is intended to directly test whether lowering CRP might benefit patient outcomes in patients with these disorders; ISIS-CRP_{Rx} is a 1st-in-class selective antisense CRP (protein found in the liver) inhibitor. In a phase I trial, the agent was administered intravenously and subcutaneously to healthy volunteers and some subjects with elevated CRPs. ISIS Pharmaceuticals, Inc., a unit of Johnson & Johnson, New Brunswick, NJ Phase II trial ongoing	Corticosteroids Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine Nonsteroidal anti-inflammatory drugs Tocilizumab Tofacitinib (investigational) Tumor necrosis factor-alpha inhibitors	Reduced CRP levels Reduced symptoms Slowed disease progression
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 currently available treatments provide only partial relief of symptoms, so better treatments are needed. Epratuzumab is a fully humanized, monoclonal antibody that is purported to bind and modulate 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. The drug is administered as a subcutaneous injection once monthly in clinical trials. UCB S.A., Brussels, Belgium Phase III trials ongoing	Belimumab Corticosteroids Cyclophosphamide Methotrexate Tumor necrosis factor-alpha inhibitors Rituximab	Delayed progression of disease Reduced symptoms Fewer flares Improved quality of life
Fostamatinib disodium for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	Fostamatinib disodium, previously referred to as R788, is a 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. The drug is taken orally. Rigel Pharmaceuticals, Inc., South San Francisco, CA Phase III trials ongoing	Corticosteroids Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine Nonsteroidal anti-inflammatory drugs Tocilizumab Tofacitinib (investigational) Tumor necrosis factor-alpha inhibitors	Decreased inflammation Slowed disease progression Reduced pain Improved function and activities of daily living Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interleukin-1-beta antagonist canakinumab (Ilaris) for treatment of systemic juvenile idiopathic arthritis	Patients in whom systemic juvenile idiopathic arthritis (SJIA) has been diagnosed	Available treatments for SJIA only partially mitigate symptoms and do not prevent long-term damage associated with the condition. Additionally, prolonged use of steroids can cause slowed growth and delayed puberty. Canakinumab (Ilaris™) is a long-acting, fully human monoclonal antibody against interleukin-1-beta (IL-1-beta). IL-1-beta is a major mediator of inflammatory responses, which are purported to play a role in SJIA pathology. Canakinumab is intended to block the inflammatory activity of IL-1-beta. In a clinical trial, canakinumab was administered as a single subcutaneous dose, 4 mg/kg of body weight, to patients aged 2–19 years. Novartis International AG, Basel, Switzerland Phase III trials ongoing; approved for cryopyrin-associated periodic syndromes	Anakinra Corticosteroids Hydroxychloroquine Methotrexate Nonsteroidal anti-inflammatory drugs Tocilizumab	Improved adapted American College of Rheumatology pediatric 30/50/70/90/100 disability criteria Improved Child Health Assessment Questionnaire clinical response Decreased Child Health Questionnaire pain intensity as assessed on a 100 mm visual analog scale Improved quality of life
Interleukin-6 receptor antagonist tocilizumab (Actemra) for treatment of systemic juvenile idiopathic arthritis	Patients 2 years of age and older in whom active systemic juvenile idiopathic arthritis (SJIA) has been diagnosed	Available treatments for SJIA only partially mitigate symptoms and do not prevent long-term damage associated with the condition. Additionally, prolonged use of steroids can cause slowed growth and delayed puberty. Tocilizumab (Actemra®) is a humanized monoclonal antibody interleukin-6 (IL-6) receptor antagonist. IL-6 is a proinflammatory cytokine produced by a variety of cell types including lymphocytes, monocytes, and fibroblasts, as well as synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes. IL-6 is purported to upregulate lymphocyte activity, initiate acute phase protein synthesis, and stimulate hematopoietic precursor cell proliferation and differentiation. IL-6 can also stimulate osteoclast activity leading to inflammation and erosion of joint structures. Inhibiting IL-6 activity may relieve symptoms associated with SJIA. Tocilizumab can be used as monotherapy or in combination with methotrexate and is administered as an intravenous infusion, 12 or 8 mg/kg of body weight in patients weighing less than or more than 30 kg, respectively, every 2 weeks. F. Hoffmann-La Roche, Ltd., Basel, Switzerland FDA approved for treating SJIA Apr 2011 and phase III trials ongoing	Anakinra Corticosteroids Hydroxychloroquine Interleukin-1-beta antagonist in development Methotrexate Nonsteroidal anti-inflammatory drugs	Improved adapted American College of Rheumatology pediatric 30/50/70/90/100 disability criteria Improved Child Health Assessment Questionnaire clinical response Decreased Child Health Questionnaire pain intensity as assessed on a 100 mm visual analog scale Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interleukin-17 antagonist (secukinumab) for treatment of ankylosing spondylitis	Patients in whom ankylosing spondylitis has been diagnosed	No cure has been found for ankylosing spondylitis. Treatments are intended to reduce inflammation and improve mobility but are not effective for all patients. Secukinumab is purported to be a monoclonal antibody antagonist for interleukin-17 (IL-17). IL-17 is purported to be involved in developing delayed-type hypersensitivity reactions by increasing chemokine production, which promotes the recruitment of inflammatory cells such as monocytes and neutrophils to the local area. By blocking the effects of IL-17 localized autoimmune reactions associated with ankylosing spondylitis, pathology could be blocked while minimizing the systemic immunosuppression associated with tumor necrosis factor (TNF) blockers, which are often used in treatment. Administered subcutaneously, 75 or 150 mg, monthly. Novartis International AG, Basel, Switzerland Phase III trial ongoing	Corticosteroids Disease-modifying antirheumatic drugs Nonsteroidal anti-inflammatory drugs Physical therapy Sulfasalazine (Azulfidine) TNF inhibitors	Reduced signs and symptoms Improved mobility Improved quality of life
JAK 1 inhibitor (GLPG0634) for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	RA is a chronic inflammatory disease that can cause permanent joint damage, deformity, and functional disability. New oral new therapies might enhance treatment adherence and tolerability compared with current biologic therapies. GLPG0634 is an oral tyrosine kinase inhibitor purported to act against the Janus kinase 1 (JAK 1) signaling pathway that is believed to mediate several processes involved in inflammatory pathways that could contribute to RA pathogenesis. In trials, GLPG0634 has been administered 100 mg, twice daily, or 200 mg, once daily. Abbott Laboratories, Abbott Park, IL GlaxoSmithKline, Middlesex, UK Phase II trial complete; Feb 2012, Galápagos NV, Mechelen, Belgium, signed global agreement with Abbott to develop and commercialize GLPG0634	Corticosteroids Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine Nonsteroidal anti-inflammatory drugs Tocilizumab Tofacitinib (investigational) Tumor necrosis factor-alpha inhibitors	Reduced inflammation Improved symptoms Improved activities of daily living Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
JAK 1/2 inhibitor (LY-3009104) 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 RA that no longer responds to disease-modifying antirheumatic drugs (DMARDs); however, biologics must be administered by intramuscular, subcutaneous, or intravenous injection and are associated with increased incidence of serious infections, including tuberculosis. DMARDs with improved efficacy, tolerability, and convenience are needed. LY-3009104 is an oral Janus kinase 1 (JAK 1) and Janus kinase 2 (JAK 2) inhibitor. JAK 1 and JAK 2 are involved in mediating the activity of many cytokines involved in RA pathogenesis; inhibiting these kinases may reduce inflammation and RA symptoms. It is administered 1–8 mg, once daily, or up to 2 mg, twice daily. Incyte Corp., Wilmington, DE Eli Lilly and Co. Indianapolis, IN Phase IIb completed; results achieved primary endpoints	Corticosteroids Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine Nonsteroidal anti-inflammatory drugs Tocilizumab Tofacitinib (investigational) Tumor necrosis factor-alpha inhibitors	Improved symptom scores as measured by the American College of Rheumatology 20/50/70 instruments
JAK 3 inhibitor (tofacitinib) for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	Tofacitinib (CP-690,550) is a selective and potent oral tyrosine kinase inhibitor that is being investigated as a targeted disease-modifying antirheumatic drug (DMARD) for treating RA. Tofacitinib inhibits a Janus kinase (JAK 3) signaling pathway believed to mediate several processes involved in chronic inflammatory diseases, such as antibody production by B cells, production of rheumatic factor and activation of T cells. By inhibiting the JAK 3 pathway, tofacitinib may suppress the inflammatory reactions that are the basis of RA. In recent trials, tofacitinib was administered in once daily, 20 mg, or twice daily, 1, 3, 5, 10, and 15 mg. A targeted therapy that might reduce RA-specific inflammatory processes in the way tofacitinib purports to may provide better symptom control with fewer adverse events than other DMARDs or nonsteroidal anti-inflammatory drug-activated anti-inflammatory pathways. Pfizer, Inc., New York, NY Phase III trial completed; May 2012, FDA's Arthritis Advisory Committee voted 8-2 to recommend approval as a treatment for adults with moderate to severe active RA that has not responded adequately to another DMARD. If approved, it would be the 1st new oral DMARD for RA in more than 10 years and the 1st JAK inhibitor to be approved; FDA decision date was extended from Aug 2012 to Nov 2012.	Corticosteroids Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine Nonsteroidal anti-inflammatory drugs Tocilizumab Tofacitinib (investigational) Tumor necrosis factor-alpha inhibitors	Reduced inflammation Improved symptoms Improved activities of daily living Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
JAK 3 inhibitor (VX-509) 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 RA that no longer responds to disease-modifying antirheumatic drugs (DMARDs); however, biologics must be administered by intramuscular, subcutaneous, or intravenous injection and are associated with increased incidence of serious infections, including tuberculosis. DMARDs with improved efficacy, tolerability, and convenience are needed. VX-509 is an oral Janus kinase (JAK 3) inhibitor. JAK 3 is involved in mediating the activity of many cytokines involved in RA pathogenesis; inhibiting this kinase may reduce inflammation and RA symptoms mediated by T cells, B cells, and monocytes. It is administered 25–150 mg, twice daily. Vertex Pharmaceuticals, Inc., Cambridge, MA Phase II trial completed	Corticosteroids Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine Nonsteroidal anti-inflammatory drugs Tocilizumab Tofacitinib (investigational) Tumor necrosis factor-alpha inhibitors	Improved symptoms scores as measured by American College of Rheumatology 20/50/70 instruments
KIT tyrosine kinase inhibitor 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 is purported to target 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 of body weight, daily. AB Science S.A., Paris, France Phase II/III trial ongoing	Corticosteroids Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine Nonsteroidal anti-inflammatory drugs Tocilizumab Tofacitinib (investigational) Tumor necrosis factor-alpha inhibitors	Improved symptom scores as measured by American College of Rheumatology 20/50/70 instruments Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
LX2931 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. LX2931 targets lymphocytes through a novel mechanism of action that may change current treatment models and paradigms. LX2931inhibits sphingosine-1-phosphate (S1P) lyase; S1P is involved in several aspects of lymphocyte growth, migration, and activity. Targeting S1P-lyase is intended to increase retention of lymphocytes in the lymphoid tissue, thereby preventing them from causing in inflammation in joints. Administered orally. Lexicon Pharmaceuticals, Inc., The Woodlands, TX Phase II trial completed; results from additional phase II trial expected 3rd quarter 2012	Corticosteroids Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine Nonsteroidal anti-inflammatory drugs Tocilizumab Tofacitinib (investigational) Tumor necrosis factor-alpha inhibitors	Improved RA symptoms Reduced number of lymphocytes in circulation Improved quality of life
MAP kinase inhibitor (FX005) for treatment of osteoarthritis	Patients with moderate osteoarthritis (OA) whose symptoms do not respond adequately to intra-articular steroid injections	Current OA treatments temporarily relieve pain and do not prevent further joint damage. Longer-lasting, effective therapies to prevent both pain and joint damage in patients with OA are needed. FX005 is purported to be a sustained-release p38 MAP kinase inhibitor intended to reduce pain and inflammation in the joint to slow disease progression. MAP kinase is involved in activating many cellular functions involved in stress responses. Local administration of FX005 is intended to reduce side effects while providing prolonged relief. It is administered as an intra-articular injection (1, 10, or 45 mg). Flexion Therapeutics, Woburn, MA Phase II trial completed	Lifestyle modification Nonsteroidal anti-inflammatory drugs Physical therapy Platelet-rich plasma therapy Total joint replacement Viscosupplementation	Improved joint function Reduced pain Slowed disease progression Improved quality of life
Monoclonal antibody (tabalumab, LY2127399) 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. Tabalumab is a fully human immunoglobulin G4 monoclonal antibody targeting B-lymphocyte stimulator (BLyS). BLyS plays an important role in stimulating B-lymphocyte production when the human body is battling infection, but overproduction can cause production of autoantibodies and initiate autoimmune-like disease symptoms in mice. By inhibiting the biologic activity of BLyS, tabalumab inhibits the stimulation, proliferation, and differentiation of B cells. Intravenous and injectable formulations are under development for RA. Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing	Corticosteroids Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine Nonsteroidal anti-inflammatory drugs Tocilizumab Tofacitinib (investigational) Tumor necrosis factor-alpha inhibitors	Reduced symptoms Delayed progression of disease Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Monoclonal antibody (tabalumab, LY2127399) 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. Tabalumab is a monoclonal antibody that acts against B-cell activating factor (BAFF), a protein related to tumor necrosis factor that promotes survival of B cells as they exit the bone marrow and also prevents them from undergoing apoptosis later on. BAFF overexpression was found in diseased brain and BAFF; referred to as a B cell-targeted therapy. Drug is delivered by subcutaneous injection every 2 or 4 weeks and taken with standard care. Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing	Belimumab Corticosteroids Cyclophosphamide Methotrexate Tumor necrosis factor-alpha inhibitors Rituximab	Improved SLE Responder Index Improved quality of life
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 less gastrointestinal and cardiovascular side effects because of the local effects of NO. NicOx S.A., Sophia Antipolis, France Phase III trials completed; manufacturer received FDA 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	Celecoxib Ibuprofen Naproxen	Increased mobility Decreased pain Improved cardiovascular effects (i.e., blood pressure)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 the 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 a "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. Use of bisphosphonates for this purpose might provide a low-cost solution to 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. Lund University Hospital, Lund, Sweden Phase II trial ongoing in 32 hip surgeries	Standard of care following arthroplasty	Reduced need for revision surgery Improved quality of life
Proteasome inhibitor (bortezomib, Velcade) for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	No cure has been found for SLE. Current treatments provide only partial symptomatic relief and can cause immunosuppression and other adverse events. Treatments with improved efficacy are needed. The proteasome is a complex of proteins that are responsible for the normal turnover of intracellular proteins, allowing their components to be recycled for new proteins to meet the changing demands of the cell. Proteasomal activity is thought to be critical for the survival of long-lived, antibody-producing plasma cells implicated in SLE pathogenesis. Bortezomib (Velcade®) is a proteasome inhibitor that might selectively inhibit the long-lived, autoantibody-producing plasma cells, while sparing the activity of normal plasma cells. Bortezomib is administered as 4 injections over an 11-day course, 1.3 mg/m^2 of body surface area per injection, and is intended to be used in combination with other disease-modifying drugs. Millennium Pharmaceuticals, Inc., subsidiary of Takeda Pharmaceutical Co., Ltd., Osaka, Japan Pilot study completed; already approved for treating multiple myeloma and mantle cell myeloma	Antimalarial drugs Belimumab (Benlysta®) Corticosteroids Cyclophosphamide and mycophenolate Intravenous immunoglobulin Methotrexate and azathioprine	Disease remission Improved symptoms Slowed disease progression

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Purine nucleoside phosphorylase inhibitor Ulodesine (BCX4208) to prevent acute gout flares	Patients in whom chronic gout has been diagnosed	Despite new treatment options, some patients do not respond adequately to current gout therapies; thus, treatments with new mechanisms of action are needed. Ulodesine (BCX4208) is purported to be a purine nucleoside phosphorylase inhibitor, which blocks the generation of uric acid precursors and works upstream of xanthine oxidase inhibitors in the metabolic pathway, thus representing a new mechanism of action to lower serum uric acid levels and potentially prevent acute gout flares. Ulodesine is intended to be used in combination with allopurinol to lower serum uric acid levels. In trials, it is administered orally, 5–40 mg, once daily. BioCryst Pharmaceuticals, Inc., Research Triangle, NC Phase II completed.	Allopurinol Febuxostat Probenecid	Reduced frequency of gout flares Reduced serum uric acid levels Improved quality of life
TissueGene-C allogeneic chondrocyte implantation for treatment of knee osteoarthritis	Patients in whom grade 3 degenerative chronic osteoarthritis of the knee has been diagnosed	Current treatments require a multi-step process to harvest autologous chondrocytes from the patient, culture them, and reimplant them in the knee; this process can lead to deposit of fibrocartilage in the patient rather than the normally endogenous hyaline cartilage (microfracture surgery). The developer asserts a novel method for inserting a therapeutic growth-factor gene into allogeneic chondrocyte cells, culturing and stabilizing them, and injecting them into the injured site in the knee. Treatment is intended to secrete growth-factor proteins to potentially regenerate and repair tissue. TissueGene-C chondrocytes have been genetically modified to express transforming growth factor-beta; intended as a permanent repair and purported to be applicable to major (full-thickness) cartilage defects rather than just minor (partial-thickness) defects. The biologic can also be mass produced and used off the shelf. TissueGene, Inc., Rockville, MD Phase II trial ongoing	Autologous chondrocyte implantation (Carticel) Microfracture surgery Mesenchymal stem-cell therapy Osteochondral autograft transfer Platelet-rich plasma Viscosupplementation	Decreased knee pain Improved knee function Delayed or avoided knee replacement surgery

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tissue-specific COX-2 inhibitor CG100649 for treatment of osteoarthritis	Patients in whom osteoarthritis (OA) has been diagnosed	Effective nonsteroidal anti-inflammatory drugs (NSAIDs) with an improved safety profile are needed to prevent cardiovascular and gastrointestinal (GI) complications. CG-100649 is purported to be an oral dual inhibitor of COX-2 and carbonic anhydrase (CA) in red blood cells; by interacting with CA in red blood cells CG100649 is purported to have a tissue-specific transport mechanism designed to deliver sustained levels of drug to inflamed joint tissues, while maintaining low systemic exposure to cardiovascular, GI, and renal tissue compared with traditional NSAIDs or COX-2 inhibitors. Administered 2 or 4 mg per day, once daily, in trials. CrystalGenomics, Seoul, South Korea Phase IIb trial completed; results achieved primary and secondary endpoints; phase III program being planned	Celecoxib Ibuprofen Naproxen	Change in rescue medication Improved global assessment scores (patient and physician) Improved results for Western Ontario and McMaster Universities OA pain score and OA Index subscales
Urate transport inhibitor (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 currently 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. Ardea Biosciences, Inc., San Diego, CA Phase III trials ongoing	Treatment: Colchicine Nonsteroidal anti-inflammatory drugs Steroids Prophylaxis: Allopurinol Febuxostat Probenecid	Reduced accumulation of uric acid and crystal formation Reduced acute flares

Table 2. AHRQ Priority Condition: 02 Cancer: 285 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
5-Aminolevulinic acid fluorescence guidance for identifying glioma-clear surgical margins	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. Medac GmbH, Hamburg, Germany Phase III trial ongoing; commercially available as Gliolan® in Europe	Standard surgical resection without fluorescence	Increased overall survival Increased progression-free survival Improved quality of life
Abiraterone (Zytiga) for treatment of castration-resistant prostate cancer	Patients with metastatic castration-resistant prostate cancer (CRPC)	Median overall survival for patients with CRPC is only about 18 months. Administered in combination with prednisone, abiraterone (Zytiga™) inhibits a cytochrome P-450 subunit (CYPC17) responsible for a step in the androgen biosynthetic pathway. CRPC may escape androgen inhibition/removal through autocrine androgen signaling/upregulation of the androgen receptor. Blocking the tumor cell's ability to produce testosterone and/or further reducing extra-gonadal androgen generation may inhibit tumor growth. Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ FDA approved Apr 2011 for treating patients who have previously undergone treatment with docetaxel; supplemental new drug application (NDA) submitted to FDA in Jun 2012 for treating patients who are chemotherapy naïve; FDA granted the NDA for this indication priority review status in Aug 2012.	Cabazitaxel Docetaxel Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
ADXS11-001 for treatment of advanced cervical cancer	Patients in whom advanced cervical cancer has been diagnosed	Advanced cervical cancer is associated with a 5% 1-year survival rate. For patients with advanced cervical cancer, no effective therapies exist, and effective therapies on inoperable tumors are needed. ADXS11-001 is an immunotherapy comprising live, attenuated *Listeria monocytogenes* bacteria that have been engineered to express the human papillomavirus 16 E7 protein, which is believed to be crucial for cervical oncogenesis; the recombinant *Listeria* are purported to be a delivery vehicle to get E7 into antigen-presenting cells to induce cellular immunity. In clinical trials, ADXS11-001 has been administered intravenously as 1x10^9, 3.3x10^9 or 1x10^10 CFUs (colony-forming units). Advaxis, Inc., Princeton, NJ Phase II trials ongoing	Cisplatin Radiotherapy	Increased overall survival Increased progression-free survival Improved quality of life
Afatinib (BIBW 2992, Tomtovok) for treatment of breast cancer	Patients in whom HER2-positive breast cancer has been diagnosed	Afatinib (BIBW 2992, Tomtovok™, previously Tovok) is a small-molecule, irreversible inhibitor of both epidermal growth factor receptor (EGFR) (HER1) and HER2 receptor tyrosine kinases; these receptor tyrosine kinases are seen 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 kinases are available, afatinib is unique in that its inhibition is irreversible. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials ongoing	Lapatinib plus capecitabine Trastuzumab plus chemotherapy (e.g., paclitaxel, docetaxel, vinorelbine, capecitabine) Trastuzumab plus lapatinib	Increased overall survival Increased progression-free survival Improved quality of life
Afatinib (BIBW 2992, Tomtovok) for treatment of head and neck cancer	Patients in whom head and neck cancer has been diagnosed	Afatinib (BIBW 2992, Tomtovok™, previously Tovok) is a small-molecule, irreversible inhibitor of both epidermal growth factor receptor (EGFR) (HER1) and HER2 receptor tyrosine kinases. Targeted EGFR-like receptor inhibition in head and neck cancers has a high relative success rate. Although multiple receptor tyrosine kinase inhibitors are available, afatinib is unique in that its inhibition is irreversible. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials ongoing	Cetuximab (Erbitux®)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Afatinib (BIBW 2992, Tomtovok) for treatment of nonsmall cell lung cancer	Patients in whom nonsmall cell lung cancer (NSCLC) has been diagnosed	Afatinib (BIBW 2992, Tomtovok™, previously Tovok) is a small-molecule, irreversible inhibitor of both epidermal growth factor receptor (EGFR) (HER1) and HER2 receptor tyrosine kinases. EGFR (HER1) and HER2 receptor tyrosine kinases are mutated/overexpressed in NSCLC in about 10% 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. Boehringer Ingelheim, GmbH, Ingelheim, Germany 1 phase III trial complete and met primary endpoint; additional phase III trials ongoing	1st-line NSCLC: platinum based chemotherapy 2nd- and 3rd-line NSCLC: docetaxel, erlotinib, pemetrexed	Increased overall survival Increased progression-free survival Improved quality of life
Aflibercept (Zaltrap) for treatment of metastatic colorectal cancer	Patients with metastatic colorectal cancer (CRC) that has recurred after oxaliplatin-based chemotherapy	Current 2nd-line and adjunctive treatments for advanced, recurrent CRC have poor response rates and this patient population has a poor overall prognosis. Aflibercept (Zaltrap™) is a vascular endothelial growth factor (VEGF)-signaling inhibitor that contains multiple copies of the VEGF receptor extracellular domain designed to bind VEGF. It is an antiangiogenic agent intended to reduce tumor vascularization, thereby inhibiting tumor growth. Being tested as an adjunct to the standard chemotherapy treatment of leucovorin, irinotecan, and 5-fluorouracil (5-FU). Collaboration between Regeneron Pharmaceuticals, Inc., Tarrytown, NY, and Sanofi, Paris, France FDA approved Aug 2012 for use with the chemotherapy regimen folinic acid, fluorouracil and irinotecan (FOLFIRI) for treating adults with CRC whose tumors have progressed after treatment with an oxaliplatin-containing regimen	5-FU-based therapy plus bevacizumab FOLFIRI (folinic acid [leucovorin], 5-FU, and irinotecan) FOLFIRI plus cetuximab or panitumumab Irinotecan Irinotecan plus cetuximab	Increased overall survival Increased progression-free survival Improved quality of life
Albumin-coupled doxorubicin (INNO-206) for treatment of soft tissue sarcoma	Patients in whom unresectable soft tissue sarcoma has been diagnosed	Patients with soft tissue sarcoma have few treatment options and a poor prognosis. INNO-206 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. CytRx Corp., Los Angeles, CA Phase IIb initiated Dec 2011; FDA granted orphan drug status	Doxorubicin	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Algenpantucel-L (HyperAcute-Pancreas) immunotherapy for pancreatic cancer	Patients in whom surgically resectable (stage I or II) adenocarcinoma of the pancreas has been diagnosed	Patients in whom pancreatic cancer has been diagnosed have a 5-year survival rate of about 5%. 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 postoperative chemotherapy. NewLink Genetics Corp., Ames, IA Phase III trial ongoing under special protocol assessment with FDA; FDA granted fast track and orphan drug status	Standard chemotherapy alone (gemcitabine plus or minus 5-fluorouracil)	Increased overall survival Increased progression-free survival Improved quality of life
Allogeneic DNA immunotherapy (Allovectin-7) for advanced melanoma	Patients in whom stage III or IV melanoma has been diagnosed	Advanced melanoma is associated with a poor prognosis. New, effective treatments with acceptable safety profile are needed. Allovectin-7® is a DNA-based immunotherapeutic composed of a lipid encapsulated plasmid expressing human leukocyte antigen (HLA)-B7 and beta2 microglobulin (required to generate a functional major histocompatibility complex ([MHC] I molecule); designed to stimulate innate and adaptive immune responses against local and distant tumors; expression of tumor antigens in the context of the MHC I molecule HLA-B7 generates an allogeneic response against tumors; lipid/DNA complexes have adjuvant activity for the vaccine. It is given as an intratumoral injection on an outpatient basis. Vical, Inc., San Diego, CA Phase III trials ongoing; FDA granted orphan drug and fast track status for invasive and metastatic melanoma	Dacarbazine Interferon Interleukin-2 Ipilimumab Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Allogeneic mesenchymal precursor cells 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 is using an off-the-shelf preparation of mesenchymal precursor cells to expand cord blood stem cells ex vivo to improve engraftment rates upon introduction to the host. Because an imperfect match may be tolerated when using cord blood as the donor source, it may provide a suitable treatment option for many patients. Mesoblast, Ltd., New York, NY Pilot studies completed by University of Texas MD Anderson Cancer Center, Houston; phase III trial protocol approved by FDA to begin	Pooled unexpanded cord blood transplant Unexpanded cord blood transplant	Improved bone marrow engraftment rate Improved rate of neutrophil recovery Improved rate of platelet recovery
Allogeneic tumor cell vaccine (belagenpumatucel-L, Lucanix) for treatment of nonsmall cell lung cancer	Patients with advanced (stage III or IV) nonsmall cell lung cancer (NSCLC) whose disease has responded to 1st-line platinum-based chemotherapy	Five-year survival rates for patients with advanced NSCLC are less than 15% with current treatments. Belagenpumatucel-L (Lucanix™) is an allogeneic tumor-cell vaccine intended to delay disease progression after successful 1st-line treatment with platinum-based chemotherapy. The vaccine consists of 4 NSCLC cell lines that are administered intradermally once monthly for up to 2 years. The tumor-cell lines have been genetically modified to express an antisense version of transforming growth factor beta 2 (TGFB2), which is intended to inhibit the expression of TGFB2. TGFB2 has been shown to have antagonistic effects on various components of the immune system, and the developer hypothesizes that its inhibition could enhance an immune response generated by the tumor-cell vaccine. NovaRx, San Diego, CA Phase III trial ongoing under a special protocol assessment with FDA; FDA granted fast track status	Watchful waiting after successful 1st-line therapy Maintenance therapy (various chemotherapy regimens determined according to NSCLC subtype)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
ALN-VSP/RNAi for treatment of secondary liver metastases	Patients with liver metastases from advanced solid tumors	Metastases to the liver from solid tumors in other parts of the body are difficult to treat and are associated with a poor prognosis despite available treatment options. ALN-VSP is an infused RNAi therapeutic that targets 2 genes involved in the disease pathway of liver cancer: kinesin spindle protein, which is involved in cancer cell proliferation, and vascular endothelial growth factor, which is involved in the growth of new blood vessels that feed tumors. Alnylam Pharmaceuticals, Cambridge, MA Phase I trial completed	Chemotherapy Immunotherapy Intrahepatic microspheres/drug-eluting beads Radiation therapy	Increased overall survival Increased progression-free survival Improved quality of life
Anaplastic lymphoma kinase inhibitor (crizotinib, Xalkori) for treatment of nonsmall cell lung cancer	Patients with nonsmall cell lung cancer (NSCLC) that harbors a genetic rearrangement that leads to constitutive activation of anaplastic lymphoma kinase (ALK)	ALK is an oncogenic tyrosine kinase that was identified in gene fusions that caused activation of ALK in lymphoblastoma. Crizotinib (Xalkori®) inhibits ALK (and Met kinase) activity; in tumors that are driven by constitutive ALK activity, it may reduce tumor growth/survival. Pfizer, Inc., New York, NY FDA approved Aug 2011 for treating locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test; additional phase III trials ongoing and met primary endpoints	1st-line: combination chemotherapy (e.g., pemetrexed plus cisplatin) 2nd-line: chemotherapy(e.g., docetaxel plus pemetrexed) Erlotinib	Increased overall survival Increased progression-free survival Improved quality of life
Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of advanced hepatocellular carcinoma	Patients with advanced hepatocellular carcinoma (HCC) who have had no prior systemic chemotherapy	Patients with advanced liver 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; intended to block the 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. In clinical trials for HCC, trebananib is being administered in combination with the multikinase inhibitors sorafenib or sunitinib to patients who may have been previously treated with locoregional therapy or systemic cytokine-based therapy. Amgen, Inc., Thousand Oaks, CA Phase II trial ongoing	Sorafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of HER2-negative breast cancer	Patients with metastatic or unresectable locally recurrent HER2-negative breast cancer; no prior systemic chemotherapy	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; intended to block the 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. In a clinical trial for breast cancer treatment, trebananib is being administered in combination with the microtubule stabilizer paclitaxel plus or minus the VEGF inhibitor bevacizumab. Amgen, Inc., Thousand Oaks, CA Phase II trial ongoing	Paclitaxel monotherapy Paclitaxel plus bevacizumab	Increased overall survival Increased progression-free survival Improved quality of life
Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of metastatic colorectal cancer	Patients with metastatic colorectal cancer (CRC) who have had 1 prior chemotherapy regimen	Patients with metastatic CRC have a poor prognosis, and more effective treatment options 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 the 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. In clinical trials for metastatic CRC, trebananib is being administered in combination with the cytotoxic chemotherapy regimen FOLFIRI (folinic acid [leucovorin], 5-fluorouracil, and irinotecan). Amgen, Inc., Thousand Oaks, CA Phase II trials ongoing	FOLFIRI FOLFIRI plus cetuximab Irinotecan Irinotecan plus cetuximab	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of metastatic gastrointestinal cancer	Patients with metastatic gastric, gastroesophageal junction, or distal esophageal adenocarcinoma who have had no prior chemotherapy	Patients with metastatic gastrointestinal 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 the 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. In clinical trials for gastric cancer, trebananib is being administered in combination with cisplatin and capecitabine. Amgen, Inc., Thousand Oaks, CA Phase II trial results reported mid-2011 for this indication were negative; development status uncertain	Cisplatin plus capecitabine	Increased overall survival Increased progression-free survival Improved quality of life
Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of ovarian, peritoneal, and fallopian tube cancers	Patients with epithelial ovarian, primary peritoneal, or fallopian tube cancer that is partially platinum sensitive or resistant	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 the 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. In clinical trials for ovarian cancer, trebananib is being administered in combination with pegylated liposomal doxorubicin or paclitaxel. Amgen, Inc., Thousand Oaks, CA Phase III trials ongoing	Docetaxel Etoposide Gemcitabine Liposomal doxorubicin Paclitaxel Topotecan	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of persistent or recurrent endometrial cancer	Patients with persistent or recurrent endometrial cancer that has not responded to prior chemotherapy	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 the 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. In the trial just starting, patients are receiving trebananib intravenously on days 1, 8, 15, and 21; courses repeat every 28 days if disease has not progressed and side effects are tolerable. Amgen, Inc., Thousand Oaks, CA Phase II trial ongoing	Carboplatin Carboplatin/paclitaxel Cisplatin Cisplatin/doxorubicin Cisplatin/doxorubicin/ paclitaxel Doxorubicin or liposomal doxorubicin Hormonal therapy Ifosfamide/paclitaxel Paclitaxel	Increased overall survival Increased progression-free survival Improved quality of life
Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of recurrent glioblastoma multiforme	Patients in whom recurrent glioblastoma multiforme has been diagnosed	Patients with glioblastoma multiforme 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 the 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. In the clinical trial for glioblastoma, trebananib is being administered intravenously in combination with the VEGF inhibitor bevacizumab. Amgen, Inc., Thousand Oaks, CA Phase II trial suspended. Study being transferred to another site.	Bevacizumab monotherapy Cyclophosphamide Nitrosurea Platinum-based cytotoxic chemotherapy Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of renal cell carcinoma	Patients in whom advanced clear cell carcinoma of the kidney has been diagnosed who have note undergone prior systemic chemotherapy	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; intended to block the 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. In clinical trials for renal cell carcinoma, trebananib is being administered in combination with the VEGFR inhibitor sorafenib. Amgen, Inc., Thousand Oaks, CA Phase II trial results reported mid-2011 were negative; phase II trial sponsored by National Cancer Institute initiated in Aug 2012	Sorafenib	Increased overall survival Increased progression-free survival Improved quality of life
Antiangiogenic multikinase inhibitor 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	Doxorubicin is currently the only FDA-approved treatment for soft tissue sarcomas (excluding GIST and liposarcomas), and no consensus treatment exists for patients who have 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. GlaxoSmithKline, Middlesex, UK FDA approved Apr 2012	No consensus 2nd-line treatment for soft tissue sarcoma Placebo Sorafenib (off label) Sunitinib (off label)	Increased overall survival Increased progression-free survival Improved quality of life
Antibody-drug conjugate (ASG-5ME) for treatment of advanced pancreatic cancer	Patients in whom advanced pancreatic cancer has been diagnosed	ASG-5ME is an antibody-drug conjugate. The antibody portion is a fully human antibody specific for SLC44A4 (solute carrier antigen family member), which is expressed by a large portion of tumors of epithelial origin. This antibody is linked to a potent antineoplastic drug, monomethyl auristatin E (MMAE, vedotin), via a linker that can be cleaved by cathepsin upon cellular uptake, releasing the drug. MMAE (a tubulin polymerization inhibitor) that is too toxic for global delivery, but would be inactive in the uncleaved configuration. Agensys, Inc., an affiliate of Astellas Pharma, Inc., Tokyo, Japan Seattle Genetics, Inc., Bothell, WA Phase I trial ongoing	Chemotherapy with gemcitabine or gemcitabine and erlotinib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Antibody-drug conjugate (ASG-5ME) for treatment of 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. ASG-5ME is an antibody-drug conjugate. The antibody portion is a fully human antibody specific for SLC44A4 (solute carrier antigen family member), which is expressed by a large portion of tumors of epithelial origin. This antibody is linked to a potent antineoplastic drug, monomethyl auristatin E (MMAE, vedotin), via a linker that can be cleaved by cathepsin upon cellular uptake, releasing the drug. MMAE (a tubulin polymerization inhibitor) that is too toxic for global delivery, but would be inactive in the uncleaved configuration. Agensys, Inc., an affiliate of Astellas Pharma, Inc., Tokyo, Japan Seattle Genetics, Inc., Bothell, WA Phase I trial ongoing	Abiraterone Cabazitaxel Docetaxel Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
Antibody-drug conjugate (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 a treatment for AML 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; a variety of dosing schedules have been reported. During a recently completed phase III trial, investigators administered gemtuzumab ozogamicin in combination with a standard chemotherapy regimen using daunorubicin and cytarabine. Pfizer, Inc., New York, NY FDA approved under accelerated approval in 2000 for treating AML. Drug was withdrawn from U.S. market in 2010 after negative study results and high toxicity observed in postmarket trials. Drug remains available in Europe. European trials have shown benefit using an altered dosing scheme. Pfizer is analyzing data to determine whether to make new FDA submissions. The drug is available in the U.S. only to patients already taking it.	Standard chemotherapy with daunorubicin and cytarabine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Antibody-drug conjugate (glembatumumab vedotin) for treatment-resistant breast cancer	Patients with advanced, treatment-refractory or resistant, glycoprotein NMB (GPNMB)-expressing breast cancer	Breast cancer is responsible for about 40,000 deaths in the U.S. each year. Therapies that can improve survival rates and/or quality of life for these patients are needed. 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. Celldex Therapeutics, Inc., Needham, MA Phase IIb trial complete; FDA granted fast track status for treating treatment-resistant or refractory breast cancer	Albumin-bound paclitaxel Capecitabine Docetaxel Doxorubicin Eribulin Gemcitabine Ixabepilone Liposomal doxorubicin Paclitaxel Vinorelbine	Increased overall survival Increased progression-free survival Improved quality of life
Antibody-drug conjugate (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. Pfizer, Inc., New York, NY Phase III trial registered, but not yet recruiting	Various combinations of the following chemotherapy agents: Anthracyclines Asparaginase Cyclophosphamide Cytarabine (ara-C) Epipodophyllotoxins Vincristine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Antibody-drug conjugate (inotuzumab ozogamicin) for treatment-refractory or recurrent non-Hodgkin's lymphoma	Patients with treatment-resistant or recurrent CD20- and CD22-positive non-Hodgkin's lymphoma (NHL) who are not candidates for high-dose chemotherapy	With current treatment options, patients with recurrent or treatment-resistant NHL have a poor prognosis. Only 5% to 10% of patients are alive 2 years after diagnosis. Cases of NHL typically express B-cell cell surface markers such as CD20 and CD22. Although an anti-CD20 antibody (rituximab) has been used in treating NHL for several years, an effective treatment targeting CD22 is not yet available. Inotuzumab ozogamicin is a novel antibody-drug conjugate that couples a CD22-specific antibody to a highly toxic chemotherapeutic agent. In clinical trials, inotuzumab ozogamicin (1.8 mg/m^2 by intravenous infusion once every 4 weeks) is being administered as an adjunct to treatment with rituximab. Pfizer, Inc., New York, NY Phase III trial ongoing; also being investigated in Phase III trial for Acute Lymphoblastic Leukemia.	Combination chemotherapies such as: Cyclophosphamide/ etoposide/ prednisone/ procarbazine plus or minus rituximab Cyclophosphamide/ etoposide/vincristine/ prednisone plus or minus rituximab Etoposide/prednisone/ vincristine/ cyclophosphamide/ doxorubicin plus or minus rituximab Gemcitabine/ dexamethasone/ cisplatin plus or minus rituximab Lenalidomide plus or minus rituximab	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti-CS1 monoclonal antibody (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 was recently identified as a glycoprotein expressed preferentially on multiple myeloma cells. Elotuzumab is a humanized, monoclonal antibody specific for CS1 that is purported to have an anticancer effect through antibody-dependent cellular cytotoxicity. In clinical trials, elotuzumab is being administered as an adjunct to conventional therapy with a combination of lenalidomide and dexamethasone. Bristol-Myers Squibb, New York, NY Phase III trials ongoing	For stem cell transplant eligible patients, 1st-line therapy such as: Bortezomib/ dexamethasone Cyclophosphamide/ dexamethasone For patients ineligible for stem cell transplant, 1st-line therapy such as: Bortezomib/ dexamethasone Lenalidomide/low-dose dexamethasone Melphalan/ prednisone plus bortezomib	Increased overall survival Increased progression-free survival Improved quality of life
Anti-CTLA-4 monoclonal antibody (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	Only about 25% of patients with advanced NSCLC respond to standard 1st-line therapies such as carboplatin/paclitaxel. 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). As 1st-line NSCLC treatment in trials, ipilimumab is being administered in combination with carboplatin and paclitaxel. Bristol Myers Squibb, New York, NY Phase III trial ongoing	Bevacizumab Carboplatin/ paclitaxel Carboplatin/ pemetrexed Cisplatin/pemetrexed Erlotinib Crizotinib	Increased overall survival Increased progression-free survival Improved quality of life
Anti-CTLA-4 monoclonal antibody (ipilimumab, Yervoy) for treatment of metastatic hormone-refractory prostate cancer	Patients in whom metastatic, chemotherapy-naïve or docetaxel-treated 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). Bristol Myers Squibb, New York, NY Phase III trials ongoing	Abiraterone Cabazitaxel Docetaxel Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti-CTLA-4 monoclonal antibody (ipilimumab, Yervoy) for treatment of metastatic melanoma	Patients in whom metastatic melanoma has been diagnosed	Few effective treatments exist for metastatic melanoma, particularly for patients in whom *BRAF* mutation-negative melanoma has been diagnosed. 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). Bristol Myers Squibb, New York, NY FDA approved Mar 2011	Dacarbazine High-dose interleukin-2 Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life
Anti-DLL4 monoclonal antibody (demcizumab, OMP-21M18) for treatment of cancer	Patients with treatment-resistant, advanced solid tumors	Although many chemotherapeutic approaches are available for advanced solid tumors, treatment is rarely curative, and the cancer typically develops resistance to therapy and progresses. Demcizumab is a monoclonal antibody specific for delta-like ligand 4 (DLL4), a protein that has been implicated in the maintenance of cancer stem cells and promotion of angiogenesis. By inhibiting DLL4, demcizumab is intended to both target the difficult-to-treat population of tumor-initiating cancer stem cells in solid tumors and reduce the blood supply to solid tumors. OncoMed Pharmaceuticals, Inc., Redwood City, CA Phase I trials ongoing	Large variety of anti-cancer chemotherapies	Increased overall survival Increased progression-free survival Improved quality of life
Anti-endoglin monoclonal antibody (TRC105) for treatment of solid tumors	Patients in whom a solid tumor (e.g., bladder, breast, liver, ovarian, prostate) has been diagnosed	Endoglin is a protein required for tumor blood vessel development (angiogenesis). Therapies specifically targeting endoglin currently are not available. TRC105 is a monoclonal antibody under study that is specific for endoglin and has the potential to inhibit tumor neovascularization. In clinical trials, TRC105 is administered as a weekly intravenous infusion. TRACON Pharmaceuticals, San Diego, CA Phase II trials ongoing	Wide range of anti-cancer therapies	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti-ErbB3 monoclonal antibody (MM-121) for treatment of ER- or PR-positive, HER2-negative breast cancer	Patients in whom estrogen receptor (ER)- and/or progesterone receptor (PR)-positive, HER2-negative breast cancer has been diagnosed	For patients whose breast cancer progresses after treatment with 1st-line antiestrogen therapy, followup antiaromatase therapy can delay progression in some but not all patients. MM-121 is a monoclonal antibody specific for the ErbB3 receptor tyrosine kinase. Like its orthologous receptor tyrosine kinases epidermal growth factor receptor and HER2, ErbB3 is capable of activating signaling pathways that control cell growth and proliferation; therefore, its inhibition has the potential to limit cancer growth and survival. In the 2nd-line setting, MM-121 is being administered in combination with the steroidal aromatase inactivator exemestane. In the neoadjuvant setting, MM-121 is being administered in combination with the taxane paclitaxel. Merrimack Pharmaceuticals, Inc., Cambridge, MA Phase II trials ongoing	2nd-line setting: Exemestane Non-steroidal aromatase inhibitors: anastrozole, letrozole Everolimus Fulvestrant Tamoxifen Toremifene Neoadjuvant setting: paclitaxel	Increased overall survival Increased progression-free survival Improved quality of life
Anti-ErbB3 monoclonal antibody (MM-121) for treatment of lung cancer	Patients in whom metastatic nonsmall cell lung cancer (NSCLC) has been diagnosed	Although anti-EGFR (epidermal growth factor receptor) therapy has improved outcomes in EGFR-positive NSCLC, the cancer becomes treatment resistant in many patients. One demonstrated mechanism of resistance to anti-EGFR therapy is activation of a related receptor tyrosine kinase ErbB3; therefore, concomitant targeting of EGFR and ErbB3 may improve outcomes. MM-121 is a monoclonal antibody inhibitor of ErbB3 that is being tested in combination with the EGFR inhibitor erlotinib. Merrimack Pharmaceuticals, Inc., Cambridge, MA, in collaboration with Sanofi, Paris, France Phase II trial ongoing	Erlotinib monotherapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Antifolate receptor monoclonal antibody (farletuzumab) for treatment of ovarian cancer	Patients with recurrent ovarian cancer that is platinum-sensitive, platinum-resistant, or platinum-refractory	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 is purported to lead 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 of body weight. In platinum-sensitive disease, farletuzumab is being tested in combination with carboplatin/taxane doublet therapy. In platinum-resistant/refractory disease, farletuzumab is being tested in combination with taxane monotherapy. Morphotek, Exton, PA, a subsidiary of Eisai Co., Ltd., Tokyo, Japan Phase III trial in platinum-resistant disease terminated in Dec 2011 after determination by Independent Data Monitoring Committee that trial was unlikely to meet primary endpoint; phase III trial in platinum-sensitive disease ongoing	Platinum-sensitive ovarian cancer: Carboplatin plus paclitaxel Carboplatin plus docetaxel or pegylated liposomal doxorubicin or gemcitabine or topotecan Cisplatin plus gemcitabine Platinum-refractory ovarian cancer: Docetaxel Etoposide Gemcitabine Paclitaxel Pegylated liposomal doxorubicin Topotecan	Increased overall survival Increased progression-free survival Improved quality of life
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 is purported to target 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. United Therapeutics Corp., Silver Spring, MD, in collaboration with the National Cancer Institute, Bethesda, MD Phase III trial complete; company lists phase III trials as ongoing but status not updated in National Clinical Trials database since Aug 2011; orphan drug designation in U.S. and European Union	Isotretinoin	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Antigen-specific cancer immunotherapeutic (GSK2132231A) for advanced melanoma	Patients with stage IIIB or IIIC cutaneous melanoma that expresses melanoma antigenic epitope (MAGE)-A3 antigen who have macroscopic lymph node involvement suitable for surgery	Patients with stage III 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. GSK2132231A is being administered as a course of 13 injections over 27 months in a multicenter, international phase III trial of 1349 patients. GlaxoSmithKline, London, UK Phase III trial ongoing	Granulocyte-macrophage colony stimulating factor Interferon-alpha Interleukin-2 Radiation therapy	Increased overall survival Increased progression-free survival Improved quality of life
Anti-MET monoclonal antibody (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 following 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) blocks ligand-mediated activation of the MET receptor tyrosine kinase and is being studied in combination with the EGFR inhibitor erlotinib in treating NSCLC. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trial ongoing	Crizotinib Docetaxel Erlotinib monotherapy Pemetrexed Tivantinib (c-Met kinase inhibitor in development)	Increased overall survival Increased progression-free survival Improved quality of life
Anti-PD-1 monoclonal antibody (CT-011) for treatment of diffuse large B-cell lymphoma	Patients with diffuse large B-cell lymphoma (DLBCL) who have undergone an autologous stem cell transplantation	Although high-dose chemotherapy followed by autologous stem cell transplant is curative in a subset of patients with DLBCL, a significant proportion of patients have recurrent disease following this treatment. CT-011 is a monoclonal antibody specific for PD-1, which is a negative regulator of the immune response that may be involved in immune tolerance of various cancers. CureTech, Ltd., Yavne, Israel Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, is investing in the research Phase II trial complete; CT-011 is also being studied for treating colorectal cancer and melanoma	No consensus treatment option for patients post-autologous stem cell transplantation	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti-PD-1 monoclonal antibody (MDX-1106) for treatment of melanoma	Patients in whom advanced (unresectable stage III or stage IV) melanoma has been diagnosed	Clinical trials with the immune checkpoint inhibitor ipilimumab have demonstrated the potential of immune therapies in melanoma; however, ipilimumab's utility is limited by its relatively low response rate, and the prognosis for patients with advanced melanoma remains poor. MDX-1106 is a fully human monoclonal antibody that targets an immune-checkpoint pathway distinct from that of ipilimumab. MDX-1106 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; blocking its activity may enhance the body's immune response, potentially overcoming immune tolerance to melanoma. In clinical trials, MDX-1106 is administered intravenously, once every 2 weeks. Bristol-Myers Squibb, New York, NY Phase II trials ongoing	Dacarbazine Ipilimumab Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life
Anti-PD-1-L1 monoclonal antibody (BMS-936559) for treatment of solid tumors	Patients in whom advanced or metastatic melanoma, nonsmall cell lung cancer, or renal cell carcinoma has been diagnosed	Advanced cancers are generally incurable, and treatments with the potential to induce long-term remission are needed. A hallmark of cancer is its ability to avoid destruction by the body's immune system by establishing immune tolerance. Immune tolerance may, in part, be established through the activity of the PD-1 pathway, which has been shown to be involved in downregulating T cell activity in cases of chronic antigen exposure (as is the case in patients with cancer). Additionally, some cancers may coopt the PD-1 pathway through expression of ligand(s) for the PD-1 receptor (i.e., PD-1-L1, PD-1-L2), thereby limiting T-cell activation within the tumor microenvironment. Inhibiting the PD-1 pathway may promote an immune response against certain tumors. BMS-936559 is a monoclonal antibody specific for the PD-1-L1 ligand. The antibody binds to PD-1-L1 and purportedly prevents it from binding to PD-1 receptors and activating the PD-1 pathway. In clinical trials, BMS-936559 was administered intravenously, once every 14 days, for up to 48 doses. Bristol-Myers Squibb, New York, NY Phase I trial complete	Chemotherapy Immunotherapy Radiation therapy Surgery	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti-placental growth factor monoclonal antibody (TB-403) for treatment of glioblastoma	Patients with recurrent glioblastoma multiforme	Current antiangiogenic antibodies (e.g., bevacizumab) are directed against vascular endothelial growth factor (VEGF); however, other angiogenic signaling growth factors may be upregulated in cancers and may play a role in resistance to anti-VEGF treatment. One such angiogenic factor is placental growth factor (PGF). TB-403 is a humanized monoclonal antibody specific for PGF. In a clinical trial, it is being administered intravenously in combination with the approved anti-VEGF antibody bevacizumab. BioInvent International AB, Lund, Sweden in collaboration with ThromboGenics Ltd, Dublin, Ireland Phase I trial complete; initial clinical development was being carried out by Roche; however, BioInvent and ThromboGenics regained development rights in Jun 2012	Bevacizumab monotherapy Temozolomide Tumor-treating fields therapy	Increased overall survival Increased progression-free survival Improved quality of life
Anti-prostate-specific membrane antigen antibody drug conjugate for treatment of metastatic castration-resistant prostate cancer	Patients with metastatic castration-resistant prostate cancer (CRPC) that has progressed on treatment with docetaxel	Current median overall survival for patients with docetaxel-resistant CRPC is only about 15 months. Prostate-specific membrane antigen (PSMA) is an antigen expressed on the surface of prostate cancer cells. PSMA-antibody drug conjugate is a conjugate between a PSMA-specific antibody and a highly cytotoxic drug (monomethyl auristatin E); the linker connecting the drug to the antibody ensures that the drug is only released upon endocytosis into a target cell, which is mediated by the binding of the antibody portion of the drug to PSMA. Progenics Pharmaceuticals, Inc., Tarrytown, NY Phase I trials ongoing	Abiraterone Cabazitaxel Enzalutamide	Increased overall survival Increased progression-free survival Improved quality of life (e.g., palliation of pain associated with metastases)
Anti-telomerase therapeutic cancer vaccine (TeloB-Vax) for treatment of prostate cancer	Patients in whom advanced prostate cancer has been diagnosed	Patients with advanced prostate cancer have a poor prognosis and few treatment options. TeloB-Vax is a cancer vaccine that is purported to work by inducing a T-cell response against human telomerase reverse transcriptase (hTRT), an enzyme expressed at high levels by many cancers and responsible for allowing cancer cells to continually divide without undergoing senescence. An hTRT-encoding plasmid is transduced into patient-derived B cells, which express the antigen for up to 5 days, potentially eliciting an immune response. Adamis Pharmaceuticals Corp., San Diego, CA Phase I trial completed	Abiraterone Docetaxel Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Antitumor endothelial marker-1 monoclonal antibody (MORAb-004) for treatment of metastatic colorectal cancer	Patients in whom treatment-refractory metastatic colorectal cancer (CRC) has been diagnosed	Patients with chemotherapy-refractory CRC have few treatment options and a poor prognosis. MORAb-004 is a humanized monoclonal antibody specific to tumor endothelial marker-1 (TEM-1), which is a cell-surface glycoprotein expressed on pericytes, tumor stromal cells, and some tumor cells. Blocking TEM-1 function by MORAb-004 has the potential to inhibit tumor growth and metastasis. In clinical trials for CRC, MORAb-004 is administered intravenously, at a dose of 8 mg/kg of body weight. Morphotek, Inc., Exton, PA Phase II trial ongoing	Regorafenib Best supportive care	Increased overall survival Increased progression-free survival Improved quality of life
Anti-VEGFR2 monoclonal antibody (ramucirumab) for treatment of hepatocellular carcinoma	Patients with hepatocellular carcinoma (HCC) whose disease is Barcelona Clinic Liver Cancer stage C or stage B and not amenable to locoregional therapy	No consensus exists on treatment for HCC that has progressed after treatment with sorafenib, and these patients have a poor prognosis. Ramucirumab is a novel monoclonal antibody that binds to the extracellular domain of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2), which is a receptor tyrosine kinase that acts as a central mediator of tumor angiogenesis. Currently 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 the inhibition of VEGF pathway signaling. In clinical trials for HCC, ramucirumab is administered intravenously, 8 mg/kg of body weight, once every 2 weeks. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing	No consensus on treatment for this patient population	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti-VEGFR2 monoclonal antibody (ramucirumab) for treatment of metastatic breast cancer	Patients with metastatic or non-resectable locally advanced HER2-negative breast cancer	Patients with metastatic or non-resectable 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 (VEFGR2), 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 the inhibition of VEGF pathway signaling. In clinical trials for breast cancer, ramucirumab is administered intravenously, 10 mg/kg of body weight, once every 3 weeks. Treatment is intended to be used in the 1st-line setting for metastatic or nonresectable disease. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trial ongoing	Taxane-based (e.g., docetaxel, paclitaxel) therapy with or without capecitabine or gemcitabine or bevacizumab or anthracycline-based therapy	Increased overall survival Increased progression-free survival Improved quality of life
Anti-VEGFR2 monoclonal antibody (ramucirumab) 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 the inhibition of VEGF pathway signaling. In clinical trials for gastric cancer, ramucirumab is intravenously administered at a dose of 8 mg/kg of body weight once every 2 weeks as an adjunct to the standard 2nd-line FOLFIRI (folinic acid [leucovorin], 5-fluorouracil, and irinotecan) regimen. Treatment is intended for patients whose disease has progressed after standard 1st-line chemotherapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trial ongoing	Various FOLFIRI-based therapies with or without cetuximab or panitumumab	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti-VEGFR2 monoclonal antibody (ramucirumab) for treatment of metastatic gastric cancer	Patients in whom metastatic gastric cancer has been diagnosed	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 the inhibition of VEGF pathway signaling. In clinical trials for gastric cancer, ramucirumab is intravenously administered at a dose of 8 mg/kg of body weight, once every 2 weeks. Treatment is intended for disease that has progressed after standard 1st-line platinum-based or fluoropyrimidine-based regimens. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing	Various irinotecan-based single and combination therapies Taxane (e.g., docetaxel, paclitaxel) monotherapy	Increased overall survival Increased progression-free survival Improved quality of life
Anti-VEGFR2 monoclonal antibody (ramucirumab) 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 the inhibition of VEGF pathway signaling. In clinical trials for NSCLC, ramucirumab is intravenously administered at a dose of 10 mg/kg of body weight, once every 3 weeks as an adjunct to standard 2nd-line chemotherapy with docetaxel. Treatment is intended for patients whose disease has progressed following 1 round of platinum-based chemotherapy. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing	Crizotinib Docetaxel Erlotinib Pemetrexed	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Assay (Progensa PCA3) 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; 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." Gen-Probe, Inc., San Diego, CA FDA approved Feb 2012; Conformité Européene (CE) marked in 2006	Digital rectal examination alone Prostate-specific antigen blood test screening	Increased sensitivity and specificity Improved predictive values Avoided unnecessary followup (i.e., biopsy)
Aurora A kinase inhibitor (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. Inhibition of aurora A has been shown to cause mitotic errors, potentially leading to aneuploidy, apoptosis, and/or cellular senescence. Alisertib is administered orally, 50 mg, twice daily. Millennium Pharmaceuticals, Inc., subsidiary of Takeda Pharmaceutical Co., Ltd., Osaka, Japan Phase III trials ongoing	Alemtuzumab Brentuximab vedotin (ALCL subtype only) Bortezomib Cyclosporine (angioimmunoblastic T-cell lymphoma subtype only) Denileukin diftitox Gemcitabine Pralatrexate Radiation therapy Romidepsin	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous dendritic cell vaccine (BPX-101) for treatment of metastatic, castration-resistant prostate cancer	Patients in whom metastatic castration-resistant prostate cancer (CRPC) has been diagnosed	Median overall survival for patients with CRPC is only about 18 months. BPX-101 is a novel autologous dendritic-cell therapeutic cancer vaccine that consists of 2 parts: (1) an antigen consisting of prostate-specific membrane antigen (PSMA), and (2) transmembrane proteins encoding a chemical induction of dimerization (CID) construct that allows activation of the CD40 pathway by addition of a chemical stimulator (AP1903). Dendritic cells (DCs) are isolated from the patient and transduced with both PSMA antigen and CID construct. On day 1 the DCs are injected into the patient and purportedly migrate to lymph nodes. On day 2 the AP1903 activator is added to activate the CD40 pathway in lymph-node resident DCs. CD40 activity potentiates the generation of cytotoxic T cells and memory B cells, potentially leading to a more robust immune response. Bellicum Pharmaceuticals, Inc., Houston, TX Phase I/II trial completed; company announced receiving funding for phase II trial in Mar 2012, but trial has not yet begun	Abiraterone Cabazitaxel Docetaxel Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
Autologous vascularized lymph node transfer for mastectomy-associated lymphedema	Patients who have undergone mastectomy	During mastectomy, lymph nodes under the arm closest to the affected breast are removed, which often leads to chronic swelling and soreness in the arm (lymphedema); lymphedema develops within 5 years in up to 40% of women who have undergone breast cancer surgery in the U.S.; it is considered generally incurable and can severely restrict activity. Autologous vascularized lymph node transfer is a microsurgical procedure to treat lymphedema; the excised lymph nodes are replaced with healthy nodes transplanted from the femoral region of the patient. The transplanted lymph nodes connect with lymph vessels improving waste filtration and drainage in the arm. Prior to implantation of the nodes, scar tissue may be excised to remove blockage of lymph vessels. Service de Chirurgie Thoracique, Hôpital Européen Georges Pompidou, Paris, France Procedure appears to be done rarely in U.S.; randomized trial beginning in France	Compression garments Physical therapy	Ability to stop physiotherapy Decreased, or resolved lymphedema assessed by isotopic lymphangiography Improved skin elasticity Improved mobility Resolution of pain

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Automated breast ultrasound for breast cancer screening of patients with 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. U-Systems, Inc., Sunnyvale, CA FDA cleared for diagnostic use; premarket approval application submitted to FDA for screening indication. In Apr 2012, FDA's Radiological Devices Panel of the Medical Devices Advisory Committee recommended approval of the system	Screening mammography alone Screening MRI imaging	Increased breast cancer sensitivity and specificity Improved positive predictive and negative values for breast cancer
Axitinib (Inlyta) for treatment-resistant advanced renal cell carcinoma	Patients previously treated for metastatic renal cell carcinoma (RCC)	Axitinib is an oral and selective inhibitor of vascular endothelial growth factor (VEGF) receptor 1 (VEGFR1), VEGFR2 and VEGFR3, which appear to have roles in tumor growth, vascular angiogenesis, and metastatic progression of cancer (the spread of tumors). Pfizer, Inc., New York, NY FDA approved Jan 2012 for RCC that has not responded to prior treatment	Everolimus Sorafenib Temsirolimus Tivozanib (in development)	Increased overall survival Increased progression-free survival Improved quality of life
Bavituximab for treatment of advanced breast cancer	Patients in whom advanced breast cancer has been diagnosed	Breast cancer remains a leading cause of cancer deaths in women, suggesting the need for new therapies with novel mechanisms of action. Bavituximab is a monoclonal antibody directed against phosphatidylserine (PS) exposed on the surface of cancer cells; PS expression is believed to be immunosuppressive; bavituximab is thought to bind to PS and block the immunosuppressive signals to improve immune responses to the tumor; also, as chemotherapy increases the exposure of PS on tumor blood vessels, bavituximab combined with chemotherapy may hold potential for synergistic therapeutic effects. Administered intravenously, 6 mg/kg of body weight for up to six 28-day cycles, in combination therapy with carboplatin and paclitaxel. Peregrine Pharmaceuticals Inc., Tustin, CA Phase II trials completed; investigator-sponsored phase I trial ongoing	Docetaxel Paclitaxel Paclitaxel plus carboplatin	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bavituximab for treatment of advanced nonsmall cell lung cancer	Patients in whom locally advanced or metastatic nonsmall cell lung cancer (NSCLC) has been diagnosed	Patients with advanced NSCLC have a poor prognosis with few therapeutic options. Bavituximab is a monoclonal antibody directed against phosphatidylserine (PS) exposed on the surface of cancer cells; PS expression is believed to be immunosuppressive; bavituximab is thought to bind to PS and block the immunosuppressive signals to improve immune responses to the tumor; also, as chemotherapy increases the exposure of PS on tumor blood vessels, bavituximab combined with chemotherapy may hold potential for synergistic therapeutic effects. Administered intravenously 3 mg/kg of body weight, weekly, in combination with carboplatin and paclitaxel in trials for 1st-line treatment of NSCLC and in combination with docetaxel in the 2nd-line treatment of NSCLC. Peregrine Pharmaceuticals Inc., Tustin, CA Phase II trials ongoing; in Sept 2012, positive data were reported from the phase II trial of use in the second-line setting; however, a subsequent company press release stated that these data should be disregarded due to discrepancies identified in treatment group coding	Carboplatin Crizotinib Docetaxel Erlotinib Paclitaxel Pemetrexed	Increased overall survival Increased progression-free survival Improved quality of life
Bavituximab for treatment of advanced pancreatic cancer	Patients in whom advanced pancreatic cancer has been diagnosed	Advanced pancreatic cancer has a poor prognosis with few therapeutic options. Bavituximab is a monoclonal antibody directed against phosphatidylserine (PS) exposed on the surface of cancer cells; PS expression is believed to be immunosuppressive; bavituximab is thought to bind to PS and block the immunosuppressive signals to improve immune responses to the tumor; also, as chemotherapy increases the exposure of PS on tumor blood vessels, bavituximab combined with chemotherapy may hold potential for synergistic therapeutic effects. Administered 3 mg/kg of body weight, weekly, in combination with gemcitabine in trials for pancreatic cancer. Peregrine Pharmaceuticals, Inc., Tustin, CA Phase II trials ongoing	Gemcitabine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bavituximab for treatment of hepatocellular carcinoma	Patients in whom hepatocellular carcinoma has been diagnosed	Patients with advanced liver cancer have a poor prognosis with few therapeutic options; new therapies with novel mechanisms of action are needed. Bavituximab is a monoclonal antibody directed against phosphatidylserine (PS) exposed on the surface of cancer cells; PS expression is believed to be immunosuppressive; bavituximab is thought to bind to PS and block the immunosuppressive signals to improve immune responses to the tumor; also, as chemotherapy increases the exposure of PS on tumor blood vessels, bavituximab combined with chemotherapy may hold potential for synergistic therapeutic effects. Administered intravenously in various dose regimens of 0.3–6.0 mg/kg of body weight, weekly for 8 or 12 weeks in clinical trials as a monotherapy and combination therapy with sorafenib. Peregrine Pharmaceuticals, Inc., Tustin, CA Phase I/II trials ongoing	Doxorubicin Sorafenib	Increased overall survival Increased progression-free survival Improved quality of life
B-cell lymphoma 2 family inhibitor (navitoclax) for treatment of chronic lymphocytic leukemia	Patients in whom chronic lymphocytic leukemia (CLL) has been diagnosed; may either be treatment naïve or have relapsed or refractory disease	Patients in whom CLL has been diagnosed often exhibit disease control with current therapies; however, these therapies are not curative, and in many patients, the disease will eventually progress. Inhibition of apoptosis is a hallmark of CLL as well as other cancers; the prevention of apoptosis may in part be due to the activity of a family of proteins related to B-cell lymphoma 2 (Bcl-2), which are often overexpressed in cancer. Navitoclax (ABT-263) is a small-molecule inhibitor of multiple Bcl-2 family members (Bcl-2, Bcl-xl, Bcl-w); it is being tested as a 1st-line therapy for CLL in combination with the anti-CD20 monoclonal antibody rituximab. Administered orally. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland, in collaboration with Abbott Laboratories, Abbott Park, IL Phase II trial ongoing	Various chemotherapy regimens such as: Alemtuzumab Bendamustine and rituximab Chlorambucil with or without prednisone Cladribine Cyclophosphamide and prednisone with or without rituximab Fludarabine, cyclophosphamide, and rituximab Rituximab	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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; new treatment options are needed. Bevacizumab (Avastin®) is a monoclonal antibody on the market for several other indications; intended to bind vascular endothelial growth factor (VEGF) and prevent 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. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Multiple phase III trials ongoing; preliminary data has been reported from 4 phase III trials	Various chemotherapy regimens, including: Paclitaxel plus carboplatin Gemcitabine plus carboplatin Pegylated liposomal doxorubicin Topotecan Paclitaxel monotherapy	Increased overall survival Increased progression-free survival Improved quality of life
Biophotonic cervical screening system (LuViva Advanced Cervical Scan) for detection of cervical disease in adolescent females	Females aged 16–21 years who are sexually active	Luviva™ consists of a base unit and a single-patient-use calibration disposable scanner; uses biophotonic technology (hyperspectral imaging spectroscopy) to identify biochemical and morphologic changes at the cellular level associated with cervical cancer and precancer painless and minimally invasive. Device gives screening results immediately. Guided Therapeutics, Inc., Norcross, GA Premarket approval (PMA) application under FDA review; in Nov 2011, FDA stated that no FDA panel review was necessary prior to making a decision; in Jan 2012, company received a non-approvable letter from FDA regarding the PMA; company continues to pursue approval and submitted formal response to FDA May 2012	Biopsy Colposcopy Human papillomavirus DNA test Pap test	Earlier detection of cervical disease Improved screening and followup adherence Reduced unnecessary referrals to biopsy and colposcopy

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bispecific T-cell-engager (BiTE) anti-CD19 antibody (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-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) specific for CD19, an antigen expressed by the immature lymphocytes expanded in ALL, and (2) specific for CD3 a molecule expressed on the surface of cytotoxic T cells; blinatumomab is purported to lead to tumor apoptosis by bridging an interaction between tumor cells and T cells. Micromet, Inc., Rockville, MD, acquired in Jan 2012 by Amgen, Thousand Oaks, CA Phase II trials ongoing; results released May 2012; FDA granted orphan drug status	Relapsed/refractory ALL: Anthracyclines (doxorubicin, daunorubicin), Asparaginase Cyclophosphamide cytarabine (ara-C) Epipodophyllotoxins (etoposide, teniposide) Vincristine Minimal residual disease–positive ALL: No current standard of care	Increased overall survival Increased progression-free survival Improved quality of life
Blocking radiation exposure of limb-draining lymph nodes for prevention of lymphedema	Patients with early-stage breast cancer who are undergoing postsurgical adjuvant radiation therapy	Lymphedema is a chronic condition that, depending on the treatment regimen, affects between 5% and 50% of women who have undergone primary treatment for breast cancer. Whole breast irradiation, which may also target lymph nodes in the axilla, is a significant risk factor for developing lymphedema. This increased risk might be mitigated by selectively blocking from exposure to radiation critical lymph nodes that drain the limb. In a recent clinical trial, limb-draining lymph nodes were identified by single-photon emission computed tomography and computed tomography and an intensity-modulated radiation therapy plan was designed to limit exposure of these nodes; in this trial, patients were limited to those with early stage breast cancer with negative sentinel lymph node biopsy or only micrometastases to sentinel lymph nodes. Mayo Clinic, Rochester, MN Unphased small trial ongoing	Standard external beam radiation therapy	Decreased rate of lymphedema Decreased radiation dose to critical lymph nodes Equivalent cancer-related progression-free survival Equivalent cancer-related overall survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
BLP25 liposome therapeutic vaccine (Stimuvax) for advanced nonsmall cell lung cancer	Patients in whom stage III unresectable nonsmall cell lung cancer (NSCLC) has been diagnosed and who have undergone primary chemoradiotherapy treatment	Patients with advanced NSCLC have a poor prognosis and the disease often responds poorly to current chemotherapeutic regimens; new treatment strategies with novel mechanisms of action are needed. Stimuvax® is a therapeutic vaccine composed of a 25-amino acid sequence of the mucin-1 (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 Stimuvax); the vaccine is then administered at 6-week intervals beginning at week 14 until documented disease progression. Merck KGaA, Darmstadt, Germany Oncothyreon, Inc., Seattle, WA Phase III trials restarted in 2011 after being halted for about a year	No established maintenance therapy in the post-chemoradiotherapy setting	Increased overall survival Increased progression-free survival Improved quality of life
BRAF kinase inhibitor (dabrafenib) for treatment of metastatic melanoma	Patients in whom metastatic melanoma characterized as having activated *BRAF* mutations has been diagnosed	Dabrafenib (GSK2118436) is an activated BRAF kinase inhibitor. The developer describes it as “a highly potent and selective adenosine triphosphate competitive BRAF inhibitor with more than 100-fold selectivity for mutant (mut) BRAF. It displays dose-dependent inhibition of MEK and extracellular signal-regulated kinase phosphorylation in mut BRAF cell lines and tumor regression in xenograft models.” GlaxoSmithKline, Middlesex, UK Positive results reported in Jun 2012 for phase III trial of dabrafenib as a monotherapy; earlier phase trials ongoing in combination with the MEK inhibitor trametinib; new drug application submitted to FDA in Aug 2012	High dose interleukin-2 Dacarbazine Ipilimumab Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
BRAF kinase inhibitor (vemurafenib, Zelboraf) for treatment of metastatic melanoma	Patients in whom metastatic melanoma with activated *BRAF* mutations has been diagnosed	Roughly half of all melanomas are caused by the V600E mutation in the gene that encodes BRAF, a protein kinase that activates the extracellular signal-regulated kinase (ERK) signaling pathway. Vemurafenib (Zelboraf®) is a small-molecule, orally administered BRAF serine/threonine kinase inhibitor. The V600E mutation causes dysregulation of BRAF activity and over stimulation of ERK. This results in spontaneous generation of melanoma and the proliferation of malignant tissue. Vemurafenib a potent inhibitor of BRAF, shuts down the ERK signaling pathway and blocks proliferation of malignant cells carrying the $BRAF^{V600E}$ mutation. It has no effect on tumor cells that lack the V600E mutation. F. Hoffmann-La Roche Ltd., Basel, Switzerland Roche Molecular Systems, Inc., Pleasanton, CA First BRAF inhibitor to be FDA approved; approved Aug 2011 for treating unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by the test approved at the same time: cobas® 4800 $BRAF^{V600}$ mutation automated molecular assay	High dose interleukin-2 Dacarbazine Ipilimumab Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life
Brentuximab vedotin (Adcetris) for treatment of recurrent/refractory anaplastic large cell lymphoma	Patients in whom recurrent and/or chemotherapy-refractory systemic CD30-positive anaplastic large cell lymphoma (ALCL) has been diagnosed	Brentuximab vedotin (Adcetris™, SGN-35 or cAC10-vcMMAE) is a monoclonal antibody-drug conjugate; monoclonal antibody portion of the drug recognizes the CD30 antigen present on some ALCLs; drug portion is the highly cytotoxic monomethyl auristatin E, which inhibits mitosis by blocking tubulin polymerization. For 2 indications: (1) treating patients with Hodgkin's lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, and (2) treating patients with systemic ALCL after failure of at least 1 prior multi-agent chemotherapy regimen. Seattle Genetics, Inc., Bothell, WA FDA approved Aug 2011, for treating systemic ALCL after failure of at least 1 prior multi-agent chemotherapy regimen	Allogeneic stem cell transplantation ASCT	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Brentuximab vedotin (Adcetris) for treatment of recurrent/refractory Hodgkin's lymphoma	Patients in whom recurrent and or radiation/chemo-therapy-refractory Hodgkin's lymphoma has been diagnosed	Hodgkin's lymphoma is a CD30-positive hematologic malignancy with limited salvage therapy options. Brentuximab vedotin (Adcetris, SGN-35 or cAC10-vcMMAE) is a monoclonal antibody-drug conjugate. Seattle Genetics, Inc., Bothell, WA FDA approved Aug 2011, for treating patients with Hodgkin's lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not ASCT candidates. Phase III trial in patients at high risk of relapse post-ASCT ongoing; phase I trial in patients with newly diagnosed disease ongoing	Standard of care	Increased overall survival Increased progression-free survival Improved quality of life
Brussels sprout extract (sulforaphane) for treatment of prostate cancer	Patients with recurrent prostate cancer after radical prostatectomy or definitive radiation therapy	Although hormone therapy for recurrent prostate cancer is known to extend survival in some patients, the treatment is rarely curative, and the disease typically progresses to castration-resistant prostate cancer over time. Sulforaphane, a chemical found in various vegetables, has been purported to have anticancer activity. One potential mechanism of action ascribed to sulforaphane is histone deacetylase activity, which can disrupt chromatin structure and may cause DNA repair inhibition or modification of cell cycle proteins that could impact quickly dividing cells. Sulforaphane is administered as an oral tablet. Oregon Health Sciences University, Portland Phase II trial ongoing	Androgen deprivation therapy Salvage radiation therapy Salvage surgery Watchful waiting	Increased overall survival Increased progression-free survival Improved quality of life
Bruton tyrosine kinase inhibitor (PCI-32765) for treatment of B-cell non-Hodgkin's lymphomas	Patients in whom B-cell non-Hodgkin's lymphoma (chronic lymphocytic leukemia/small lymphocytic lymphoma, diffuse large B-cell lymphoma, or mantle cell lymphoma) has been diagnosed	Patients with treatment-resistant B-cell malignancy have a poor prognosis and few treatment options. Many B-cell malignancies depend on B cell receptor (BCR) signaling for survival. PCI-32765 is a novel kinase inhibitor that is specific for the Bruton tyrosine kinase, which is a signaling kinase essential for transduction of the BCR signaling pathway. PCI-32765 is administered orally, once daily. Pharmacyclics, Inc., Sunnyvale, CA Phase II trials ongoing; interim results released Jun 2012	Various cytotoxic chemotherapy regimens combined with various immunotherapeutic drugs	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cabozantinib (XL 184) for treatment of advanced medullary thyroid cancer	Patients in whom unresectable, locally advanced, or metastatic medullary thyroid cancer has been diagnosed	No treatments exist for advanced thyroid cancer that target MET, which may be responsible for drug resistance in patients treated with current receptor tyrosine kinase inhibitors. Cabozantinib 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. Administered 25 and 100 mg once daily. Exelixis, Inc., San Francisco, CA Phase III trial reported as meeting primary endpoint in Oct 2011; new drug application accepted by FDA in Jul 2012 and granted priority review status; FDA granted orphan drug status for follicular, medullary, and anaplastic thyroid carcinoma	Radiotherapy Sorafenib Sunitinib Vandetanib	Increased overall survival Increased progression-free survival Improved quality of life
Cabozantinib (XL 184) for treatment of advanced or recurrent breast cancer	Patients in whom advanced or recurrent breast cancer has been diagnosed	Few treatment options exist for advanced breast cancer, and none of them target MET, which may be responsible for drug resistance in patients treated with current receptor tyrosine kinase inhibitors. Cabozantinib 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. Administered 100 mg, once daily, in breast cancer trials. Exelixis, San Francisco, CA Phase II trials ongoing	Cyclophosphamide Doxorubicin Paclitaxel	Reduced bone metastasis Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cabozantinib (XL 184) for treatment of advanced or recurrent hepatocellular carcinoma	Patients in whom advanced or recurrent hepatocellular carcinoma (HCC) has been diagnosed	Few treatment options exist for advanced HCC, and none of them target MET, which may be responsible for drug resistance in patients treated with current receptor tyrosine kinase inhibitors. Cabozantinib 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. Administered 100 mg, once daily, in trials. Exelixis, San Francisco, CA Phase II trial ongoing	Chemotherapy Radiation Sorafenib	Reduced bone metastasis Increased overall survival Increased progression-free survival Improved quality of life
Cabozantinib (XL 184) for treatment of advanced or recurrent melanoma	Patients in whom advanced or recurrent melanoma has been diagnosed	Few treatment options exist for advanced melanoma, and none of them target MET, which may be responsible for drug resistance in patients treated with current receptor tyrosine kinase inhibitors. Cabozantinib 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. Administered 100 mg, once daily, in trials. Exelixis, San Francisco, CA Phase II trial ongoing	BCG (bacillus Calmette Guérin) injection Carboplatin Cisplatin Dacarbazine Imiquimod Interferon alpha Interleukin 2 Ipilimumab Paclitaxel Radiation therapy Surgery Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cabozantinib (XL 184) for treatment of advanced or recurrent nonsmall cell lung cancer	Patients in whom advanced, recurrent, or metastatic nonsmall cell lung cancer (NSCLC) has been diagnosed	Few treatment options exist for advanced NSCLC, and none of them target MET, which may be responsible for drug resistance in patients treated with current receptor tyrosine kinase inhibitors. Cabozantinib 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. Administered 100 mg, once daily, in trials. Exelixis, San Francisco, CA Phase Ib/II trial ongoing	Bevacizumab Cetuximab Cisplatin Docetaxel Erlotinib Gemcitabine Paclitaxel Pemetrexed Radiotherapy Surgery Vinorelbine	Reduced bone metastasis Increased overall survival Increased progression-free survival Improved quality of life
Cabozantinib (XL 184) for treatment of advanced or recurrent primary ovarian peritoneal or fallopian tube cancer	Patients in whom advanced or recurrent ovarian, primary peritoneal, or fallopian tube carcinoma has been diagnosed	Few treatment options exist for advanced or recurrent primary ovarian peritoneal or fallopian tube cancer, and none of them target MET. Cabozantinib 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. Administered 100 mg, once daily, in trials. Exelixis, San Francisco, CA Phase II trial ongoing	Carboplatin Carboplatin/ docetaxel Carboplatin/ gemcitabine Carboplatin/ liposomal doxorubicin Carboplatin/ paclitaxel Cisplatin Cisplatin/ gemcitabine Docetaxel Etoposide Gemcitabine Liposomal doxorubicin Paclitaxel Topotecan	Reduced bone metastasis Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cabozantinib (XL 184) for treatment of castration-resistant prostate cancer	Patients with castration-resistant prostate cancer (CRPC) that may include bone metastasis	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 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. Administered 100 mg, once daily, in trials. Exelixis, San Francisco, CA Phase II and phase III trials ongoing	Abiraterone Cabazitaxel Denosumab Docetaxel Enzalutamide Radium-223 (in development)	Reduced bone metastasis Reduced bone pain Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Carbon ion beam radiation therapy for cancer	Patients with cancer amenable to treatment with radiation	The properties of heavy ion beams (e.g., carbon ion) may allow improved administration of radiation therapy compared with photon or proton beam radiation. Like proton beams, particles in carbon ion beams lose the majority of their energy immediately before depositing the energy at a tumor target. This phenomenon is known as the Bragg peak, which potentially allows planning for targeting the radiation dose to a specific tissue depth and sparing adjacent tissue. Compared with protons, the path of heavier carbon ions is less influenced by passage through overlying tissue and, therefore, the peak of ionizing radiation is tighter, potentially allowing more precise targeting and delivery. Additionally, heavier particles such as carbon ions have a more severe impact on atoms within target cells, which produces more intense cellular damage and can potentially increase the biologic effectiveness of carbon ion beams relative to proton or photon beams. In particular, the relative biologic effectiveness of carbon ions purportedly increases with tissue depth, coinciding with the Bragg peak. Lastly, collisions between carbon ions and atomic nuclei produce positrons through nuclear fragmentation. The generated positrons can be imaged using positron emission tomography (PET), potentially allowing visualization of the delivered dose distribution. Developers include Ion Beam Applications S.A., Louvain-la-Neuve, Belgium, in joint venture with SAPHYN (SAnté et PHYsique Nucléaire, or Nuclear Health and Physics, a semi-public company, Caen, France) and financial partners; Siemens AG, Munich, Germany Five carbon ion beam facilities are currently operating—3 in Japan, 1 in Germany, and 1 in China with another planned to open in Germany in 2012. Ten trials are ongoing or planned in Germany. In the U.S. in 2010, Colorado State University announced a partnership with the Japanese center to perform carbon ion therapy research with the aim of bringing carbon ion therapy to the U.S. The University updated progress of that initiative in Apr 2012, announcing plans develop a cancer institute that would include plans for carbon ion therapy.	Photon radiation therapy Proton radiation therapy	Increased overall survival Increased progression-free survival Decreased adverse/side effects from radiation therapy Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Carfilzomib (Kyprolis) for treatment of multiple myeloma	Patients in whom recurrent or treatment-refractory multiple myeloma has been diagnosed	Multiple myeloma patients typically respond to current therapy only 11% of the time and typically survive for only 6–10 months after diagnosis, so effective treatments are needed. 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. Onyx Pharmaceuticals, Inc., South San Francisco, CA FDA granted accelerated approval Jul 2012 for treating patients "with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy."	Combination therapies Cytotoxic chemotherapies (bendamustine, cyclophosphamide, doxorubicin, melphalan, vincristine) Immunomodulatory drugs (lenalidomide, thalidomide) Proteasome inhibitors (bortezomib) Steroids (dexamethasone, prednisone)	Increased overall survival Increased progression-free survival Improved quality of life
CD40 agonist (CP-870,893) for treatment of pancreatic cancer	Patients in whom unresectable pancreatic cancer has been diagnosed	The 5-year survival rate for patients in whom pancreatic cancer has been diagnosed is only about 5%; therefore, novel therapies for this condition are needed. CP-870,893 is an intravenously administered monoclonal antibody that functions as a CD40 agonist and is intended to stimulate a patient's immune response, potentially eliminating the tumor. Although CP-870,893 was originally intended to activate T cells, preliminary data indicate that the therapy may actually lead to macrophage activation, which leads to the destruction of supporting tumor stroma; in current clinical trials, CP-870,893 is being administered in combination with the standard of care chemotherapy drug gemcitabine. Pfizer, Inc., New York, NY, in collaboration with University of Pennsylvania, Philadelphia Phase I trial complete; 2nd phase I trial ongoing	Gemcitabine monotherapy Gemcitabine plus erlotinib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
CD56-specific antibody-drug conjugate (lorvotuzumab mertansine; IMGN901) for treatment of multiple myeloma	Patients in whom CD56-positive relapsed or relapsed/ refractory multiple myeloma has been diagnosed	Patients in whom relapsed multiple myeloma has been diagnosed have few treatment options and median survival of less than 1 year. 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 multiple myeloma; in current clinical trials, Lorvotuzumab mertansine is being administered as an adjunct to a conventional cytotoxic chemotherapy regimen of lenalidomide and dexamethasone. ImmunoGen, Inc., Waltham, MA Phase I trial ongoing; FDA granted orphan drug status	Lenalidomide plus dexamethasone	Increased overall survival Increased progression-free survival Improved quality of life
CD56-specific antibody-drug conjugate (lorvotuzumab mertansine; IMGN901) for treatment of small cell lung cancer	Patients in whom advanced small cell lung cancer (SCLC) has been diagnosed; may be chemotherapy naïve or have received previous systemic chemotherapy treatment	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 small cell lung cancer. In current clinical trials, lorvotuzumab mertansine is being administered as an adjunct to a conventional cytotoxic chemotherapy regimen (carboplatin plus etoposide). ImmunoGen, Inc., Waltham, MA Phase II trial ongoing; FDA granted orphan drug status	Carboplatin plus etoposide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Chimeric antigen receptor gene therapy for treatment of chronic lymphocytic leukemia	Patients in whom recurrent chronic lymphocytic leukemia (CLL) has been diagnosed	Although CLL can typically be controlled for many years with current chemotherapy options, these treatments are not curative and disease typically recurs. One treatment option under study is the use of chimeric antigen receptor (CAR) gene therapy to genetically modify autologous T lymphocytes to promote T-cell activation, T-cell proliferation, and immune memory; in a recently reported study, a lentiviral vector was used to transfect autologous T cells with a CAR transgene that consisted of 4 parts: (1) an extracellular domain consisting of an antibody variable chain specific for CD19 (a cell surface marker expressed by CLLs); (2) a hinge region; (3) a costimulatory domain (in this case a portion of CD137); and (4) CD3-zeta (a signal transduction component of the T-cell receptor); binding of the extracellular domain of this recombinant protein to CD19 on target cells induces the activation of the pathways typically downstream of major histocompatibility complex activation and CD137 stimulation, activating a persistent immune response against CD19. University of Pennsylvania, Philadelphia Case studies reported; in Aug 2012, Novartis entered into an agreement with the University of Pennsylvania to collaborate on research and development of this technology	Allogeneic stem cell transplant	Increased overall survival Increased progression-free survival Improved quality of life
c-Met kinase inhibitor (tivantinib) for treatment of hepatocellular carcinoma	Patients with unresectable hepatocellular carcinoma (HCC) that has failed to respond to 1 prior therapy	In patients who 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. 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). There is no currently available c-Met inhibitor. ArQule, Inc., Woburn, MA Phase II trial complete with results released Jun 2012; phase III trials planned	Placebo	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
c-Met kinase inhibitor (tivantinib) for treatment of metastatic colorectal cancer	Patients with metastatic colorectal cancer (CRC) with wild-type KRAS who have received prior systemic chemotherapy	Although many treatment options are available for metastatic CRC, 5-year survival rates are only about 25%, and more effective treatment is needed. 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). There is no currently available c-Met inhibitor. For this indication, tivantinib is being administered in combination with the topoisomerase inhibitor irinotecan and the anti-EGFR (epidermal growth factor receptor) antibody cetuximab. ArQule, Inc., Woburn, MA in collaboration with Daiichi Sankyo, Tokyo, Japan Phase I/II trial ongoing	Irinotecan plus cetuximab CapeOX Cetuximab monotherapy FOLFIRI (folinic acid [leucovorin], 5-fluorouracil [5-FU], and irinotecan) FOLFIRI plus cetuximab FOLFOX (folinic acid [leucovorin], 5-FU, oxaliplatin) Irinotecan plus or minus oxaliplatin Panitumumab	Increased overall survival Increased progression-free survival Improved quality of life
Combined digital breast tomography and diffuse optical tomography for diagnosing breast cancer	Patients who are undergoing followup diagnostic imaging for breast cancer after a suspicious result on mammography screening	Diffuse optical tomography uses laser technology coupled with optical equipment software to detect hemoglobin, angiogenesis, and increased metabolism. Several optical imaging systems are on the market; digital breast tomography uses x-ray images to create 3-dimensional reconstructions of breast tissue; researchers hypothesize that using sequential optical/radiographic imaging would improve detection of breast cancer and improve discrimination between benign and cancerous lesions based on differential metabolic activities observed in these tissues. Multiple manufacturers Early phase trials	Computed tomography Digital breast tomography alone Diffuse optical tomography alone MRI Standard mammography Ultrasound	Increased sensitivity, leading to earlier detection and improved outcomes Increased specificity, leading to a reduced number of biopsy procedures and their attendant emotional stress

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Computer-aided multispectral digital analysis (MelaFind) for assessing atypical skin lesions	Patients in whom pigmented skin lesions are present requiring diagnosis	Computer-aided multispectral digital analysis (MelaFind®) uses a device that uses light to image skin through a thin layer of liquid (alcohol or oil) to try to make lesion structures visible under the skin surface; a digital camera inside the probe captures images and differentiates pigmented skin lesions to try to determine melanoma risk using algorithms. MELA Sciences, Inc., Irvington, NY FDA approved Nov 2011 "for use on clinically atypical cutaneous pigmented lesions with 1 or more clinical or historical characteristics of melanoma, excluding those with a clinical diagnosis of melanoma or likely melanoma. MelaFind is designed to be used when a dermatologist chooses to obtain additional information for a decision to biopsy. MelaFind should NOT be used to confirm a clinical diagnosis of melanoma." Conformité Européene (CE) marked Sept 2011.	Biopsy Physician observation of skin lesions (dermoscope)	Increased sensitivity and specificity Reduced number of biopsies performed on suspect lesions Earlier detection of suspect lesions Increased overall survival Improved quality of life
Computer-assisted system (Sedasys) for automated propofol sedation during gastrointestinal endoscopy procedures	Patients who are undergoing propofol-induced sedation during colonoscopy or upper gastrointestinal (GI) procedures	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 over-sedation) for delivery of propofol. The system is intended to enable nonanesthesiologists (i.e., other physicians or nurses) to administer sedation for endoscopic GI procedures. Ethicon Endo-Surgery unit of Johnson & Johnson, New Brunswick, NJ Premarket approval (PMA) rejected by FDA Oct 2010; Ethicon appealed and in Mar 2011 FDA agreed to a 2nd review by the Medical Devices Dispute Resolution Panel, which was scheduled to meet mid-Dec 2011; however, before panel meeting FDA agreed to undertake a 2nd review of the PMA; Ethicon received an approvable letter for Sedasys in Mar 2012	Propofol sedation administered and monitored by anesthesiologist	Successful and safe propofol sedation without need for an anesthesiologist

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Concomitant colorectal cancer screening and annual influenza vaccination program	Patients recommended for routine colorectal cancer (CRC) screening (i.e., between 50 and 75 years of age) who are receiving influenza vaccinations	Although CRC screening methods are widely available and known to be effective in reducing morbidity and mortality from CRC, adherence with the recommended screening guidelines is low. In the annual influenza vaccination and CRC screening (FLU-FOBT) program, nurses in community clinics provide patients seeking annual influenza vaccinations with fecal occult blood tests (FOBT) for CRC screening. University of California, San Francisco Large randomized control trials completed	Primary care physician recommended CRC screening	Increased rate of adherence with CRC screening guidelines Reduced morbidity from CRC Reduced mortality from CRC Reduced costs of care through earlier intervention Reduced health disparities
Cordycepin (OVI-123) for treatment of refractory acute lymphoblastic leukemia	Patients in whom refractory negative acute lymphoblastic leukemia (ALL) has been diagnosed	Many patients with ALL are successfully treated, however patients with refractory disease (often adults) have few options and disease progresses quickly. Cordycepin is an adenosine nucleoside analog that is purported to have activity against terminal deoxynucleotidyl transferase (TdT)-positive cells; expression of TdT is a hallmark of ALL; although the mechanism of action for cordycepin remains largely unknown, cordycepin is believed to induce apoptosis in leukemia cells. Administered intravenously on days 1, 2, and 3 of a 21-day cycle. OncoVista Innovative Therapies, Inc., San Antonio, TX Phase I/II trials ongoing; FDA granted orphan drug status for ALL	Allogeneic bone marrow transplant Asparaginase Chemotherapy Dasatinib Imatinib Nilotinib Nelarabine Radiation Steroids	Increased overall survival Increased progression-free survival Improved quality of life
Cotara (131 iodine-chTNT-1/B-linked monoclonal antibody) for treatment of glioblastoma multiforme	Patients in whom glioblastoma multiforme has been diagnosed	Glioblastoma multiforme is the most common and most deadly form of brain cancer; complete surgical resection is generally not possible, and the prognosis is poor; more effective adjuvant therapies are needed. Cotara consists of a monoclonal antibody linked to a radioactive isotope, iodine 131, which is intended to bind to the DNA histone complex that is exposed in dead and dying cells at the center of solid tumors; intended to target dying cells at the center of tumors, delivering its radioactive payload there to minimize radiation to healthy surrounding tissue. Administered as a single interstitial infusion over about 25 hours at a dose of 2.5 mCi/cc. Peregrine Pharmaceuticals, Inc., Tustin, CA Phase II trials completed	Personalized therapeutic vaccines (investigational) Radiotherapy Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
CP-4126 (CO-101) for treatment of advanced pancreatic cancer	Patients in whom advanced pancreatic cancer has been diagnosed	CP-4126 is a lipid-conjugated version of the anticancer agent gemcitabine (nucleoside analog); gemcitabine is a standard chemotherapeutic treatment for pancreatic cancer; however, many pancreatic cancers do not readily take up gemcitabine (possibly because they express low levels of the main gemcitabine transporter). The lipid conjugation purports to overcome this problem by allowing the nucleoside to cross the lipid bilayer without having to use the transporter. Clavis Pharma ASA, Oslo, Norway Clovis Oncology, Boulder, CO Phase II trial complete; other phase II trials ongoing	Gemcitabine	Increased overall survival Increased progression-free survival Improved quality of life
Custirsen (OGX-011) for treatment of advanced nonsmall cell lung cancer	Patients in whom nonsmall cell lung cancer (NSCLC) has been diagnosed	Custirsen (OGX-011) is an antisense RNA molecule intended for treating advanced, unresectable NSCLC; given intravenously (IV) in combination with docetaxel: 3 loading doses of custirsen 640 mg IV are given over 2 hours in 5–9 days prior to day 1 of cycle 1; then custirsen 640 mg IV weekly every 21-day cycle. OncoGenex Pharmaceuticals, Inc., Bothell, WA Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel Phase II trials completed; phase III trials planned but not yet enrolling	Conventional chemotherapy	Increased overall survival Increased progression-free survival Improved quality of life
Custirsen (OGX-011) 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 (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. OncoGenex Pharmaceuticals, Inc., Bothell, WA Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel Phase III trials (SATURN and SYNERGY) ongoing under FDA special protocol assessment; FDA granted fast track status	Abiraterone Cabazitaxel Docetaxel Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
CYT387 small-molecule inhibitor of JAK 1 and JAK 2 for treatment of myelofibrosis	Patients in whom myelofibrosis has been diagnosed	CYT387 is an inhibitor of Janus kinase 1 (JAK 1) and Janus kinase 2 (JAK 2); hypothesis is that constitutively active JAK 2 protein drives myelofibrosis pathology in some cases; inhibiting this causative protein factor of the disease state could reverse disease course. YM Biosciences, Mississauga, Ontario, Canada Phase I/II trials completed; phase II trial ongoing	Ruxolitinib	Increased overall survival Increased progression-free survival Improved quality of life (reduced spleen enlargement, bone pain, easy bruising, fatigue)
Cytokine cocktail (Multikine) immune therapy for head and neck cancer	Patients in whom head and neck cancer has been diagnosed	Multikine is a mix of immune stimulators (tumor necrosis factor, interleukin-1, other cytokines); intended to be delivered before conventional treatment (surgery, radiotherapy, chemotherapy); manufacturer believes this is when the immune system is best able to mount an immune response. Cytokine mixture delivered directly to the tumor and nearby lymph nodes 5 times a week for 3 weeks. CEL-SCI Corp., Vienna, VA Phase III trial ongoing	Chemoradiation therapy Surgical resection	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cytotoxic alkaloid (omacetaxine mepesuccinate, Omapro) 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 (Omapro®) is a cytotoxic alkaloid derived from the evergreen tree *Cephalotaxus harringtonia*. Omacetaxine mepesuccinate purportedly acts as a reversible, transient inhibitor of protein elongation. This inhibition leads to cell death through multiple mechanisms of action, including inhibition of HSP90, which leads to destabilization of BCR-ABL and downregulation of the antiapoptotic protein MCL-1. In clinical trials, omacetaxine mepesuccinate was administered twice daily, by subcutaneous injection. Cephalon unit of Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, (previously developed by ChemGenex Pharmaceuticals, Ltd., which was acquired by Cephalon) Phase II trials complete; FDA granted orphan drug status in 2009; previously submitted new drug application to FDA for accelerated approval based on phase II trial data in patients whose CML harbored a specific mutation in BCR-ABL. The company received a complete response letter from FDA regarding the assay used to determine BCR-ABL mutation status. Cephalon intends to resubmit for treating patients whose disease has not responded to at least 2 tyrosine kinase inhibitors.	Allogeneic stem cell transplant Investigational multi-targeted kinase inhibitor	Increased overall survival Increased progression-free survival Improved quality of life
Dendritic cell vaccine (ICT-107) for treatment of glioblastoma multiforme	Patients in whom glioblastoma multiforme has been diagnosed and who have undergone surgical debulking and chemoradiation therapy	Glioblastoma multiforme is difficult to treat, with few effective options. 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 for the potential intradermal treatment of glioblastoma. ImmunoCellular Therapeutics Ltd., Los Angeles, CA Phase IIb trial ongoing; FDA granted orphan drug status in 2010	Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Digital breast tomosynthesis for mammography screening	Women undergoing routine mammography to screen for breast cancer	A limitation of 2-dimensional (2-D) conventional mammography is that the x-ray images capture information from all tissue constituents along the path from the x-ray source to the detector. Therefore, features of the breast may be obscured by tissues that are in line with the x-ray path and above or below the feature of interest. Digital breast tomosynthesis is x-ray imaging that purports to overcome this potential pitfall by imaging stabilized breast tissue in multiple angles for a given view by rotating the x-ray source in an arc around the target tissue. Breast tissue features that may obscure each other in 1 angle are shifted relative to one another in other angles. By combining the information from each beam angle at the point where it crosses a given depth in the breast under examination, digital breast tomosynthesis can reconstruct images that represent serial slices through the breast. Developers propose that this imaging technology will improve mammographic imaging, potentially resulting in reduced number of recalls for inconclusive results, reduced number of biopsies, and increased cancer detection. The 1st commercially available system was the Selenia® Dimensions® 3D System. This system is a software and hardware upgrade to the existing Selenia Dimensions 2D full-field digital mammography system. Hologic, Inc., Bedford, MA FDA approved for marketing Mar 2011	Standard 2-D digital mammography	Increased sensitivity and specificity Increased predictive values Reduced unnecessary followup procedures
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. BioCancell Therapeutics, Inc., Jerusalem, Israel Phase IIb trial ongoing; FDA granted fast track status	5-Fluorouracil/ leucovorin monotherapy Gemcitabine monotherapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Dual ALK and EGFR kinase inhibitor (AP26113) for treatment of nonsmall cell lung cancer	Patients with ALK translocation-positive nonsmall cell lung cancer (NSCLC)	Although the development of an anaplastic lymphoma kinase (ALK) inhibitor has improved outcomes for the small subset of patients in whom ALK translocation-positive NSCLC has been confirmed, many patients who initially respond to currently available ALK inhibitors develop resistance to the therapy. Studies have identified multiple resistance mechanisms, including mutations to the ALK kinase domain and activation of the epidermal growth factor receptor (EGFR) signaling pathway. AP26113 is a novel kinase inhibitor that has the potential to address both of these resistance mechanisms. AP26113 has activity against both resistant forms of the ALK kinase and activated forms of the EGFR kinase. ARIAD Pharmaceuticals, Inc., Cambridge, MA Phase I/II trial ongoing	Bevacizumab Cisplatin Crizotinib Erlotinib Pemetrexed	Increased overall survival Increased progression-free survival Improved quality of life
Dual p16-INK4a/ Ki-67 staining test (CINtec PLUS) for triage of abnormal cervical cancer screening results	Patients who have received an abnormal cervical cancer screening test result (e.g., atypical squamous cells of undetermined significance [ASC-US], low-grade squamous intraepithelial lesion [LSIL], Pap negative/human papilloma virus [HPV] positive)	The prognostic value of identification of dysplastic lesions of the uterine cervix cannot be adequately determined by Pap (Papanicolaou) cytology/HPV testing alone, potentially leading to underdiagnosis or delayed treatment of cervical cancer and/or excessive colposcopy procedures. Two molecular markers that may aid in the diagnosis of abnormal Pap results are p16-INK4a (a cell cycle regulator overexpressed in neoplastic cells) and Ki-67 (a marker of cellular proliferation). The CINtec PLUS testing kit detects both of these markers as indicators of cell cycle dysregulation that occurs in transformed cells. In clinical trials, the CINtec PLUS test kit has been used to triage abnormal Pap results and Pap-negative/HPV-positive results. Roche mtm laboratories AG, Heidelberg, Germany Multiple clinical trials completed as of Sept 2011; Conformité Européene (CE) marked; device will initially be available in the U.S. as a Class I in vitro diagnostic product without claims as to an application; the company intends to submit a premarket approval application	Colposcopy HPV testing Watchful waiting with repeat Pap smears	Increased sensitivity and specificity for cases of CIN2+ in women exhibiting ASC-US, LSIL, or Pap-negative/HPV-positive Improved diagnostic accuracy Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
EGFRvIII-directed immunotherapy (rindopepimut) for treatment of glioblastoma multiforme	Patients with newly diagnosed glioblastoma multiforme who have undergone primary resection of the bulk tumor	Glioblastoma multiforme typically recurs within 6 months; a splice variant of the epidermal growth factor receptor (EGFR) that is found predominantly on cancerous tissues, EGFRvIII represents a potential target antigen for anticancer therapy. Rindopepimut (CDX-110) is a peptide based vaccine designed to be specific for the EGFRvIII variant; in current clinical trials, rindopepimut is being administered in combination with the immune stimulant granulocyte macrophage colony-stimulating factor and standard maintenance chemotherapy (temozolomide). Celldex Therapeutics, Inc., Needham, MA Phase III trial ongoing	Temozolomide alone	Increased overall survival Increased progression-free survival Improved quality of life
Electrical impedance scanner (Nevisense) for melanoma diagnosis	Patients in whom a suspicious skin lesion that may be melanoma has been identified	Distinguishing melanoma from nonmelanotic skin lesions is difficult and requires a significant amount of training. The Nevisense™ uses differences in electrical impedance between melanotic tissue and other tissue types to detect melanoma in an automated fashion; the system consists of an impedance spectrometer and a disposable probe that has microscopic electrode spikes that penetrate the skin. SciBase AB, Stockholm, Sweden International pivotal investigational device exemption SIMPS trial completed (1,900 patients; 2400 lesions); FDA premarket approval submission planned for 1st quarter 2013; Europe and Australia launch planned for 1st quarter 2013	Dermatologist diagnosis MelaFind computer-aided multispectral dermatoscope	Increased sensitivity and specificity for melanoma Improved positive and negative predictive values Reduction in unnecessary biopsies
Electro-immunotherapy (OncoSec Medical System) for treatment of metastatic melanoma	Patients in whom metastatic melanoma has been diagnosed	Patients with metastatic melanoma have a median survival time of about 18 months when treated with current therapies. The OncoSec Medical System™ is an electroporation device that is intended to enhance the ability of cells to take up DNA. In clinical trials, it is being used to enhance delivery of a plasmid encoding the cytokine interleukin-12 (IL-12). Expression of IL-12 by cancer cells could potentially stimulate a systemic immune response against tumor antigens. In the treatment, IL-12 plasmid is injected at the tumor site followed by electrical stimulation using the OncoSec Medical System. OncoSec Medical, Inc., San Diego, CA Phase II trial ongoing	Dacarbazine High-dose interleukin-2 Ipilimumab Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
EndoVe electrical field generator to improve chemotherapy uptake	Patients undergoing chemotherapy for solid localized tumors	EndoVe endoscopic device applies a local electrical field to the tumor; hypothesized to increase the rate at which cells take up chemotherapeutic agents. Its use would allow use of lower doses of chemotherapeutic agents. Mercy Hospital, Cork, Ireland Phase I trial ongoing for rectal cancer	Conventional chemotherapy administration	Increased overall survival Increased progression-free survival Reduced chemotherapy dose, potentially reducing side effects Lower costs associated with lower doses of chemotherapy Improved quality of life
Enkephalin (NTDDS NP2) gene therapy for chronic cancer pain	Patients experiencing intractable pain stemming from metastatic disease	Opioids are the mainstay of treatment for chronic severe cancer pain, but are associated with many undesired side effects and are potentially addictive. Enkephalin gene therapy is a nerve targeting drug delivery system that is a herpes virus-based gene therapy delivery vector; it encodes the natural opioid peptide, enkephalin, which is intended to lead to expression of enkephalin in peripheral nerves, thereby interrupting pain signals to the central nervous system to treat chronic cancer pain; it has potential to have significantly reduced side effects relative to systemic opioids because of its targeted nature. Diamyd Medical AB, Stockholm, Sweden Phase II trial ongoing	Oral and intravenous opioid pain medications	Reduced cancer-related pain Reduced side effects from pain medication Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Enzalutamide (Xtandi) for treatment of castration-resistant prostate cancer	Patients in whom metastatic castration-resistant prostate cancer (mCRPC) has been diagnosed	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 develop resistance. Enzalutamide (Xtandi) is an androgen receptor antagonist that is purported to inhibit 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-naive patients and patients who have previously been treated with docetaxel. Enzalutamide is administered at a dose of 160 mg (four 40 mg capsules) taken orally once daily. Medivation, Inc., San Francisco, CA Astellas Pharma Inc., Northbrook, IL FDA approved Aug 31, 2012, for patients with mCRPC who have previously been treated with docetaxel. Trials ongoing for chemotherapy-naïve prostate cancer patients.	Chemotherapy-naive CRPC: Abiraterone plus prednisone Docetaxel Sipuleucel-T Pretreated CRPC: Abiraterone plus prednisone Cabazitaxel	Increased overall survival Increased progression-free survival Improved quality of life
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. Gamida Cell, Ltd., Jerusalem, Israel Phase III trial ongoing	Pooled unexpanded cord blood transplant Unexpanded cord blood transplant	Improved bone marrow engraftment rate Improved neutrophil recovery rate Improved platelet recovery rate Increased overall survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
FLT3 kinase inhibitor (quizartinib) for treatment of acute myeloid leukemia bearing FLT3 mutations	Patients with treatment-refractory acute myeloid leukemia (AML) bearing an internal tandem duplication in the FLT3 gene (ITD-FLT3)	No FLT3 inhibitors are available for treating AML, and patients with recurrent or treatment-refractory AML have no effective treatment options. About 30% of AML cases bear an activating mutation in the gene encoding the receptor tyrosine kinase FLT3, which causes constitutive activation of various cell proliferative and antiapoptotic 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 under study as a treatment for AML. Ambit Biosciences, San Diego, CA Phase IIb trial ongoing; received fast track status from FDA	Cladribine/cytarabine/ granulocyte colony-stimulating factor plus or minus mitoxantrone or idarubicin Fludarabine/cytarabine/ granulocyte colony stimulating factor plus or minus idarubicin High-dose cytarabine and anthracycline Mitoxantrone/ etoposide/cytarabine	Increased overall survival Increased progression-free survival Improved quality of life
Galeterone (TOK-001) for treatment of castration-resistant prostate cancer	Patients in whom castration-resistant prostate cancer (CRPC) has been diagnosed	CRPC is thought to overcome androgen deprivation through multiple mechanisms such as production of its own androgens, reliance on adrenal androgens, and upregulation of the androgen receptor. Both androgen receptor antagonists (e.g., bicalutamide) and androgen synthesis inhibitors (e.g., abiraterone) have been approved for treating advanced prostate cancer. However, no currently available pharmaceutical functions by downregulating the cell surface expression of the androgen receptor. Galeterone purportedly functions through all 3 of these mechanisms: acting as an androgen receptor inhibitor, limiting androgen synthesis through CYP17 inhibition, and downregulating androgen receptor expression levels. Galeterone is intended for patients who have received no prior therapy; in a phase I trial, it is being administered orally, twice daily. Tokai Pharmaceuticals, Inc., Cambridge, MA Phase I trial ongoing	Abiraterone Bicalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gene-mediated cytotoxic immunotherapy for malignant glioma	Patients in whom malignant glioma has been diagnosed	Median survival of patients diagnosed with malignant glioma is only about 15 months and current treatments are often unsuccessful. Gene-mediated cytotoxic immunotherapy (GMCI) purportedly leads to direct tumor cytotoxicity as well as a protective immune response. Treatment consists of an adenovirus vector that contains a herpes simplex virus (HSV) thymidine kinase gene (Adv-tk); following injection of the virus into the tumor site, the patient is administered 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 malignant glioma, GMCI is being administered in combination with radiation therapy and surgical resection. Advantagene, Inc., Auburndale, MA Phase II completed; data reporting expected late 2012	Chemotherapy Radiation therapy Surgical resection Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life
Gene-mediated cytotoxic immunotherapy for pancreatic adenocarcinoma	Patients in whom pancreatic adenocarcinoma has been diagnosed	Patients in whom pancreatic cancer has been diagnosed have a 5-year survival rate of only 5%; therefore, novel treatments for pancreatic cancer are needed. Gene-mediated cytotoxic immunotherapy (GMCI) is being tested for prevention of recurrence following conventional therapy; GMCI purports to lead to direct tumor cytotoxicity as well as a protective immune response. Treatment consists of an adenovirus vector that contains a herpes simplex virus (HSV) thymidine kinase gene (Adv-tk); following 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 pancreatic cancer, GCMI is being administered in combination with radiation therapy in locally advanced disease and in combination with surgical resection in surgically resectable disease. Advantagene, Inc., Auburndale, MA Phase I/II trial completed.	Chemotherapy Chemoradiation therapy Gemcitabine Radiation therapy Surgical resection	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gene-mediated cytotoxic immunotherapy (ProstAtak) for prostate cancer	Patients in whom intermediate to high-risk localized prostate cancer has been diagnosed	Prostate cancer recurrence rates following 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 to prevent recurrence following 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 an herpes simplex virus (HSV) thymidine kinase gene (Adv-tk). Following 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. Advantagene, Inc., Auburndale, MA Phase III trial ongoing under FDA Special Protocol Assessment	Androgen deprivation therapy Radiation therapy Surgical resection	Increased overall survival Increased disease-free survival Improved quality of life
Genetic test (Insight ALK Screen Assay) for identifying ALK-activating gene fusions/mutations in patients with cancer	Patients with cancer types driven by underlying activated anaplastic lymphoma kinase (ALK) mutations	Genetic test to identify mutations in the *ALK* gene. Test would allow identification of patients for whom ALK inhibitory pharmaceuticals (e.g., crizotinib) might be appropriate. Insight Genetics, Nashville, TN Early phase development; available as research-use-only product; partnered with QIAGEN to produce a companion diagnostic test	Fluorescence in situ hybridization to identify chromosomal translocations/ deletions leading to ALK fusions Immunohistochemistry Variant-specific polymerase chain reaction	Informed targeted therapy for cancer patients Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Genetic test (Methylated Septin 9 Plasma DNA Test) for colorectal cancer screening	All patients undergoing routine colorectal cancer (CRC) screening	Genetic test (Methylated Septin 9 Plasma DNA Test; RealTime mS9 Colorectal Cancer Test) screens DNA from plasma samples for a specific methylated version of the septin 9 gene that is commonly found in CRC. Epigenomics AG, Berlin, Germany (developer) Abbott Laboratories, Abbott Park, IL (licensee) First-generation test kit (Epi proColon) available in Europe; 2nd-generation test kit (Epi proColon 2.0) was anticipated to be available in Europe in 2011; Epigenomics will submit the 3rd module of a premarket approval application to FDA in Dec 2012	Colonoscopy Computed tomographic colonography Fecal DNA tests Sigmoidoscopy	Increased sensitivity and specificity Increased predictive values Avoided unnecessary followup procedures Improved adherence with colorectal screening Earlier intervention for identified cancer
Ghrelin receptor agonist (anamorelin) for treatment of cancer-related cachexia/anorexia	Patients 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 the ability of patients to tolerate 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 as a daily dose of 100 mg. Helsinn Healthcare S.A., Lugano/Pazzallo, Switzerland Phase III trials ongoing	Anti-cytokine antibodies Appetite stimulants: Cannabinoids Corticosteroids Cyproheptadine Progesterone derivatives Dietary counseling Melanocortin antagonists Metabolic disturbance modulators: Pentoxifylline Thalidomide	Improved lean body mass Improved muscle strength Increased body weight Increased overall survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gonadotropin-releasing hormone analogs for prevention of chemotherapy-induced menopause	Women undergoing 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. 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 are administered concomitantly with standard cytotoxic chemotherapy regimens. SWOG, Ann Arbor, MI, and International Breast Cancer Study Group IBCSG, Bern, Switzerland Phase III trial complete	No standard therapies available	Decreased rate of amenorrhea at 12 months post-chemotherapy Improved quality of life
HER2-dimerization inhibitor (pertuzumab, Perjeta) for treatment of metastatic breast cancer	Patients with metastatic HER2-positive breast cancer who are receiving 1st-line trastuzumab and docetaxel	No curative treatment for patients in whom metastatic breast cancer has been diagnosed 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 is purported to function 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 is purported to function 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 undergoing studies in combination with trastuzumab to ascertain whether a more comprehensive inhibition of HER2 activity can improve outcomes in patients with metastatic breast cancer. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials ongoing; phase III trial in previously untreated, metastatic breast cancer met primary endpoint Jul 2011; biologics license application submission accepted for priority review by FDA in Feb 2012; FDA approved Jun 2012	Trastuzumab plus capecitabine Trastuzumab plus docetaxel Trastuzumab plus paclitaxel plus or minus carboplatin Trastuzumab plus vinorelbine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
HER2 therapeutic cancer vaccine (NeuVax) for breast cancer	Patients with HER2-positive early stage breast cancer. Patients must be positive for human leukocyte antigen (HLA)-A2 and/or HLA-A3.	Although many patients in whom early-stage breast cancer has been diagnosed 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 trastuzumab. 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 patients whose tumors express low levels of the HER2 protein. RXi Pharmaceuticals Corp., Worcester, MA Phase III ongoing under FDA special protocol assessment	Aromatase inhibitors Tamoxifen	Increased overall survival Increased progression-free survival Improved quality of life
Histamine dihydrochloride (Ceplene) for treatment of acute myeloid leukemia	Patients with acute myeloid leukemia (AML) who are in remission following consolidation chemotherapy	Although many patients in whom AML has been diagnosed will achieve remission following induction and consolidation chemotherapy, the majority of these patients will experience disease recurrence. Ceplene® is being studied as a maintenance therapy to prevent disease recurrence in this setting; it is purported to act as an immune stimulant, which may activate a T-cell response against leukemia cells. In clinical trials, it is being administered as an adjunct to the cytokine interleukin-2. Ceplene is administered as a subcutaneous injection. EpiCept Corp., Tarrytown, NY Phase III trial completed; new drug application submitted to FDA late 2010 and rejected; EpiCept is working with FDA to generate a special protocol assessment for a new phase III Ceplene trial; Ceplene is approved for use in EU	No consensus treatment exists for postremission patients	Decreased relapse rate Increased overall survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Histone deacetylase 6 inhibitor (ACY-1215) for treatment of multiple myeloma	Patients with treatment-resistant or recurrent multiple myeloma	Although treatments for multiple myeloma have improved, the median life expectancy is only 5–7 years. ACY-1215 is a novel histone deacetylase (HDAC) inhibitor that is specific for HDAC6. Although multiple HDAC inhibitors have come to market, none are approved for treating multiple myeloma. Additionally, currently available HDAC inhibitors are pan-HDAC inhibitors, which have inhibitory activity against a wide range of HDACs. By targeting HDAC6 specifically, ACY-1215 might avoid some of the toxicity associated with pan-HDAC inhibition. HDAC6 is purported to be an appropriate anticancer target because of its function in a protein degradation pathway known as the aggresome. Due to their high rate of protein production, cancer cells produce a large number of aggresome substrates (e.g., misfolded proteins) and HDAC6 may lead to the preferential accumulation of toxic levels of waste proteins in cancer cells. Acetylon Pharmaceuticals, Inc., Boston, MA Phase I/II trial ongoing	Various chemotherapies, singly and/or in various combinations at standard or high doses: Bendamustine Bortezomib Cisplatin Cyclophosphamide Dexamethasone Doxorubicin Etoposide Lenalidomide Thalidomide	Increased overall survival Increased progression-free survival Improved quality of life
Histone deacetylase inhibitor (panobinostat) for treatment of relapsed multiple myeloma	Patients with multiple myeloma whose disease requires retreatment following at least 1 round of chemotherapy treatment	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. Histone deacetylase (HDAC) inhibitors are a class of anticancer drugs whose exact mechanism of action is unclear but might be related to DNA damage repair inhibition 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 currently 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. Novartis International AG, Basel, Switzerland Phase III trial ongoing	Various chemotherapies, singly and/or in various combinations at standard or high doses: Bendamustine Bortezomib Cisplatin Cyclophosphamide Dexamethasone Doxorubicin Etoposide Lenalidomide Thalidomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Histone deacetylase inhibitor (SB939) for treatment of recurrent or metastatic prostate cancer	Patients in whom recurrent or metastatic prostate cancer (hormone refractory prostate cancer) has been diagnosed	SB939 is a broad spectrum histone deacetylase (HDAC) inhibitor, intended to work against class I, II, III, and IV HDACs; mechanism of tumor inhibition by HDAC inhibitors unclear, but may be caused by DNA repair inhibition or modification of cell cycle proteins. S*BIO Pte, Ltd., Singapore Phase II trial ongoing	Abiraterone Cabazitaxel Docetaxel Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
Histone deacetylase inhibitor (vorinostat) for treatment of multiple myeloma	Patients with multiple myeloma who have undergone at least 1 prior round of chemotherapy	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. Histone deacetylase (HDAC) inhibitors are a class of anticancer drugs whose exact mechanism of action is unclear, but might be related to DNA damage repair inhibition 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 currently approved for treating multiple myeloma. In an ongoing pivotal clinical trial, vorinostat (oral tablets at 400 mg/day) is being tested in combination with the proteasome inhibitor bortezomib. Merck & Co. Inc., Whitehouse Station, NJ Phase III trial ongoing; preliminary results released in Dec 2011 indicated that vorinostat met its primary endpoint of extending progression-free survival, which was extended by 25 days	Various chemotherapies, singly and/or in various combinations at standard or high doses: Bendamustine Bortezomib Cisplatin Cyclophosphamide Dexamethasone Doxorubicin Etoposide Lenalidomide Thalidomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Hsp90 inhibitor (ganetespib) for treatment of advanced nonsmall cell lung cancer	Patients with treatment-resistant, 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. In addition, 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. Synta Pharmaceuticals Corp., Lexington, MA Phase II/III trial ongoing	Docetaxel monotherapy	Increased overall survival Increased progression-free survival Improved quality of life
Huachansu for treatment of pancreatic cancer	Patients in whom pancreatic cancer has been diagnosed	Patients in whom pancreatic cancer has been diagnosed have few treatment options and a poor prognosis. Huachansu is a traditional Chinese medicine derived from Bufo toad venom. The agent is delivered intravenously. It has been approved in China for use against lung cancer, liver cancer, and pancreatic cancer. In current clinical trials for pancreatic cancer, huachansu is administered by intravenous infusion in combination with the standard chemotherapy drug gemcitabine and is intended for use as part of 1st-line treatment. University of Texas MD Anderson Cancer Center, Houston Phase II trial completed	5-Fluorouracil/ leucovorin Gemcitabine alone	Increased overall survival Increased progression-free survival Improved quality of life
Human papillomavirus vaccination (Gardasil) for prevention of anal cancer	Males and females 9–26 years of age	The incidence of anal cancer in the U.S. is rising and human papillomavirus (HPV) infection is associated with 90% of cases. Gardasil® is a quadrivalent HPV vaccine against HPV types 6, 11, 16, and 18 that has been approved for prevention of cervical, vulvar, and vaginal cancer. Merck & Co., Inc., Whitehouse Station, NJ FDA granted supplemental approval Dec 2010 for preventing anal cancer	Abstinence from anal intercourse Abstinence from sexual activity Safer sex practices	Decreased rate of anal intraepithelial neoplasia Decreased rate of anal cancer

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Hypoxia-activated DNA alkylating agent (TH-302) for treatment of advanced and metastatic soft tissue sarcoma	Patients in whom locally advanced unresectable or metastatic soft tissue sarcoma has been diagnosed	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 is purported to be 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. Threshold Pharmaceuticals, South San Francisco, CA Merck & Co., Inc. Whitehouse Station, NJ Phase III trial ongoing in soft tissue sarcoma; also under study in other cancer types including pancreatic cancer; companies signed agreement in Feb 2012 to co-develop and commercialize TH-302	Doxorubicin monotherapy	Increased overall survival Increased progression-free survival Improved quality of life
ICE COLD-PCR amplification for detection of small quantities of mutated DNA	Populations undergoing screening for cancer	Co-amplification at lower denaturing temperature polymerase chain reaction (ICE COLD-PCR) is an amplification step that can be used before traditional laboratory screening methods (e.g., Sanger sequencing, TaqMan polymerase chain reaction [PCR], high-performance liquid chromatography [HPLC]). Small amounts of mutant DNA can be amplified selectively from a background of high concentration wild-type DNA, such as exists in cancer-derived DNA from patient plasma samples. Dana-Farber Cancer Institute, Boston, MA Transgenomic, Omaha, NE Development studies completed; collaboration with University of Texas MD Anderson Cancer Center, Houston, initiated' in Jun 2012, Transgenomic announced the commercial launch of the ICE COLD-PCR technology	Various methods including: Antiprimer quenching real-time PCR Denaturing HPLC/Surveyor™ Ligation-mediated PCR Matrix assisted laser desorption/ionization time-of-flight analysis Peptide nucleic acid-3-locked nucleic acids Sequencing Restriction fragment length polymorphism analysis	Earlier detection of cancer presence

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Immunomodulator (Imprime PGG) for treatment of advanced colorectal cancer	Patients in whom advanced 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 purported to induce an antitumor response through binding and stimulating neutrophils, which typically play a major role in innate immune responses, but not antitumor responses; Imprime PGG is purported to work synergistically with monoclonal antibody therapy such as cetuximab. Administered 4 mg/kg of body weight injection, weekly, in each treatment cycle. Biothera, Eagan, MN Phase III trial ongoing	Cetuximab monotherapy Regorafenib	Increased overall survival Increased progression-free survival Improved quality of life
Immunotherapy (Arcelis) for treatment of renal cell carcinoma	Patients in whom renal cell carcinoma has been diagnosed	Arcelis™ (formerly AGS-003) is a personalized RNA-loaded dendritic cell immunotherapy in which dendritic cells from the patient are removed and loaded with messenger RNA isolated from the patient's tumor, then readministered to the patient. AGS-003 given in combination with sunitinib. Argos Therapeutics, Inc., Durham, NC Phase III trial planned	Everolimus Interferon alpha Interleukin-2 Sorafenib Sunitinib Temsirolimus	Increased overall survival Increased progression-free survival Improved quality of life
Injected hydrogel (SpaceOAR) to protect healthy tissue during radiation therapy	Patients undergoing radiation therapy treatment for cancers that are adjacent to delicate healthy structures (e.g., prostate cancer)	SpaceOAR™ system (spacing organs at risk) is a hydrogel injected as a liquid that forms a solid in the body and is intended for use during radiation therapy to distance organs at risk of collateral radiation damage from the targeted tumor (e.g., displace the rectum from the prostate). Augmenix, Inc., Waltham, MA Phase III trial ongoing; approved for marketing in EU; 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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Insulin-like growth factor receptor inhibitor (linsitinib) for treatment of adrenocortical carcinoma	Patients in whom locally advanced or metastatic adrenocortical carcinoma has been diagnosed	Current 2nd- and 3rd-line treatments for adrenocortical carcinoma are largely ineffective, and only about 10% of patients with metastatic disease survive 5 years after the disease is diagnosed. Insulin-like growth factor (IGF) signaling has been implicated in adrenocortical carcinoma pathogenesis through the finding that IGF-2 is often upregulated in these tumors. Linsitinib is an orally administered, small-molecule inhibitor of an IGF-2 target, the IGF-1 receptor (IGF-1R). IGF-1R signaling purportedly regulates multiple cancer-related properties, including cell growth, energy metabolism, differentiation, and apoptosis; therefore, its inhibition may have anticancer activity. In clinical trials, linsitinib is being administered twice daily, at a dose of 150 mg. Astellas Pharma, Inc., Tokyo, Japan (previously developed by Osi Pharmaceuticals, which was acquired by Astellas) Phase III trial ongoing	Etoposide/doxorubicin/ cisplatin plus mitotane Streptozotocin plus mitotane	Increased overall survival Increased progression-free survival Improved quality of life
Integrated positron emission tomography and magnetic resonance imaging system (Biograph mMR) for diagnosis and monitoring of cancer	Patients in whom cancer has been diagnosed	Imaging exams that combine positron emission tomography (PET) with MRI (Biograph™ mMR) to provide simultaneous acquisition of morphologic, functional, and metabolic imaging data; intended to take 30 minutes to perform the exam, compared with 60 minutes or more for sequential PET with MRI exams. Siemens Healthcare, Malvern, PA Received FDA 510(k) clearance Jun 2011	Stand-alone MRI and PET exams	Improved imaging Improved patient throughput Increased patient satisfaction
Integrin antagonist (cilengitide) 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 processes such as cell survival, cell 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. 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. Treatment is intended for use against newly diagnosed glioblastoma that exhibits methylation of the methylguanine-DNA methyltransferase gene (a marker of temozolomide sensitivity). EMD Serono, Inc., Rockland, MA Phase III trial ongoing; also in trials for nonsmall cell lung cancer	Temozolomide plus radiation therapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interleukin-3 receptor-targeting biologic conjugate (SL-401) for treatment-refractory acute myeloid leukemia	Patients with treatment-refractory acute myeloid leukemia (AML)	Patients with treatment-refractory AML have few treatment options and typically survive for less than a year when disease recurs. SL-401 is a novel biologic conjugate between interleukin-3 (IL-3) and diphtheria toxin that targets cells expressing the IL-3 receptor (CD123). The IL-3 receptor has been shown to be expressed by leukemic cells known as cancer stem cells, which may be highly resistant to conventional chemotherapy and have high potential to cause recurrence. SL-401 is intended to target the cancer stem cell component of AML. Stemline Therapeutics, Inc., New York, NY Phase I/II trial complete; FDA granted orphan drug status	Cladribine/cytarabine/granulocyte macrophage colony-stimulating factor (GM-CSF) plus or minus mitoxantrone or idarubicin High dose cytarabine/ anthracycline Fludarabine/ cytarabine/ GM-CSF plus or minus idarubicin Mitoxantrone/ etoposide/ cytarabine	Increased overall survival Increased progression-free survival Improved quality of life
Interleukin-12 gene therapy (TheraPlas, EGEN-001) for recurrent or persistent ovarian cancer	Patients in whom recurrent or persistent ovarian or fallopian tube cancer has been diagnosed; must have received at least 1 round of treatment with a platinum-based cytotoxic chemotherapy regimen	Patients in whom advanced ovarian cancer has been diagnosed often have recurrent disease and a poor prognosis. EGEN-001 (TheraPlas™) is a novel gene therapy intended to induce the expression of interleukin-12 (IL-12) in tumor cells; IL-12 expression is purported to lead to 3 antitumor activities: (1) activation/proliferation of natural killer (NK) cells, leading to an innate immune response against the tumor; (2) maturation/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 administered by intraperitoneal catheter to the local tumor microenvironment. EGEN, Inc., Huntsville, AL Phase II trial ongoing; FDA granted orphan drug status	Carboplatin Carboplatin/ docetaxel Carboplatin/ gemcitabine Carboplatin/ liposomal doxorubicin Carboplatin/ paclitaxel Cisplatin Cisplatin/ gemcitabine Docetaxel Etoposide Gemcitabine Liposomal doxorubicin Paclitaxel Topotecan	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Irreversible electroporation (NanoKnife) for treatment of hepatocellular carcinoma	Patients in whom early-stage hepatocellular carcinoma (HCC) that is not surgically resectable has been diagnosed	Surgical resection and/or ablation of locally advanced tumors is the only potentially curative treatment option for patients in whom hepatocellular cancer has been diagnosed. 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 formation 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 suffer “heat sink” effects and can leave the extracellular structure of large blood vessels intact, potentially allowing local ablation of tumors in close proximity to vessels while retaining vessel patency. In treating HCC, irreversible electroporation is performed in a minimally invasive laparoscopic procedure. AngioDynamics, Latham, NY Phase II trial ongoing; cleared by FDA through the 510(k) process for the surgical ablation of soft tissue; under investigational device exemption status for a premarket approval application for this indication	Cryotherapy RF ablation	Increased overall survival Increased clinical downstaging to surgically resectable tumor Improved adverse event profile Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Irreversible electroporation (NanoKnife) for treatment of pancreatic cancer	Patients 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 in whom pancreatic cancer has been diagnosed. 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 formation 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 suffer "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 is performed in a minimally invasive laparoscopic procedure. AngioDynamics, Latham, NY Phase II trial ongoing; cleared by FDA through the 510(k) process for the surgical ablation of soft tissue; in trials for various cancer applications under premarket approval process	Cryotherapy RF ablation	Increased overall survival Increased rate of clinical downstaging to surgically tumor Improved adverse event profile Improved quality of life
JAK 1/2 inhibitor (ruxolitinib, Jakafi) for treatment of myelofibrosis	Patients in whom myelofibrosis (primary myelofibrosis, post-polycythemia vera myelofibrosis, or post essential thrombocythemia myelofibrosis) has been diagnosed	Janus kinase (JAK) inhibitor (INCB018424, ruxolitinib, Jakafi™) that inhibits kinase activity of both JAK 2 and JAK 1. Half of myelofibrosis cases bear an activating mutation in JAK 2; therefore, its inhibition is a key target. Incyte Corp., Wilmington, DE, in collaboration with Novartis International AG, Basel, Switzerland FDA approved Nov 2011; 1st quarter 2012 sales from product launch suggest rapid acceptance by physicians and patients	None Off-label treatments are only palliative	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
JAK 2 inhibitor (pacritinib) for treatment of myelofibrosis	Patients in whom myelofibrosis has been diagnosed	Few treatment options are available for myelofibrosis. Janus kinase 2 (JAK 2) appears to play a central role in the majority of myelofibrosis pathophysiology; therefore, inhibition of JAK 2 is seen as a promising intervention for myelofibrosis, as demonstrated by the recent marketing approval of a dual Janus kinase 1 (JAK 1)/JAK 2 inhibitor (ruxolitinib, Jakafi™) for this indication. Pacritinib is a novel JAK kinase inhibitor that is selective for JAK 2, potentially altering the drug's efficacy and/or side effect profile. Pacritinib is administered orally, once daily. S*BIO Pte, Ltd., Singapore Phase II trial complete	Ruxolitinib	Increased overall survival Increased progression-free survival Reduced spleen size Improved quality of life
Kinase inhibitor (ENMD-2076) for platinum-based treatment-resistant ovarian cancer	Patients in whom ovarian cancer has been diagnosed	ENMD-2076 is a kinase inhibitor that targets aurora A (cell cycle progression) and angiogenic kinases vascular endothelial growth factor receptor 2, Flt-3, and fibroblast growth factor receptor 3 (tumor vascularization). EntreMed, Inc., Rockville, MD Phase II trials ongoing; FDA granted orphan drug status	Carboplatin Carboplatin/ docetaxel Carboplatin/ gemcitabine Carboplatin/ liposomal doxorubicin Carboplatin/ paclitaxel Cisplatin Cisplatin/ gemcitabine Docetaxel Etoposide Gemcitabine Liposomal doxorubicin Paclitaxel Topotecan	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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. DARA BioSciences, Inc., Raleigh, NC Phase II trial completed; FDA granted fast-track status	NSAIDs Opioid analgesics	Reduced pain Improved quality of life
Lansoprazole (PrevOnco) for treatment of advanced unresectable hepatocellular carcinoma	Patients in whom advanced unresectable hepatocellular carcinoma has been diagnosed	PrevOnco™ incorporates lansoprazole, a proton-pump inhibitor (commonly marketed antiulcer compound); incorporates proprietary NexACT drug delivery technology, which is designed to reduce by 7 times the dose needed. The drug has shown strong anticancer activity in mice bearing human liver tumors; taken orally. Apricus Biosciences, Inc., San Diego, CA Phase III trial special protocol assessment under discussion with FDA; FDA granted orphan drug status	Doxorubicin Sorafenib	Increased overall survival Increased progression-free survival Improved quality of life
Levonorgestrel-release intrauterine device (Mirena) for uterus-sparing treatment of endometrial hyperplasia and early endometrial carcinoma	Females with endometrial hyperplasia or stage 1A endometrial cancer who wish to preserve fertility	Intrauterine device (Mirena®) is a levonorgestrel (a progestogen)-release intrauterine device, plus gonadotropin-releasing hormone. It has shown some efficacy against endometrial cancer and precancers in preliminary studies. Bayer AG, Leverkusen, Germany Multiple trials ongoing	Radical hysterectomy	Preserved fertility with similar clinical outcome to surgery

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Liposomal small interfering RNA formulation targeting protein kinase N3 (Atu027) for treatment of solid tumors	Patients in whom advanced solid malignancies have been diagnosed	The activity of the phosphoinositide 3-kinase (PI3K) pathway is known to be upregulated in a wide range of cancer types. Preclinical studies have demonstrated that protein kinase N3 (PKN3) functions downstream of PI3K in tumor growth and endothelial cell migration; therefore, it might be a suitable target for an antitumor and antiangiogenic therapy. Atu027 is a preparation of small, interfering RNAs (siRNAs) packaged in a liposomal delivery mechanism. SiRNAs contained in Atu027 are intended to reduce levels of PKN3 messenger RNA, potentially reducing PKN3 activity and inhibiting solid tumor growth and/or angiogenesis. Atu027 is administered by intravenous infusion. Silence Therapeutics, plc, London, UK Phase I trial ongoing	Various chemotherapeutic regimens	Increased overall survival Increased progression-free survival Improved quality of life
Liposome encapsulated irinotecan (MM-398) for treatment of pancreatic cancer	Patients with treatment-refractory, metastatic pancreatic cancer	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 (PEP-02) 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. In clinical trials, MM-398 is being administered by intravenous infusion as a monotherapy. Merrimack Pharmaceuticals, Inc., Cambridge, MA Phase III trial ongoing; FDA granted orphan drug status for treating 2nd-line pancreatic cancer	Capecitabine Capecitabine/ oxaliplatin FOLFOX (folinic acid [leucovorin], 5-fluorouracil, oxaliplatin) Gemcitabine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Liposome encapsulated 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 is purported to allow the slow release of vincristine over a period of time, 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. Talon Therapeutics, Inc., San Mateo, CA FDA granted Marqibo orphan drug status for treating ALL in the salvage setting; FDA approved Aug 9, 2012, for patients whose leukemia has recurred 2 or more times, or whose leukemia has progressed after 2 or more regimens of anti-leukemia therapy	Various chemotherapy regimens including: combinations of vincristine, steroids, and anthracyclines; asparaginase and methotrexate; high-dose cytarabine	Increased overall survival Increased disease-free survival Improved quality of life
Liver chemosaturation drug/device combination (melphalan-Chemosat) for treatment of melanoma metastases to the liver	Patients with ocular or cutaneous melanoma that has metastasized to the liver	Liver cancer is largely refractory to standard systemic chemotherapy; although targeted chemotherapy delivery options are available for treating liver cancer (e.g., hepatic artery delivered chemotherapy, trans-arterial chemoembolization), systemic side effects preclude the use of maximum chemotherapy doses. The Chemosat® system is a delivery method that introduces a chemotherapy drug (melphalan) through the hepatic artery and removes the drug by filtering blood exiting the liver through the venous system. In this way, high doses of chemotherapy can be delivered while sparing the patient systemic side effects. Adjunctive therapy to treat the primary melanoma and nonhepatic metastases may also be administered. Delcath Systems, New York, NY Phase III trial completed; FDA returned new drug application (NDA) in Feb 2011 asking for further safety data; pre-NDA held with FDA in Jan 2012 and company intended to refile NDA in 2nd quarter 2012; Conformité Européene (CE) marked for liver cancer	Hepatic artery-delivered chemotherapy Trans-arterial chemoembolization	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 thereby allowing the surgeon to resect additional tissue during the same surgical procedure; the system uses radiofrequency spectroscopy to discern differences in the electromagnetic signature of cancerous cells relative to normal tissue. Dune Medical Devices, Inc., Framingham, MA Pivotal trial completed; premarket approval application submitted May 2011; FDA granted expedited review; FDA's General & Plastic Surgery Devices advisory panel voted 10-1 to approve the MarginProbe System; system is available in Europe	No currently marketed comparator in the U.S.	Reduced number of re-excision surgeries performed Improved rate of complete surgical resection (e.g., no positive margin)
Marine depsipeptide (plitidepsin) for treatment of relapsed/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. PharmaMar subsidiary of Grupo Zeltia, Madrid, Spain Phase III trial ongoing	Various chemotherapy regimens such as: Bendamustine/ bortezomib Bortezomib/ dexamethasone Cyclophosphamide/ lenalidomide/ dexamethasone Dexamethasone/ cyclophosphamide/ etoposide/cisplatin High-dose cyclophosphamide Lenalidomide/ dexamethasone Thalidomide/ dexamethasone	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
MEK inhibitor (selumetinib) for treatment of advanced solid tumors	Patients in whom advanced solid cancers have been diagnosed	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 (AZD6244, ARRY-886) is an orally administered, MEK inhibitor under study for treating various cancers, including ovarian cancer, colorectal cancer, melanoma, nonsmall cell lung cancer, and hepatocellular carcinoma. AstraZeneca, London, UK Phase II trials ongoing	Standard chemotherapeutic regimens	Increased overall survival Increased progression-free survival Improved quality of life
MEK inhibitor (trametinib) for treatment of advanced melanoma with activating *BRAF* mutation	Patients with stage IIIc or IV malignant cutaneous melanoma that harbors an activating *BRAF* mutation	Patients with metastatic melanoma have a poor prognosis with current treatments yielding a 5-year survival rate of less than 10%. 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 (GSK1120212) is an inhibitor of MEK 1 and MEK 2, which may have antineoplastic activity in tumors dependent on MAPK/ERK pathway activation. GlaxoSmithKline, Middlesex, UK Phase III trial as a monotherapy versus standard chemotherapy was reported to have met its primary endpoint in early 2012 and a new drug application for this indication was submitted to FDA in Aug 2012; phase II trial ongoing in patients previously treated with or without a *BRAF* inhibitor; phase II trial ongoing in combination with the *BRAF* inhibitor dabrafenib	High dose interleukin-2 Dacarbazine Ipilimumab Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
MEK inhibitor (trametinib) for treatment of pancreatic cancer	Patients in whom 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. The survival and proliferation of many cancers is maintained in part by activation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway of which MEK is a member; trametinib (GSK1120212) is an inhibitor of MEK 1 and MEK 2, which may have antineoplastic activity in tumors dependent on MAPK/ERK pathway activation. In a current clinical trial, trametinib is administered in combination with gemcitabine. GlaxoSmithKline, Middlesex, UK Phase II trial ongoing	Gemcitabine alone	Increased overall survival Increased progression-free survival Improved quality of life
Microtubule destabilizing agent (ombrabulin) for treatment of soft tissue sarcoma	Patients with advanced soft tissue sarcoma who have undergone prior systemic chemotherapy with anthracycline (e.g., doxorubicin) and ifosfamide	Doxorubicin is the only FDA-approved treatment for soft tissue sarcomas (excluding gastrointestinal stromal tumors and liposarcomas), and no consensus on treatment exists for patients whose disease has progressed during doxorubicin-based chemotherapy. Ombrabulin (AVE8062) is a novel, small-molecule agent that is purported to function through the depolymerization of microtubules. Although the exact antitumor mechanism of ombrabulin is unclear, it is thought to act as a vascular targeting agent that preferentially disrupts existing tumor vasculature, leading to ischemia and subsequent tumor necrosis. In a late-phase trial, ombrabulin is being administered by intravenous infusion in combination with cisplatin. Sanofi, Paris, France Phase III trial ongoing	Pazopanib Sorafenib (off label) Sunitinib (off label)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mitochondrial metabolism disruptor (CPI-613) for treatment of various cancers	Patients in whom an advanced malignancy, in particular pancreatic cancer or acute myeloid leukemia (AML), has been diagnosed	The metabolic activity of cancer cells is altered significantly compared with 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 is purported to function by leading to the inhibition of 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). Cornerstone Pharmaceuticals, Inc., Cranbury, NJ Phase I/II trials ongoing in hematologic malignancies; phase I/II trial ongoing in pancreatic cancer; FDA granted orphan drug status for AML and pancreatic cancer	Various chemotherapy regimens	Increased overall survival Increased progression-free survival Improved quality of life
Mobile telemedicine for cervical screening	Patients in rural areas in need of routine cervical screening	Females living in rural areas face barriers to access to cervical screening; options to improve rates of routine screening are needed. Visual inspection of the cervix with application of 4% acetic acid (VIA) is an inexpensive alternative to cytology-based screening; in remote, resource-limited areas, photographic inspection with acetic acid can be performed by a clinician, who sends photographic images of a patient's cervix treated with 4% acetic acid and taken using a mobile phone; images are transmitted by MMS to a regional medical center for evaluation by a trained health care practitioner for signs of disease. Department of Dermatology, University of Pennsylvania, Philadelphia Pilot study conducted in Gaborone, Botswana	Pap (Papanicolaou) screening VIA	Reduced cost of care Increased rate of cervical cancer screening Reduced rates of cervical disease Increased screening adherence

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Modified HER2/neu peptide (AE37) therapeutic vaccine to prevent recurrent breast cancer	Patients with HER2/neu expression who have completed treatment of lymph-node-positive breast cancer or high-risk lymph-node-negative breast cancer with no evidence of remaining disease	Despite numerous 1st-line treatment options for breast cancer, many women experience disease recurrence; therefore, a need exists for a treatment that could kill residual tumor cells missed by 1st-line treatments or destroy recurrent disease. AE37 is a modified peptide vaccine directed against the HER2/neu receptor, which is overexpressed in about 30% of breast cancers; the peptide can be displayed by major histocompatibility complex (MHC) class II and, therefore, could activate helper T cells, which could improve establishment of long-term immunity; the peptide has been modified with a 4-amino acid sequence called the li-Key, which may improve class II MHC presentation by enabling the AE37 peptide to displace antigens from class II MHC and present the HER2/neu derived peptide. Antigen Express, Inc., Worchester, MA Phase IIb trial ongoing	Trastuzumab	Increased overall survival Increased progression-free survival Reduced breast cancer recurrence Improved quality of life
mTOR inhibitor (everolimus, Afinitor) for treatment of estrogen-receptor-positive breast cancer	Patients with metastatic estrogen-receptor-positive breast cancer that has progressed after 1st-line hormone therapy	For patients whose breast cancer progresses following 1st-line treatment with antiestrogen therapy, followup antiaromatase therapy may delay progression; however, not all patients respond. Everolimus (Afinitor®) is a small-molecule inhibitor of the protein mammalian target of rapamycin (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); however, its use in breast cancer treatment has not yet been approved. In the current clinical trial, everolimus is being administered in combination with the 2nd-line hormone therapy exemestane. Novartis International AG, Basel, Switzerland FDA approved Jul 2012 for treating postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ breast cancer) in combination with exemestane after failure of treatment with letrozole or anastrozole	Exemestane monotherapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
mTOR inhibitor (everolimus, Afinitor) for treatment of pancreatic neuroendocrine tumors	Patients with surgically unresectable pancreatic neuroendocrine tumors (PNETs) that have progressed within the past year	Patients with PNETs have few treatment options, and existing treatments are of limited efficacy. The mammalian target of rapamycin (mTOR)/phosphoinositide 3-kinase pathway is a central regulator of cell growth, cell proliferation, cell death, and cell migration. Inhibition of mTOR has exhibited anticancer activity in a number of disease settings. Everolimus (Afinitor®) is an mTOR inhibitor FDA approved for treating renal cell carcinoma and subependymal giant cell astrocytomas. It is proposed for treating PNETs. In clinical trials of patients with PNETs, everolimus was administered in a daily, oral dose of 10 mg. Novartis International AG, Basel, Switzerland FDA approved May 2011 for treating PNETs	5-Fluorouracil Capecitabine Dacarbazine Doxorubicin Streptozocin Sunitinib Temozolomide	Increased overall survival Increased progression-free survival 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 currently 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. Prima BioMed, Ltd., Melbourne, Australia Phase II/III trial ongoing	Bevacizumab Paclitaxel	Increased of overall survival Increased progression-free survival Improved quality of life
MUC1 therapeutic vaccine (TG4010) for nonsmall cell lung cancer	Patients with chemotherapy-naïve nonsmall cell lung cancer (NSCLC) who are mucin-1 (MUC-1)-positive	Only about 25% of patients with NSCLC respond to standard 1st-line therapies such as carboplatin/paclitaxel. TG4010 is a therapeutic cancer vaccine administered by subcutaneous injection; it comprises a viral vector encoding both a tumor antigen (MUC-1) and an immune stimulant (interleukin-2); about 60% of NSCLC tumors express MUC-1. 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. Transgene SA, Cedex, France Phase IIb/III trial ongoing; FDA granted fast track status	Melanoma antigenic epitope-A3 therapeutic vaccine in development Paclitaxel/carboplatin	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multikinase inhibitor (brivanib) 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. Brivanib is a novel multikinase inhibitor that inhibits the activity of multiple tyrosine kinases including vascular endothelial growth factor (VEGF) receptors and fibroblast growth factor receptors (FGFRs). Brivanib's activity against FGFRs differentiates it from multikinase inhibitors currently available for treating HCC. 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 fibroblast growth factor pathways may have synergistic anticancer effects. In late-stage clinical trials, brivanib is administered orally, 800 mg, daily. Brivanib is under study in 3 HCC indications: 1st- and 2nd-line chemotherapy after treatment with sorafenib and adjunctive therapy with transarterial chemoembolization (TACE). Bristol-Myers Squibb, New York, NY Phase III trials ongoing; phase III trial in the 2nd-line setting failed to meet its primary endpoint; however, additional phase III trials continue	Sorafenib alone TACE alone	Increased overall survival Increased progression-free survival Improved quality of life
Multikinase inhibitor (dovitinib) for treatment of metastatic renal cell carcinoma	Patients with metastatic renal cell carcinoma (RCC) previously treated with both vascular endothelial growth factor (VEGF) targeted therapy (e.g., axitinib, bevacizumab, pazopanib, sunitinib, tivozanib) and mTOR inhibitor therapy (e.g., everolimus, ridaforolimus, temsirolimus)	Metastatic RCC that has progressed after VEGF-targeted and mammalian target of rapamycin (mTOR) inhibitor therapies has not been treatable, and patients have a poor prognosis. Dovitinib is a novel multikinase inhibitor that inhibits the activity of 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 currently 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. Novartis International AG, Basel, Switzerland Phase III trial ongoing	Sorafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multikinase inhibitor (lenvatinib) for treatment of differentiated thyroid cancer	Patients with differentiated thyroid cancer that is resistant to radioiodine therapy	Differentiated thyroid cancer (e.g., papillary, follicular) comprises the majority of diagnosed thyroid cancers. Although many differentiated thyroid cancers are treated successfully with radioiodine, patients with disease that is resistant to 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, cell proliferation, and angiogenesis (e.g., vascular endothelial growth factor receptors 2 and 3). In a late-phase clinical trial, lenvatinib is being administered as a once-daily dose of 24 mg, taken in an oral tablet. Eisai Co., Ltd., Tokyo, Japan Phase III trial ongoing	Pazopanib (off label) Sorafenib (off label) Sunitinib (off label)	Increased overall survival Increased progression-free survival Improved quality of life
Multikinase inhibitor (masitinib) for treatment of activating *c-KIT* mutation-positive, metastatic melanoma	Patients with non-resectable 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), currently 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. AB Science S.A., Paris, France Phase III trial ongoing	Dacarbazine Interleukin-2 Ipilimumab Nilotinib (in development)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multikinase inhibitor (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 given in a twice-daily oral dose for 2 weeks. Patients are administered midostaurin following both induction therapy with cytarabine and daunorubicin and consolidation therapy with high-dose cytarabine. Novartis International AG, Basel, Switzerland Phase III trial ongoing	Cytarabine/ daunorubicin	Increased overall survival Increased progression-free survival Improved quality of life
Multikinase inhibitor (nilotinib, Tasigna) for treatment of activating *c-KIT* mutation-positive, metastatic melanoma	Patients with non-resectable or metastatic melanoma who harbor an activating *c-KIT* mutation	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 tumor), currently no KIT kinase inhibitor is approved for treating *c-KIT* mutation-positive melanoma. Nilotinib (Tasigna®) is an orally administered, tyrosine kinase inhibitor approved for treating Philadelphia chromosome–positive chronic myelogenous leukemia. In addition to inhibiting the Philadelphia chromosome–encoded BCR-ABL, nilotinib also has activity against KIT and a number of additional kinases. Nilotinib is under study as a monotherapy for treating melanoma. Novartis International AG, Basel, Switzerland Phase II trials ongoing	Dacarbazine Interleukin-2 Ipilimumab Masitinib (in development)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multikinase inhibitor (nintedanib, Vargatef) for chemotherapy-resistant ovarian cancer	Patients in whom chemotherapy-naive treatment-resistant 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, twice daily. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trial ongoing	Intraperitoneal carboplatin/paclitaxel Intravenous carboplatin/paclitaxel	Increased overall survival Increased progression-free survival Improved quality of life
Multikinase inhibitor (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 (pemetrexed monotherapy or docetaxel monotherapy). Nintedanib is administered as an oral tablet, twice daily. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials ongoing	Various combination therapies including: Bevacizumab Carboplatin Crizotinib Docetaxel Erlotinib Pemetrexed	Increased overall survival Increased progression-free survival Improved quality of life
Multikinase inhibitor (pazopanib, Votrient) to prevent recurrence of ovarian cancer after successful 1st-line therapy	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 in whom ovarian cancer is diagnosed often respond to 1st-line treatment with cytoreduction and chemotherapy; however, a large number of these patients will experience disease recurrence, and 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 dose of 800 mg/day, for up to 2 years. GlaxoSmithKline, London, UK Phase III trial ongoing; FDA approved for renal cell carcinoma	Bevacizumab may be used as maintenance therapy after bevacizumab-containing treatment regimens Paclitaxel Watchful waiting	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multikinase inhibitor (regorafenib) for treatment of gastrointestinal stromal tumors	Patients with advanced/ metastatic gastrointestinal stromal tumors (GIST) that progressed following 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 and overall survival times of 100 and 300 days, respectively. Regorafenib 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). Bayer AG, Leverkusen, Germany Phase II and phase III trials ongoing; In Feb 2011, FDA granted orphan drug status for GIST; in Apr 2012, Bayer announced that regorafenib had improved survival in a phase III trial; in Aug 2012, Bayer announced that a new drug application for this indication had been submitted to FDA	Sorafenib	Increased overall survival Increased progression-free survival Improved quality of life
Multikinase inhibitor (regorafenib) for treatment of hepatocellular carcinoma	Patients with unresectable hepatocellular carcinoma (HCC) that has progressed after treatment with the multikinase inhibitor sorafenib	In patients who 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. No 2nd-line therapy is available after sorafenib. Regorafenib 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., sunitinib). Bayer AG, Leverkusen, Germany Phase II trial ongoing	Placebo	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multikinase inhibitor (regorafenib) for treatment of metastatic colorectal cancer	Patients with metastatic colorectal cancer (CRC) as both a 1st-line treatment in combination with standard cytotoxic chemotherapy (FOLFOX) and as a salvage treatment after all available treatments have been tried	Many treatment options are available for 1st-line treatment of metastatic CRC, but 5-year survival rates are only about 25%. No multikinase inhibitors have been approved for use in metastatic CRC. Regorafenib 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., sunitinib). Bayer AG, Leverkusen, Germany Phase III trial for salvage therapy was reported as having met its primary endpoint in Oct 2011; FDA granted regorafenib fast-track status for this indication; phase II trial for 1st-line therapy ongoing; FDA approved for metastatic colorectal cancer Sept 2012.	1st-line therapy comparators include: FOLFOX (folinic acid [leucovorin], 5-fluorouracil [5-FU], oxaliplatin) alone FOLFOX plus targeted therapy (e.g., bevacizumab, cetuximab, panitumumab) Other cytotoxic chemotherapy regimens plus or minus targeted therapy (e.g., CapeOX, FOLFIRI, [leucovorin, 5-FU, and irinotecan], 5-FU/leucovorin, capecitabine, FOLFOXIRI [FOLFIRI plus oxaliplatin])	Increased overall survival Increased progression-free survival Improved quality of life
Multikinase inhibitor (regorafenib) for treatment of renal cell carcinoma	Patients in whom metastatic or unresectable renal cell carcinoma (RCC) has been diagnosed	No curative treatments are currently available for unresectable/metastatic RCC, and this drug represents a new treatment option with a novel multikinase inhibitory profile. Regorafenib 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., sunitinib). Bayer AG, Leverkusen, Germany Phase II trial ongoing	Axitinib Bevacizumab plus or minus interferon Everolimus High-dose interleukin-2 Pazopanib Sorafenib Sunitinib Temsirolimus Tivozanib (in development)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multikinase inhibitor (sunitinib, Sutent) for treatment of pancreatic neuroendocrine tumors	Patients with surgically unresectable pancreatic neuroendocrine tumors (PNETs) that have progressed within the past year	Patients with PNETs have few treatment options and existing treatments are of limited efficacy. Like many tumors, PNETs depend on receptor tyrosine kinase activity to drive angiogenic and mitogenic processes. PNETs have been shown to express a range of receptor tyrosine kinases that could mediate these processes, such as certain platelet-derived growth factor receptors, vascular endothelial growth factor receptors, and stem-cell factor receptors. Sunitinib (Sutent®) is an orally administered, small-molecule inhibitor of the kinase activity of these receptors. In clinical trials it was administered at a daily dose of 37.5 mg. Pfizer, Inc., New York, NY FDA approved May 2011 for treating PNETs	5-Fluorouracil Capecitabine Dacarbazine Doxorubicin Everolimus Streptozocin Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life
Multi-targeted kinase inhibitor (ponatinib) 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, so 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 are harder to treat); ponatinib is a next-generation BCR-ABL tyrosine kinase inhibitor rationally designed to be effective against common mutations conferring resistance to current BCR-ABL tyrosine kinase inhibitors. Administered orally, 45 mg, once daily. Ariad Pharmaceuticals, Inc., Cambridge, MA Phase II trials ongoing; submitted new drug application to FDA in Jul 2012 for accelerated approval; FDA granted orphan drug status for CML and Philadelphia chromosome–positive ALL.	Dasatinib Imatinib Nilotinib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Necitumumab for treatment of advanced nonsmall cell lung cancer	Patients in whom advanced squamous nonsmall cell lung cancer (NSCLC) has been diagnosed	Advanced NSCLC has a high mortality rate and patients have a poor prognosis; new therapies that can improve survival are needed. 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; may be administered as an 800 mg intravenous infusion on days 1 and 8 of every 3-week cycle; may be used in combination with gemcitabine-cisplatin. The drug is in a similar class as cetuximab, which is used for treating many cancers but is not labeled for treating NSCLC. Eli Lilly and Co., Indianapolis, IN Bristol-Myers Squibb Co., Princeton, NJ Phase III trials ongoing	Cetuximab (off label) Erlotinib Panitumumab	Increased overall survival Increased progression-free survival Improved quality of life
Off-label human papillomavirus vaccination (Gardasil and Cervarix) to prevent head and neck cancer	Persons engaging in oral sexual activity and kissing	Oncogenic human papillomavirus (HPV) strains can cause cervical and anal cancer, as well as other cancers including head and neck cancer; between 1984 and 1989, only 16% of oropharyngeal cancers were linked to HPV; between 2000 and 2004, HPV was responsible for 75% of oropharyngeal cancers; if current trends continue, oropharyngeal cancer in men will surpass incidence of cervical cancer in 2025. Both commercially available HPV vaccines (Gardasil®, Cervarix®) contain virus-like particles for oncogenic HPV types 16 and 18 which are responsible for the majority of HPV associated cancers; HPV vaccines may be used off label for the prevention of head and neck cancers due to HPV 16 or 18 despite the current lack of data and no apparent attempt to generate data on this indication by vaccine manufacturers. Gardasil, Merck & Co., Inc., Whitehouse Station, NJ; Cervarix, GlaxoSmithKline, Middlesex, UK Both vaccines FDA approved for preventing cervical cancer	Abstinence No vaccination Safer sex-practices Selective choice of partners	Reduced incidence of head and neck cancers and precancers

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label metformin for treatment of breast cancer	Patients in whom breast cancer has been diagnosed.	Retrospective studies of patients with diabetes taking metformin and 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 mammalian target of rapamycin pathway. Additionally, metformin's actions in reducing circulating insulin levels may be antineoplastic due to 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. Phase II trials ongoing in neo-adjuvant setting; phase III trial ongoing in adjuvant setting to prevent recurrence; phase I/II trials ongoing in metastatic disease	Various chemotherapy regimens Various hormone therapies	Increased overall survival Increased progression-free survival Improved quality of life
Off-label rosuvastatin 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 within 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 is believed to have potential as a chemopreventive agent for colon cancer. Under study by National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA, and the National Cancer Institute, Bethesda, MD Phase III trial ongoing	No commonly used chemopreventive agent exists for treating colorectal cancer Compounds under investigation include: Aspirin Calcium supplements Curcumin Nonsteroidal anti-inflammatory drugs Omega-3 fatty acids	Reduced recurrence rate of adenomatous polyps Increased overall survival
Off-label zoledronic acid (Zometa) for treatment of breast cancer	Postmenopausal women with stage II/III breast cancer who have undergone surgery and/or surgical resection	Zoledronic acid (Zometa®) is a bisphosphonate used to prevent skeletal fractures in cancer patients at risk of fracture from bone metastases; recent studies suggest that the drug may also treat the primary cancer, improve overall survival, and reduce cancer recurrence rates in women with low estrogen levels (e.g., post-menopausal patients). Given that the drug is commercially available, its off-label use for this may be an option exercised by oncologists. Novartis International AG, Basel, Switzerland Two phase III trials completed; 1 trial (ABCSG-12) reported positive results; however, a 2nd (AZURE) trial observed a benefit only in post-menopausal women. Based on AZURE trial results, Novartis decided not to pursue expanded label for zoledronic acid; however, physicians may prescribe off label; additional phase III trials of zoledronic acid for breast cancer are ongoing	Chemotherapy Hormone therapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label zoledronic acid (Zometa) for treatment of early stage multiple myeloma	Patients in whom early stage multiple myeloma has been diagnosed	Zoledronic acid is a bisphosphonate used to prevent skeletal fractures in cancer patients, including those in whom multiple myeloma is diagnosed. Recent studies suggest that Zometa® confers increased overall survival in patients with multiple myeloma, which may support off-label use. In a trial, the drug was given with and without thalidomide. Zoledronic acid dose was 4 mg^2 intravenously on day 1 every 84 days for 1 year and once per year thereafter. Mayo Clinic, Rochester, MN, in collaboration with National Cancer Institute Phase III trial (NCT00432458) completed Apr 2012	Chemotherapy Hematopoietic stem-cell transplantation Medicines: Alendronate Etidronate Oral clodronate (trial comparator) Pamidronate Other bisphosphonates	Increased overall survival Increased progression-free survival Improved quality of life
Oncolytic reovirus (Reolysin) for treatment of advanced *KRAS* mutant colorectal cancer	Patients with advanced or metastatic *KRAS* mutant colorectal cancer (CRC) who have undergone prior treatment with an oxaliplatin-based chemotherapy regimen	Oncolytic reovirus (Reolysin®) is intended to treat various cancers and cell proliferative disorders, including CRC; Reolysin replicates specifically in cells that have activated RAS; 50% of CRCs are believed to have activated RAS. Given in combination with folinic acid (leucovorin), 5-fluorouracil, and irinotecan combination. Oncolytics Biotech, Inc., Calgary, Alberta, Canada Phase I trial ongoing	Folinic acid (leucovorin), 5-fluorouracil, and irinotecan Irinotecan	Increased overall survival Increased progression-free survival Improved quality of life
Oncolytic reovirus (Reolysin) for treatment of advanced pancreatic cancer	Patients in whom advanced pancreatic cancer has been diagnosed	Oncolytic reovirus (Reolysin®) is intended to treat various cancers and cell proliferative disorders, including pancreatic cancer for which no effective options are available. Reolysin replicates specifically in cells that have activated RAS. Activated RAS is seen in 90% of pancreatic cancers. Administered intravenously in combination with gemcitabine. Oncolytics Biotech, Inc., Calgary, Alberta, Canada Phase II trials ongoing	Gemcitabine and platin-based combination chemotherapy regimens Erlotinib Fluoropyrimidine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oncolytic reovirus (Reolysin) for treatment of platinum-resistant head and neck cancer	Patients in whom platinum-resistant head and neck cancer has been diagnosed and who have undergone 1st-line treatment with a platinum-based chemotherapy regimen	Reolysin® is an oncolytic reovirus being developed to treat various cancer and cell proliferative disorders; replicates specifically in cells that have activated RAS, which may play a role in more than 2/3 of all cancers; administered in combination with paclitaxel and carboplatin. Oncolytics Biotech, Inc., Calgary, Alberta, Canada Phase III trial ongoing	Various platin-based multiple agent chemotherapy regimens 5-fluorouracil Bleomycin Docetaxel Gemcitabine Ifosfamide Methotrexate Paclitaxel	Increased overall survival Increased progression-free survival Improved quality of life
Oncolytic reovirus (Reolysin) for treatment of recurrent or persistent ovarian cancer	Patients in whom recurrent or persistent ovarian, fallopian tube, or primary peritoneal cancer has been diagnosed	Reolysin® is a formulation of oncolytic reovirus being developed for treating various cancers and cell proliferative disorders; has been shown to replicate specifically in cells that have activated RAS; activating mutations of RAS and its upstream elements may play a role in more than 2/3 of all human cancers, including most metastatic disease. Oncolytics Biotech, Inc., Calgary, Alberta, Canada Phase II trial ongoing	Various platin-based multiple agent chemotherapy regimens Docetaxel Etoposide Gemcitabine Liposomal doxorubicin Paclitaxel Topotecan	Increased overall survival Increased progression-free survival Improved quality of life
Oncolytic reovirus (Reolysin) for treatment-refractory solid tumors in children	Pediatric patients in whom relapsed or refractory solid tumor has been diagnosed	Reolysin® is a formulation of oncolytic reovirus being developed for treating various cancers and cell proliferative disorders. It has been shown to replicate specifically in cells that have activated RAS. Activating mutations of the RAS and its upstream elements may play a role in more than 2/3 of all human cancers, including most metastatic disease. Reolysin is being examined in combination with cyclophosphamide in pediatric patients with relapsed or refractory solid tumors. Oncolytics Biotech Inc., Calgary, Alberta, Canada Phase I trial ongoing	Chemotherapy Radiation Surgery	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oncolytic virus (Cavatak) for treatment of late-stage melanoma	Patients with advanced (stage IIIc or IV) melanoma who have undergone no more than 1 systemic therapy	Although the availability of treatments such as BRAF inhibitors and anti-CTLA4 antibodies has improved outcomes for patients with advanced melanoma, these patients still have few treatment options and a poor prognosis. Cavatak™ is a preparation of coxsackievirus A21. Preclinical research indicated that melanoma cells upregulate a cell-surface molecule, ICAM-1, a viral receptor that may promote preferential infection of tumor cells. Cavatak™ is intended to treat melanoma through direct lysis of virally infected tumor cells, thereby generating an immune response to tumor antigens. In clinical trials, Cavatak is administered by intratumoral injection. Viralytics, Ltd., Pymble, New South Wales, Australia Phase II trial ongoing	Dacarbazine Ipilimumab Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life
Oncolytic virus (JX-594) for treatment of nonresectable hepatocellular carcinoma	Patients in whom nonresectable hepatocellular carcinoma has been diagnosed	Less than 20% of liver cancer can be treated surgically, and effective treatments are needed for the nonsurgical patients. JX-594 is a genetically modified vaccinia virus with 2 genetic modifications: (1) the viral thymidine kinase gene is deleted, so the virus is dependent on host thymidine kinase for replication—sufficient levels are found in tumor cells; and (2) a gene encoding colony-stimulating factor is added. It is proposed to marshal an immune response to infected cells; vaccinia virus also has natural tropism to tumor cells. Therapeutic effects are mediated by immune response and by tumor cell/tumor vasculature cell lysis caused by the viral life cycle. Jennerex Biotherapeutics, Inc., San Francisco, CA Phase II trials ongoing	Sorafenib Transcatheter arterial chemoembolization (cisplatin, doxorubicin)	Increased overall survival Increased progression-free survival Improved quality of life
OncoVex GM-CSF 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. OncoVex granulocyte macrophage colony-stimulating factor (GM-CSF; talimogene laherparepvec) is an oncolytic virus; the virus is purported to replicate only in tumor cells; OncoVex is engineered to lyse tumors cells and express tumor-specific antigens and GM-CSF, which help to generate tumor specific immune responses for additional benefit. Administered up to 4 mL of 10^8 pfu/mL/per intratumoral injection in trials. Amgen, Inc., Thousand Oaks, CA Phase III trial ongoing	Dacarbazine Interleukin-2 Ipilimumab Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Orteronel (TAK 700) for treatment of 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. Many prostate tumors remain dependent on androgens for growth and survival; new treatments that can disrupt the production of bioactive androgens may provide effective tumor therapy. Orteronel (TAK 700) is a steroid 17-alpha-hydroxylase inhibitor; this enzyme is involved in the formation of dehydroepiandrosterone (DHEA) and androstenedione, which may ultimately be metabolized into testosterone; testosterone is required for the growth of many prostate tumors; orteronel may be used in chemotherapy-naive patients or after docetaxel, in combination with prednisone. Millennium Pharmaceuticals, Inc., Cambridge, MA Phase III trials ongoing	Abiraterone Cabazitaxel Docetaxel Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
P53 activator (APR-246) for treatment of hematologic malignancies or prostate cancer	Patients with a hematologic malignancy or prostate cancer	*P53* is a tumor-suppressor gene that plays a prominent role in promoting apoptosis. The loss of *p53* function is associated with many cancer types; however, no therapy attempting to restore *p53* function is currently available. APR-246 is a small, peptide molecule that has been shown to promote restoration of the transcriptional activity of mutated *p53*, potentially restoring *p53* function and apoptosis of cancer cells. Aprea AB, Solna, Sweden Phase I/II trial completed. Positive data reported.	Various cancer therapies	Increased overall survival Increased progression-free survival Improved quality of life
Pan-RAF inhibitor (MLN-2480) for treatment of metastatic melanoma	Patients in whom metastatic melanoma has been diagnosed	The identification of activating *BRAF* mutations in about 50% of melanomas, and the demonstrated antimelanoma activity of BRAF inhibitors has implicated the centrality of RAF kinase activity in the pathogenesis of melanoma. Although targeting *BRAF* has demonstrated significant anticancer activity, its activity is limited to the subset of melanomas with activating *BRAF* mutations, and the majority of these cancers develop resistance to *BRAF* inhibition. Pan-RAF inhibition might allow targeting of a wider range of melanomas and/or overcome some of the resistance mechanisms associated with *BRAF* inhibition. Millennium Pharmaceuticals, Inc., subsidiary of Takeda Pharmaceutical Co., Ltd., Osaka, Japan, in collaboration with Sunesis Pharmaceuticals, South San Francisco, CA Phase I trial ongoing	Dacarbazine Ipilimumab Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Partial wave spectroscopy for lung cancer screening	Patients at high risk of developing lung cancer (e.g., smokers, ex-smokers)	Partial wave spectroscopy is proposed as a new microscopy technique that is intended to increase the resolution of detection down to "nanoscale." It is purported to enable detection of subtle changes in cellular architecture in noncancerous tissue located at a distance from cancerous lesion (known as "field carcinogenesis"). Northwestern University, Chicago, IL Preliminary validation study completed on 135 smokers	No screening equivalent currently available Other tests for lung cancer screening: Chest radiograph Computed tomography Sputum cytology	Increased sensitivity and specificity Increased predictive value Avoided unnecessary testing Earlier intervention and treatment Increased overall survival
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 who 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. It is administered through intramuscular injection on outpatient basis. Polaris Pharmaceuticals, Inc., San Diego, CA Phase III trial initiated under FDA special protocol assessment; FDA granted orphan drug status	Placebo	Increased overall survival Increased progression-free survival Improved quality of life
Pegylated human recombinant hyaluronidase (PEG-PH20) for treatment of pancreatic cancer	Patients with metastatic pancreatic cancer and no prior treatment	Only about 25% of patients with metastatic pancreatic cancer have disease that responds to 1st-line therapy with gemcitabine; effective treatments are needed for those whose disease does not respond. PEG-PH20 is a formulation of the enzyme hyaluronidase, which functions to degrade the hyaluronan (HA) component of the extracellular matrix. HA is a gel-like substance that is a component of normal tissues of the body (e.g., skin, cartilage), but it also forms a layer on the surface of tumors, which may limit exposure of the tumor to therapeutic compounds. PEG-PH20 is purported to temporarily degrade HA, potentially increasing the efficacy of chemotherapy. In clinical trials for treating pancreatic cancer, PEG-PH20 is being administered in combination with the standard chemotherapy drug gemcitabine. Halozyme Therapeutics, San Diego, CA Phase I/II trial ongoing	5-Fluorouracil/ leucovorin Gemcitabine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Peptide vaccine (FPI-01) to prevent relapse or delay progression of acute myeloid leukemia	Patients with acute myeloid leukemia (AML) who have achieved complete remission after standard 1st-line therapy	Although many patients respond to 1st-line chemotherapy for AML and achieve a complete remission, about 80% of these patients eventually experience disease relapse. FPI-01 is a therapeutic cancer vaccine that is intended to prevent relapse or prolong the interval to disease relapse. The vaccine is based on multiple peptides derived from the protein product of the Wilms' Tumor-1 (*WT-1*) gene, which is overexpressed in many cancer types including AML. Vaccine is delivered subcutaneously. Formula Pharmaceuticals, Inc., Berwyn, PA Phase II trial ongoing	No AML maintenance comparator available	Increased overall survival Increased progression-free survival Improved quality of life
Peptide-cytokine complex (NGR-hTNF) for treatment of advanced nonsmall cell lung cancer	Patients in whom advanced or recurrent nonsmall cell lung cancer has been diagnosed	NGR-hTNF (human tumor necrosis factor) is a peptide-cytokine complex; the NGR peptide binds preferentially to tumor vasculature, and TNF can induce an immune cell reaction/apoptosis. Being tested in combination with conventional chemotherapy regimens. Given in dosage of 0.8 mcg/m² as 60-minute intravenous infusion every 3 weeks until confirmed evidence of disease progression or unacceptable toxicity occurs. MolMed, S.p.A., Milan, Italy Phase II trial ongoing	Standard chemotherapy regimens including: Cisplatin/gemcitabine plus or minus bevacizumab Cisplatin/paclitaxel or docetaxel plus or minus bevacizumab Cisplatin/pemetrexed plus or minus bevacizumab Crizotinib Erlotinib	Increased overall survival Increased progression-free survival Improved quality of life
Peptide-cytokine complex (NGR-hTNF) for treatment of advanced or metastatic hepatocellular carcinoma	Patients in whom advanced or metastatic hepatocellular carcinoma has been diagnosed	NGR-hTNF (human tumor necrosis factor) is a peptide-cytokine complex; the NGR peptide binds preferentially to tumor vasculature, and TNF can induce an immune cell reaction/apoptosis. NGR-hTNF is being given as an intravenous infusion as a single agent every 3 weeks or weekly in patients previously treated with not more than 1 systemic regimen. MolMed, S.p.A., Milan, Italy Phase II trial ongoing	Chemoembolization Standard systemic chemotherapy: Gemcitabine/oxaliplatin Sorafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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. Given in dosage of 0.8 mcg/m² as 60-minute intravenous infusion every 3 weeks until confirmed evidence of disease progression or unacceptable toxicity occurs. MolMed, S.p.A., Milan, Italy 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	Pemetrexed plus cisplatin as 1st-line treatment Single-agent chemotherapy as a 2nd-line treatment (e.g., doxorubicin, gemcitabine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life
Peptide-cytokine complex (NGR-hTNF) for treatment of metastatic colorectal cancer	Patients in whom metastatic colorectal cancer has been diagnosed that has not responded to standard treatment	NGR-hTNF (human tumor necrosis factor) is a peptide-cytokine complex; the NGR peptide binds preferentially to tumor vasculature, and TNF can induce an immune cell reaction/apoptosis. Being tested in combination with oxaliplatin-based chemotherapy. NGR-hTNF is being given at low (0.8 mcg/sqm) and high (45 mcg/sqm) doses. MolMed, S.p.A., Milan, Italy Phase II trials ongoing	Oxaliplatin/ capecitabine Regorafenib	Increased overall survival Increased progression-free survival Improved quality of life
Peptide-cytokine complex (NGR-hTNF) for treatment of metastatic ovarian cancer	Patients in whom metastatic ovarian cancer has been diagnosed that is refractory to platinum-based chemotherapy	NGR-hTNF (human tumor necrosis factor) is a peptide-cytokine complex; the NGR peptide binds preferentially to tumor vasculature, and TNF can induce an immune cell reaction/apoptosis. Being tested in combination with doxorubicin at a dosage of 0.8 mcg/m² over a 60-minute intravenous infusion every 3 or 4 weeks until confirmed evidence of disease progression or unacceptable toxicity occurs. MolMed, S.p.A., Milan, Italy Phase II trial ongoing	Standard 2nd-line chemotherapies: Docetaxel Doxorubicin Etoposide Gemcitabine Tamoxifen Topotecan	Increased overall survival Increased progression-free survival Improved quality of life
Peptide-cytokine complex (NGR-hTNF) for treatment of metastatic small cell lung cancer	Patients in whom metastatic small cell lung cancer has been diagnosed that is refractory to standard chemotherapy	NGR-hTNF (human tumor necrosis factor) is a peptide-cytokine complex; the NGR peptide binds preferentially to tumor vasculature, and TNF can induce an immune cell reaction/apoptosis. Being tested in combination with doxorubicin at a dosage of 0.8 mcg/m² over a 60-minute intravenous infusion every 3 or 4 weeks until confirmed evidence of disease progression or unacceptable toxicity occurs. MolMed, S.p.A., Milan, Italy Phase II trial ongoing	Doxorubicin monotherapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Peptide-cytokine complex (NGR-hTNF) for treatment of soft tissue sarcomas	Patients in whom locally advanced or metastatic soft tissue sarcoma has been diagnosed	NGR-hTNF (human tumor necrosis factor) is a peptide-cytokine complex; the NGR peptide binds preferentially to tumor vasculature, and TNF can induce an immune cell reaction/apoptosis. Being tested as monotherapy or in combination with doxorubicin. MolMed, S.p.A., Milan, Italy Phase II trial ongoing	Doxorubicin monotherapy	Increased overall survival Increased progression-free survival Improved quality of life
Peptide-loaded dendritic cell vaccine (SL-701) for treatment of recurrent glioma	Patients in whom expressing human leukocyte antigen (HLA)-A2 positive high-grade recurrent glioma has been diagnosed	Median survival of patients with malignant glioma is about 15 months, and current treatments are often ineffective. SL-701 is a therapeutic cancer vaccine that consists of autologous dendritic cells preloaded with a set of HLA-A2-restricted peptides derived from glioma associated antigens (EphA2, interleukin-13 R alpha2, YKL-40, and gp100). The vaccine is administered in combination with an immunostimulant (Poly ICLC). Stemline Therapeutics, Inc., New York, NY Phase I/II trial completed; trial results released	Bevacizumab Bevacizumab plus irinotecan, BCNU/CCNU, temozolomide Cyclophosphamide Nitrosourea Nitrosourea wafer Combination PCV (CCNU, procarbazine, and vincristine) Platinum-based chemotherapy Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life
Perifosine (KRX-0401) for treatment of chronic lymphocytic leukemia	Patients in whom chronic lymphocytic leukemia (CLL) has been diagnosed	Many patients with CLL do not achieve an initial treatment response, and most patients eventually relapse, demonstrating the need for new and effective treatments. Perifosine (KRX-0401) is an oral anticancer agent that inhibits Akt activation in the phosphatidylinositol-3-kinase pathway by interfering with the membranes of cancer cells, through disruption of “lipid rafts”; other key signal transduction pathways can also be affected, including c-Jun amino-terminal kinase (JNK), limiting cell growth and proliferation; perifosine may be administered 50 mg, orally, twice a day, for a maximum of six 28-day cycles as a single oral agent and in combination with novel therapies. Aeterna Zentaris, Inc., Quebec, Quebec, Canada; all license rights reverted back to Aeterna Zentaris from Keryx Biopharmaceuticals, Inc., New York, NY, in May 2012 Phase II trial ongoing	Chemotherapy Prednisolone Rituximab	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Perifosine (KRX-0401) for treatment of multiple myeloma	Patients in whom multiple myeloma has been diagnosed	Perifosine (KRX-0401) anticancer agent inhibits Akt activation in the phosphoinositide 3-kinase pathway; also affects other key signal transduction pathways, including c-Jun amino-terminal kinase (JNK); intended for treating several tumor types. Administered as a single oral agent and in combination with standard multiple myeloma therapies. Aeterna Zentaris, Inc., Quebec, Quebec, Canada; all license rights reverted back to Aeterna Zentaris from Keryx Biopharmaceuticals, Inc., New York, NY, in May 2012 Phase III trials ongoing for multiple myeloma under FDA special protocol assessment	Various combination chemotherapeutic regimens that include 1 or more of the following : Bendamustine Bortezomib Cyclophosphamide Dexamethasone Etoposide Lenalidomide Liposomal doxorubicin Lenalidomide Thalidomide	Increased overall survival Increased progression-free survival Improved quality of life
Phosphatidylinositol-3-kinase inhibitor (GDC-0941) for treatment of breast cancer	Postmenopausal women with estrogen receptor (ER)-positive, metastatic breast cancer that is resistant to aromatase inhibitor therapy	Women with ER-positive, metastatic breast cancer that is resistant to aromatase inhibitor therapy have a poor prognosis (median survival of less than a year) and few treatment options. Phosphoinositide 3-kinases (PI3Ks) are a family of kinases that function in a signal transduction pathway controlling multiple cellular activities related to cancer (e.g., apoptosis, angiogenesis, cell growth and proliferation, cell migration, and metastasis). Aberrant PI3K activity has been identified in multiple cancer types. GDC-0941 is an inhibitor of PI3K activity that is under study as an adjunct to treatment with the ER antagonist fulvestrant. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase II trial ongoing	Fulvestrant monotherapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Phosphatidylinositol-3-kinase inhibitor (PX-866) for treatment of castration-resistant prostate cancer	Patients in whom symptomatic castration-resistant prostate cancer (CRPC) has been diagnosed	Patients with CRPC have few treatment options and median overall survival is less than 2 years. Phosphoinositide 3-kinases (PI3Ks) are a family of kinases that function in a signal transduction pathway controlling multiple cellular activities related to cancer (e.g., apoptosis, angiogenesis, cell growth and proliferation, cell migration, and metastasis). Aberrant PI3K activity has been identified in multiple cancer types. PX-866 is a derivative of the well-characterized PI3K inhibitor wortmannin. Like wortmannin, PX-866 irreversibly inhibits all 4 class I PI3Ks; however, it has been modified to improve its stability, toxicity profile, and biologic activity. PX-866 is administered orally and is under study as a 1st-line monotherapy in clinical trials for treating symptomatic CRPC. Oncothyreon, Inc., Seattle, WA Phase II trial ongoing	Docetaxel	Increased overall survival Increased progression-free survival Improved quality of life
Photodynamic therapy (Cevira System) with hexaminolevulinate ointment for treatment of cervical intraepithelial neoplasia	Patients in whom low-grade cervical intraepithelial neoplasia has been diagnosed	Current treatment options for cervical intraepithelial neoplasia have the potential to cause damage to surrounding healthy tissue and to cause side effects such as posttreatment infections. The Cevira System® consists of a photosensitive drug (hexaminolevulinate ointment), which preferentially accumulates in diseased tissue. The disposable device is fitted inside the vaginal cavity so that it remains in contact with the cervix while it delivers treatment over a period of 10 hours. A cup holds the ointment against the cervix and once the ointment is absorbed, a few hours later, a light source within the cup emits light at a specific wavelength continuously over several hours to deliver the therapy. Photocure ASA, Oslo, Norway, in collaboration with Sagentia, Ltd., Cambridge, UK Phase IIb trial ongoing	Cryotherapy Laser therapy Loop electrosurgical excision Surgical conization	Complete lesion eradication

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Photodynamic therapy with Tookad photosensitive agent for treatment of localized prostate cancer	Patients in whom localized low-risk prostate cancer has been diagnosed	Current treatment of localized prostate cancer can adversely affect surrounding healthy tissue and also lead to debilitating temporary and long-term side effects or complications. Tookad is a photosensitive agent that can be excited by a specific wavelength of light to release energy that can cause local necrosis. In a photodynamic therapy procedure using Tookad, the drug is injected by needle into the prostate. After the drug diffuses into the prostate, laser light is used to excite the drug, potentially leading to destruction of targeted prostate tissue while sparing surrounding healthy tissue. Steba Biotech S.A., Cedex, France Phase III trial ongoing	Radiation therapy Radical prostatectomy Watchful waiting	Increased overall survival Increased progression-free survival Fewer therapy-related side effects Improved quality of life
PI3 kinase delta isoform inhibitor (GS-1101) for treatment of chronic or small lymphocytic leukemia	Patients in whom chronic lymphocytic leukemia or small lymphocytic leukemia have been diagnosed	GS-1101 (formerly CAL-101) inhibits the activity of a novel target: phosphoinositide 3-kinase (PI3K) delta, which is a kinase that promotes cell survival, cell division, and cell growth. The delta isoform of Class I PI3K is only expressed in the blood, and targeted inhibition could treat blood-based cancers without side effects on nonblood tissues. Under study in combination with rituximab. Gilead, San Dimas, CA Phase III trial ongoing	Various combination chemotherapies that include 1 or more of the following: Cyclophosphamide Doxorubicin Fludarabine Prednisolone Rituximab Vincristine	Increased overall survival Increased progression-free survival Improved quality of life
Poly ADP-ribose polymerase inhibitor (iniparib) for treatment of metastatic nonsmall cell lung cancer	Patients in whom treatment-naive stage IV metastatic nonsmall cell lung cancer (NSCLC) has been diagnosed	The 5-year survival rate for patients with stage IV NSCLC is less than 10%, and effective treatments are needed. Iniparib is intended to inhibit poly adenosine diphosphate (ADP)-ribose polymerase (PARP), which functions in 1 type of DNA repair. It has been observed that cancers are often deficient in a 2nd type of DNA repair, and loss of both types of DNA repair is hypothesized to result in cancer cell lethality in response to DNA damage. No PARP inhibitors are currently on the market. Iniparib is being administered in combination with a DNA damage inducing chemotherapy regimen (gemcitabine, carboplatin). BiPar Sciences, San Francisco, CA Sanofi, Paris, France Phase III trial ongoing	Cytotoxic chemotherapy (e.g., gemcitabine, carboplatin) alone	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Polydisperse oligonucleotide (defibrotide) 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 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 daily doses of 20 or 40 mg/kg of body weight. Gentium S.p.A., Villa Guardia, Italy Phase III trial complete. FDA granted orphan drug and fast track status; Gentium submitted new drug application to FDA in Jul 2011; FDA issued a refuse to file response and the company withdrew the application in Aug 2011, stating that it will work to address the issues and resubmit	Analgesia Diuresis Renal replacement therapy Transfusion	Increased overall survival Improved quality of life
Pomalidomide 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 is a novel thalidomide derivative that has modulatory effects on angiogenesis, inflammation, and immune cell costimulation. In clinical trials for treating multiple myeloma, pomalidomide is administered orally, at a daily dose of 4 mg, in combination with low-dose dexamethasone. Celgene Corp., Summit, NJ Phase III trial ongoing; in Apr 2012, Celgene submitted a new drug application to FDA for accelerated approval on the basis of phase II trial results; FDA Oncologic Drugs Advisory Panel to consider application on Nov 8, 2012.	Bendamustine Dexamethasone/ cyclophosphamide/ etoposide/cisplatin Dexamethasone/ thalidomide/cisplatin/ doxorubicin/ cyclophosphamide/ etoposide with or without bortezomib High-dose cyclophosphamide Thalidomide/ dexamethasone	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Positron emission tomography-based tumor hypoxia imaging to inform personalization of cancer treatment	Patients in whom a solid tumor has been diagnosed	Tumor cells may adapt to hypoxic conditions in such a way that renders them less susceptible to the effects of radiation therapy and/or chemotherapy. Therefore, the identification of hypoxic tumor regions might allow the physician to adapt the radiation therapy or chemotherapeutic dose to more efficiently target tumor cells. Several agents that could potentially allow identification of hypoxic regions of tumors through the use of positron emission tomography (PET) imaging are under development. Alberta Health Services, Edmonton, Alberta, Canada (FAZA) Siemens AG, Munich, Germany (HX4) University of Wisconsin, Madison (Cu-ATSM) Washington University, St. Louis, MO (Cu-ATSM) Phase II trials ongoing	No currently available in vivo hypoxia imaging technology	Concurrence with immunohistochemical markers of hypoxia (e.g., HIF1-alpha, CA-IX) Improved prognosticating and treatment decision making Increased overall survival Increased progression-free survival Improved quality of life
Positron emission tomography imaging agent (F18-ML10, EarliTest) for assessing tumor response to treatment	Patients undergoing treatment for solid tumors	The availability novel diagnostic tools that could allow detection of tumor response early during treatment could allow earlier modification of ineffective treatments. EarliTest™ is a positron emission tomography (PET) imaging agent (F18-ML10) that specifically labels cells undergoing a process of apoptosis that is often the result of anticancer treatments. By directly monitoring the cellular outcome of therapy, the product is purported to give an earlier indication of whether a therapy is having an antitumor effect. Aposense, Ltd., Petach Tikva, Israel Phase II trials ongoing	Circulating Tumor Cell detection Fluorodeoxyglucose computed tomography imaging MRI PET imaging	Correlation between EarliTest result and tumor response Correlation between EarliTest result and improved patient outcomes (e.g., overall survival, progression-free survival)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Progesterone receptor antagonist (mifepristone, Korlym) for treatment of endogenous Cushing's syndrome	Patients with endogenous Cushing's syndrome who experience persistent hypercortisolemia after surgery or radiation therapy or whose tumor is ineligible for surgery or radiation therapy	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 or radiation therapy or both, patients who are ineligible for these treatments or who have persistent elevation of cortisol following treatment had 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 was taken once daily in clinical trials. Corcept Therapeutics, Menlo Park, CA FDA approved Feb 2012 to control hyperglycemia in adults with endogenous Cushing's syndrome	Ketoconazole (off label) Metyrapone (off label) Mitotane (off label)	Improved symptoms of Cushing's syndrome (e.g., diabetes, glucose intolerance, hypertension)
Prophage series G-200 therapeutic vaccine for gliomas	Patients diagnosed with primary or recurrent brain and central nervous system cancers (gliomas)	Prophage (vitespen and 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. These antigens are delivered in weekly/biweekly injections in an attempt to stimulate an immune response against residual cancer cells. Under development for both adults and pediatric patients. Agenus, Inc., Lexington, MA Phase II trials ongoing in adults; phase I trial planned for pediatric brain cancers; FDA granted orphan drug status	Bevacizumab Bevacizumab plus irinotecan, BCNU/CCNU, temozolomide Combination PCV (CCNU, procarbazine, and vincristine) Cyclophosphamide Nitrosourea Nitrosourea wafer Platinum-based chemotherapy Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
ProstVac immune therapy for castration-resistant prostate cancer	Patients in whom castration-resistant prostate cancer (CRPC) has been diagnosed	Men with progressive metastatic, CRPC often have a poor prognosis and few treatment options. No currently available viral vector vaccine is available. 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 prime step and then weekly injections to generate an immune response. BN ImmunoTherapeutics, Mountain View, CA Phase III trial ongoing	Abiraterone Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
Protein kinase C-beta inhibitor (enzastaurin) for treatment of diffuse large B-cell lymphoma	Patients with diffuse large B-cell lymphoma (DLBCL) who have achieved complete remission after R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone) chemotherapy	The majority of patients in whom DLBCL is diagnosed achieve complete remission following 1st-line therapy; however, disease recurs in about 25% to 30% of patients. Enzastaurin is a small-molecule inhibitor of protein kinase C beta (PKC-beta) that is being studied as maintenance therapy to prevent DLBCL recurrence. PKC family members play a central role in a diverse range of cellular functions including the passage of signals from receptor tyrosine kinases controlling cell growth, cell survival, and endothelial cell migration. Inhibition of PKC-beta by enzastaurin is hypothesized to limit tumor growth and survival and angiogenesis. Enzastaurin is being administered in a daily oral dose of 500 mg in a phase III trial. Eli Lilly and Co., Indianapolis, IN Phase III trial ongoing	No currently employed maintenance therapy for DLBCL	Increased overall survival Increased progression-free survival Improved quality of life
Psilocybin for treatment of anxiety in patients with advanced cancer	Patients with advanced cancer who are not responsive to conventional anxiety and mood therapies	Moderate dose (0.2 mg/kg of body weight) is intended to reduce anxiety and pain for up to 6 months without adverse psychological or physiological events. Various organizations, including New York University and Los Angeles Biomedical Research Institute Trial ongoing and estimated to complete in 2014	Conventional depression/anxiety drug therapy Psychotherapy	Reduced anxiety Reduced need for pain medication Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Radiofrequency ablation of liposomal-encapsulated doxorubicin (ThermoDox) for treatment of hepatocellular carcinoma	Patients in whom hepatocellular carcinoma (HCC) has been diagnosed	ThermoDox™ is a heat-labile liposomal encapsulation of the chemotherapeutic agent doxorubicin. When radiofrequency (RF) energy is applied to the target tissue, it induces local hyperthermia (39.5^{o} to 42^{o} C), which releases the agent locally. Celsion Corp., New York, NY Phase III trial ongoing; National Cancer Institute recommended phase III trial as priority for HCC; granted orphan drug status by FDA Mar 2009	RF tumor ablation alone Surgical resection Transcatheter arterial chemoembolization	Decreased need for liver transplantation Reduced side effects Increased overall survival Increased progression-free survival Improved quality of life
Radiolabeled antibody (I-124-cG250, Redectane) for detection of clear cell renal cell carcinoma using positron emission tomography	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 the diagnosis of ccRCC and to monitor ccRCC treatment efficacy and screen patients for ccRCC recurrence and metastasis. Redectane is administered by intravenous infusion. Wilex AG, Munich, Germany Phase III trial complete	CT imaging alone	Increased sensitivity and specificity for ccRCC
Radiopharmaceu-tical (tilmanocept) for sentinel lymph node detection	Selected patients undergoing surgical resection of primary breast, melanoma, or head and neck tumors	The radiopharmaceuticals currently used to detect tumor-site draining lymph nodes for sentinel lymph node biopsy have several shortcomings, such as slow injection-site clearance, a relatively long half-life, and significant lymph node pass-through. Tilmanocept (Lymphoseek®) is a novel radiopharmaceutical preparation that is intended to improve on these by using a technetium-99 radiolabel. This radiolabel is coupled to a macromolecule that contains multiple units of mannose, which bind to the surface of dendritic cells and macrophages present in lymph nodes. Tilmanocept is administered by injection prior to the procedure. Navidea Biopharmaceuticals (formerly NeoProbe), Dublin, OH Phase III trials complete. In Oct 2011, FDA accepted new drug application for review; in Sept 2012, FDA issued a Complete Response Letter to the company due to manufacturing deficiencies.	Technetium sulfur colloid Vital blue dye (e.g., isosulfan blue)	Increased sentinel node detection sensitivity and specificity Improved patient outcomes Optimized treatment selection

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Radium-223 (Alpharadin) 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. Alpharadin® is a preparation of radium-223, an alpha-particle-emitting isotope that has a natural affinity for bone; Alpharadin 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. Alpharadin is administered in multiple intravenous doses. Algeta ASA, Oslo, Norway, in collaboration with Bayer HealthCare Pharmaceuticals, Wayne, NJ Phase III trial complete; new drug application submission to FDA expected in 2012; granted fast track status by FDA	Standard therapy plus denosumab or cabozantinib (in development) Standard therapy with and without Alpharadin	Increased overall survival Increased progression-free survival Increased rate of alkaline phosphatase normalization Reduced pain from bone metastases Improved quality of life
Raman spectroscopy device (Verisante Aura) for melanoma screening	Patients in whom a suspicious skin lesion has been identified	Available methods for melanoma screening have significant false positive rates that lead to a large number of biopsy procedures on benign skin lesions. The Verisante Aura device provides the user with a binary outcome regarding whether an assayed lesion should be biopsied. The device analyses suspicious lesions using a noninvasive method based on Raman spectroscopy, which is purported to detect biochemical differences between benign and malignant lesions. Verisante Technology, Inc., Vancouver, British Columbia, Canada 1,000 lesion clinical trial completed; approved for marketing approval in Canada and EU; company stated plans to pursue FDA approval in 2012	Dermatologist visual screening MelaFind computer-aided multispectral dermatoscope	Increased sensitivity and specificity for lesion detection Increased positive and negative predictive values Reduced unnecessary biopsies Improved quality of life
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. Dr. Douglas Chepeha, University of Michigan, Ann Arbor 1 case report	Laryngectomy	Preserved larynx and reconstructed cricoid Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Retroviral replicating vector (Toca-511) for treatment of high-grade glioma	Patients in whom recurrent high-grade glioma (e.g., glioblastoma multiforme, anaplastic astrocytoma) has been diagnosed	These patients have limited treatment options and a poor prognosis. Toca-511 is a novel, virus-based treatment for cancer that consists of a retrovirus that stably inserts itself in the genome of dividing cells. The virus has been genetically modified to encode the enzyme cytosine deaminase, which can convert the antifungal prodrug flucytosine (5-FC) to the anticancer agent 5-fluorouracil (5-FU). Following intratumoral injection of the viral vector, an extended-release formulation of 5-FC (toca-FC) is administered systemically. This combination is intended to generate high levels of 5-FU in cancer cells transfected by the viral vector encoding cytosine deaminase. Tocagen, Inc., San Diego, CA Phase I/II trial ongoing	Bevacizumab Bevacizumab plus irinotecan, BCNU/CCNU, temozolomide Temozolomide Nitrosourea Nitrosourea wafer Combination PCV (CCNU, procarbazine, and vincristine) Cyclophosphamide Platinum-based chemotherapy	Increased overall survival Increased progression-free survival Improved quality of life
Rexin-G for chemotherapy-resistant metastatic pancreatic cancer	Patients with gemcitabine-resistant, metastatic pancreatic cancer	Patients with gemcitabine-resistant pancreatic cancer have a very poor prognosis and few treatment options. Rexin-G is a viral vector that encodes a dominant negative version of cyclin G1. Cyclin G1 is a central mediator of cell cycle progression, and its inhibition leads to cell-cycle arrest and apoptosis. The viral vector is targeted to cancerous sites by the incorporation of a collagen-binding peptide into the viral coat. Collagen is preferentially exposed on cells involved in rearrangement associated with tumor invasion, angiogenesis, and stroma formation. Epeius Biotechnologies, San Marino, CA Phase III trial planned; FDA granted fast-track status	Fluoropyrimidine-based chemotherapy (e.g., FOLFIRINOX [leucovorin, 5-FU, irinotecan, and oxaliplatin])	Increased overall survival Increased progression-free survival Improved quality of life
Rexin-G for chemotherapy-resistant sarcoma	Patients with chemotherapy-resistant, recurrent or metastatic soft tissue sarcoma	Patients with chemotherapy-resistant, recurrent or metastatic soft tissue sarcoma have limited therapeutic options when their disease fails to respond to currently available chemotherapy. Rexin-G is a viral vector that encodes a dominant negative version of cyclin G1. Cyclin G1 is a central mediator of cell-cycle progression, and its inhibition leads to cell cycle arrest and apoptosis. The viral vector is targeted to cancerous sites by the incorporation of a collagen-binding peptide into the viral coat. Collagen is preferentially exposed on cells involved in rearrangement associated with tumor invasion, angiogenesis, and stroma formation. Epeius Biotechnologies, San Marino, CA Phase I/II trial complete; phase III trial planned	Pazopanib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Rose Bengal (PV-10) for treatment of advanced melanoma	Patients in whom stage IIIB or IIIC 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, which is administered by intralesion injection. Rose Bengal preferentially accumulates in cancer cells because of the increased lipid content of its cell membranes, which allows the drug to cross the membranes. 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 noninjected lesions exhibit a response to treatment. This effect is thought to be due to uptake of tumor antigens by immune system cells after tumor lysis, leading to a systemic immune response. Provectus Pharmaceuticals, Inc., Knoxville, TN Phase III trial special protocol assessment is being discussed with FDA	Dacarbazine Granulocyte colony stimulating factor Interleukin-2 Ipilimumab Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life
Selective estrogen receptor alpha agonist (Capesaris) for treatment of advanced prostate cancer	Patients in whom advanced prostate cancer has been diagnosed	Current treatment of advanced prostate cancer uses medical or surgical castration to reduce testosterone. However, current mechanisms of antiandrogen therapy result in significant side effects such as bone loss and hot flashes, which may lead to patient morbidity or poor treatment adherence. Capesaris™ (GTx-758) is a novel antiandrogen therapy that acts as a selective estrogen receptor-alpha agonist to achieve castration levels of testosterone through feedback inhibition of the pituitary and hypothalamus without causing bone loss and hot flashes. GTx, Inc., Memphis, TN Phase II trial completed; additional phase II trials were put on hold by FDA in Feb 2012 because of reports of increased rates of venous thromboembolic events or blood clots; GTx issued a response to FDA in Apr 2012	Bilateral orchiectomy Luteinizing-hormone-releasing hormone agonists	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Smac mimetic (LCL161) for treatment of solid tumors	Patients in whom solid tumors have been diagnosed	Patients with locally advanced or metastatic solid tumors typically have a poor prognosis with current treatment options. In cell homeostasis, a family of proteins known as inhibitors of apoptosis (IAPs) counteracts the proapoptotic (i.e., pro-cell death) activity of caspases. In turn, cellular Smac (2nd mitochondria-derived activator of caspases) functions to inhibit IAPs, thereby acting as an activator of apoptosis. LCL161 is a Smac mimetic that purportedly promotes cell death by inhibiting IAPs. LCL161 may be administered in combination with currently available treatment options to potentiate the proapoptotic activity of these treatments. Novartis International AG, Basel, Switzerland Phase I trial for solid tumors ongoing; phase II trial for triple-negative breast cancer registered	Wide range of disease- and stage-specific chemotherapy and targeted therapy options	Increased overall survival Increased progression-free survival Improved quality of life
Small-molecule drug conjugate (vintafolide) 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. vintafolide is administered intravenously and is being studied in combination with pegylated liposomal doxorubicin. Endoctye, Inc., West Lafayette, IN, in collaboration with Merck & Co., Inc., Whitehouse Station, NJ Phase III trial ongoing	Docetaxel Etoposide Gemcitabine Paclitaxel Pegylated liposomal doxorubicin Topotecan	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 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 anti-apoptotic form, which is generated by post-translational 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 anti-apoptotic eIF5A1. By altering the balance of pro-apoptotic and anti-apoptotic eIF5A1, SNS01-T is purported to promote cell death over cell growth and cell survival. In clinical trials, SNS01-T is administered by intravenous infusion, twice weekly. Senesco Technologies, Inc., New Brunswick, NJ Phase I/II trial ongoing; FDA granted orphan drug status	Various chemotherapeutic regimens, including one or more of the following: Bendamustine Bortezomib Cisplatin Cyclophosphamide Dexamethasone Etoposide Lenalidomide Liposomal doxorubicin Thalidomide	Increased overall survival Increased progression-free survival Improved quality of life
Stool DNA molecular test for colorectal cancer screening	All patients undergoing routine colorectal cancer (CRC) screening	Genetic test (Cologuard™) screens 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 1 genetic locus. Exact Sciences Corp., Madison, WI Clinical trial ongoing (phase unstated)	Colonoscopy Computed tomographic colonography Fecal occult blood testing Sigmoidoscopy	Increased sensitivity and specificity for precancerous lesions and CRC Improved positive and negative predictive values Reduced unnecessary followup for screening

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Survivin antisense inhibitor (LY2181308) for treatment of metastatic nonsmall cell lung cancer	Patients with treatment-resistant, metastatic nonsmall cell lung cancer (NSCLC)	Patients with advanced NSCLC that has progressed after chemotherapy have a poor prognosis and few treatment options. LY2181308 is an antisense drug that targets the messenger RNA of survivin, a protein that is overexpressed specifically in a number of cancers. Survivin (BIRC5) has been shown to inhibit the activation of pro-apoptotic caspases. Inhibition of survivin may increase caspase activity and lead to cancer-cell apoptosis. In the current clinical trial, LY2181308 is being administered intravenously as an adjunct to the standard 2nd-line chemotherapy drug docetaxel. Eli Lilly and Co., Indianapolis, IN (licensed from ISIS Pharmaceuticals, a unit of Johnson & Johnson, New Brunswick, NJ) Phase II trial completed	Combination therapy: Bevacizumab, cisplatin, docetaxel, pemetrexed Monotherapy for appropriately selected patients: Crizotinib Erlotinib	Increased overall survival Increased progression-free survival Improved quality of life
Survivin peptide vaccine (DPX-Survivac) to prevent recurrence of ovarian cancer	Patients with stage IIc–IV ovarian cancer who have undergone successful debulking surgery and treatment with carboplatin/ paclitaxel	Patients in whom ovarian cancer has been diagnosed often relapse following successful initial treatment of their disease; therefore, maintenance therapies that prolong the time to recurrence or prevent recurrence are needed. DPX-Survivac is a novel peptide vaccine that consists of survivin peptides in a lipid-based depot formulation (DepoVax™). Survivin is a tumor-associated antigen that has been shown to be overexpressed in multiple cancers including ovarian cancer. In clinical trials, DPX-Survivac is being administered in 3 injected doses in combination with or without a low dose of cyclophosphamide (intended to act as an immune stimulant). Immunovaccine, Inc., Halifax, Nova Scotia, Canada Phase I/II trial ongoing	Bevacizumab Paclitaxel	Increased overall survival Increased recurrence-free survival Improved quality of life
Targeted cytotoxic (AEZS-108) for treatment of luteinizing-hormone-releasing hormone-receptor-positive cancers	Patients in whom luteinizing-hormone-releasing hormone (LHRH) receptor-expressing cancer has been diagnosed, including ovarian, endometrial, prostate, or bladder cancer	Cytotoxic chemotherapy such as doxorubicin has proven anticancer effects; however, efficacy is inhibited by dose-limiting toxicities on normal tissues. AEZS-108 is a conjugate between a 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, AEZS-108 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 doses of 128, 160, 210, or 267 mg/m^2, every 3 weeks, up to 6 treatment cycles. Æterna Zentaris, Inc., Quebec, Quebec, Canada Phase II trials ongoing; pivotal trial in endometrial cancer anticipated to be initiated in 2012	Doxorubicin	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tasquinimod for treatment of castration-resistant prostate cancer	Patients in whom castration-resistant prostate cancer (CRPC) has been diagnosed	Advanced prostate tumors can become resistant to androgen-deprivation therapy; new treatments with novel mechanisms of action are needed to limit the growth of advanced CRPC. Tasquinimod is a novel oral antiangiogenic compound that is intended to restrict blood flow to prostate tumors thus inhibiting growth; tasquinimod which may also exert antitumor effects. Administered at doses of 0.25, 0.5, or 1.0 mg/day. Active Biotech, AB, Lund, Sweden Phase III trial ongoing	Abiraterone Enzalutamide Orteronel (in development) Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
Telomerase inhibitor (imetelstat) for treatment of nonsmall cell lung cancer	Patients in whom advanced/ metastatic nonsmall cell lung cancer (NSCLC) has been diagnosed whose disease has not progressed after treatment with platinum-based cytotoxic chemotherapy with or without the addition of biologic therapy with bevacizumab	Patients with advanced/metastatic NSCLC have a poor prognosis and disease often recurs or progresses following initial treatment. One cause of disease recurrence may be the existence of “cancer stem cells,” which are typically refractory to cytotoxic chemotherapy and have the potential to regenerate tumors following cessation of cytotoxic chemotherapy. A hallmark of cancer stem cells is the expression of an enzyme called telomerase that is essential for maintaining the fidelity of chromosome termini (telomeres), which typically degrade after repeated cell divisions. Imetelstat is an oligonucleotide that binds the active site of telomerase, inhibiting its activity. Imetelstat is under study as a maintenance therapy following a successful cytotoxic chemotherapy regimen and may be administered in combination with the antiangiogenic monoclonal antibody bevacizumab. Geron Corp., Menlo Park, CA Phase II trial ongoing	Bevacizumab Observation	Increased overall survival Increased progression-free survival Improved quality of life
Tengion Neo-Urinary Conduit for postcystectomy urinary diversion	Patients who have undergone a cystectomy (bladder removal), usually as treatment for bladder cancer	Tengion Neo-Urinary Conduit™ obtains a fat-cell sample from the patient prior to cystectomy and in the laboratory, a biodegradable scaffold is used to grow a smooth muscle tube from the fat cell sample. The tube is used to divert urine from the ureters to the outside the body after bladder removal. Tengion, Inc., East Norriton, PA Phase I trial ongoing	Ileal conduit urinary diversion (uses a portion of the intestine as the urinary conduit) Studer’s ileal neobladder (uses a portion of the intestine to form a bladder-like pouch that is controlled by abdominal muscles)	Successful routing of urine outside the body without disrupting the gastrointestinal tract

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tesetaxel (oral taxane) for treatment of advanced cancers	Patients in whom advanced gastric cancer, melanoma, prostate cancer, breast cancer, or bladder cancer has been diagnosed	Current microtubule stabilizing taxanes (e.g., docetaxel, paclitaxel) are administered by intravenous infusion and have been associated with infusion site reactions. Tesetaxel would be the 1st orally administered taxane; other oral taxanes are in development but not as far along. Additionally, preclinical studies suggested that tesetaxel could evade a common mechanism by which cancer cells develop taxane resistance and, therefore, could potentially be used to treat taxane-resistant cancers. Genta, Inc., Berkeley Heights, NJ Phase II trials ongoing	Conventional (injected) taxanes: Docetaxel Paclitaxel	Reduced taxane-administration-related adverse events Increased overall survival Increased progression-free survival Improved quality of life
Therapeutic cancer vaccine (POL-103A) to prevent recurrent melanoma	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. Polynoma LLC subsidiary of CK Life Sciences Int'l (Holdings), Inc., Hong Kong Phase III trial ongoing	High-dose interferon	Increased overall survival Increased progression-free survival Improved quality of life
Therapeutic vaccine (BiovaxID) for indolent follicular non-Hodgkin's lymphoma	Patients in whom indolent follicular non-Hodgkin's lymphoma has been diagnosed and who are in their 1st complete remission	Personalized cancer vaccine (BiovaxID®) works by producing B-cell hybridomas from the patient's cancer cells. Cancer-specific antibody idiotype is amplified, isolated, and conjugated to an immunostimulant; then readministered with granulocyte macrophage colony-stimulating factor in attempt to induce anti-idiotypic response to the lymphoma tumor. Biovest International, Inc., Tampa, FL Phase III trial complete; FDA granted orphan drug status	Watchful waiting	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Therapeutic vaccine (BiovaxID) for mantle cell lymphoma	Patients in whom mantle cell lymphoma has been diagnosed	Personalized cancer vaccine (BiovaxID®) works by producing B-cell hybridomas from patient's cancer cells; cancer-specific antibody idiotype is amplified, isolated, and conjugated to an immunostimulant, then readministered with granulocyte macrophage colony-stimulating factor, in an effort to induce anti-idiotypic response to the lymphoma/tumor. Biovest International, Inc., Tampa, FL Phase II trial complete; FDA granted orphan drug status	Chemotherapy Lymphocyte transplantation Monoclonal antibodies Radioimmunotherapy (ibritumomab and tositumomab) Radiation	Increased overall survival Increased progression-free survival Improved quality of life
Therapeutic vaccine (GI-4000) for pancreatic cancer harboring activating RAS mutations	Patients with surgically resectable pancreatic cancer that expresses an activated form of RAS	Patients in whom pancreatic cancer has been diagnosed who have undergone surgical resection of the primary tumor have median survival of about 2 years with current adjuvant chemotherapy options. GI-4000 is a novel immune therapy that targets pancreatic cancers harboring an activating mutation in the *RAS* gene, which is present in the majority of pancreatic cancers. GI-4000 is composed of heat-killed yeast cells that have been genetically modified to express a tumor-specific antigen; in the case of GI-4000, activated RAS. The modified yeast cells are purportedly taken up by antigen-presenting cells of the immune system and elicit a cytotoxic T-cell response targeted to antigens derived from activated RAS produced by cancer cells. In clinical trials, GI-4000 is administered subcutaneously in combination with the 1st-line standard adjuvant chemotherapy drug gemcitabine. GlobeImmune, Inc., Louisville, CO Phase II trial ongoing	5-Fluorouracil/ leucovorin Gemcitabine	Increased overall survival Increased progression-free survival Improved quality of life
Therapeutic vaccine (GSK1572932A) for MAGE-A3-positive nonsmall cell lung cancer	Patients in whom nonsmall cell lung cancer (NSCLC) has been diagnosed that expresses the melanoma antigenic epitope (MAGE)-A3 biomarker	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 as an adjuvant to conventional chemotherapy. GlaxoSmithKline, Middlesex, UK Phase III trial ongoing	Surgery Various chemotherapies Radiation therapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Therapeutic vaccine (IMA901) for renal cell carcinoma	Patients in whom renal metastatic and/or locally advanced renal cell carcinoma (RCC) has been diagnosed	RCC is typically highly resistant to conventional chemotherapy/radiation therapy, and few treatment options exist for patients with RCC. IMA901 is a rationally designed 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 is purported to have a stable, off-the-shelf formulation. The vaccine is administered intradermally with granulocyte macrophage colony-stimulating factor and sunitinib as a 1st-line therapy. Immatics Biotechnologies GmbH, Tübingen, Germany Phase III trial ongoing	Sunitinib	Increased overall survival Increased progression-free survival Improved quality of life
Therapeutic vaccine (tertomotide, GV-1001) for pancreatic cancer	Patients in whom pancreatic cancer has been diagnosed	Advanced pancreatic cancer has a 5-year survival rate of about 5% with few therapeutic options. Tertomotide (GV-1001) is a therapeutic peptide vaccine against telomerase, a protein responsible for adding telomeres, noncoding DNA at the ends of chromosomes, which help to determine the life span of cells; overexpression of telomerase can lead to immortalization of cells and oncogenesis; tertomotide is purported to induce cellular immune responses against telomerase. Tertomotide is administered intradermally in combination with granulocyte macrophage colony-stimulating factor on days 1, 3, and 5 in week 1, once weekly in weeks 2, 3, 4, and 6, and then once a month in the absence of disease progression or unacceptable toxicity; patients may also be concurrently treated with gemcitabine. KAEL-GemVax Co., Ltd., Seoul, South Korea Phase III trial ongoing (data expected 2nd half of 2012)	5-fluorouracil/leucovorin Gemcitabine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Therapeutic vaccine (TVI-Brain-1) for recurrent glioma	Patients in whom recurrent stage IV glioma has been diagnosed	A personalized vaccine (TVI-Brain-1) consisting of irradiated cancer cells derived from the patient and administered with granulocyte macrophage colony-stimulating factor; “precursor killer T cells” are generated after the 1st administration of the vaccine; then vaccine-induced killer T cells are collected from the patient's blood for additional priming at the manufacturer's laboratory and reinfused intravenously into the patient’s bloodstream. TVAX Biomedical, LLC, Lenexa, KS Phase II trial ongoing	Bevacizumab Bevacizumab plus irinotecan, BCNU/CCNU, temozolomide Combination PCV (CCNU, procarbazine, and vincristine) Cyclophosphamide Nitrosourea Nitrosourea wafer Platinum-based chemotherapy Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life
Tivozanib (AV-951) for treatment of advanced or metastatic breast cancer	Patients in whom advanced or metastatic breast cancer has been diagnosed that is refractory to standard chemotherapy	Tivozanib (AV-951) is a quinoline-urea–derived vascular endothelial growth factor (VEGF) receptor (VEGFR) inhibitor that inhibits several tyrosine kinases. The theoretical basis for VEGFR inhibitors in treating solid tumors is that VEGF is a key mediator of normal and tumor-induced angiogenesis, or the proliferation and survival of endothelial cells, and vascular permeability. When VEGFRs are activated by VEGF, endothelial cells migrate and proliferate, resulting in the formation of new tumor vasculature. If the VEGF pathway is disrupted, a tumor can no longer trigger the development of its own blood supply, thereby impeding the tumor’s growth and dissemination. The drug is being studied in combination with paclitaxel. It is administered orally. AVEO Pharmaceuticals, Inc., Cambridge, MA Phase I/II trial complete	Paclitaxel alone	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tivozanib (AV-951) for treatment of advanced renal cell carcinoma	Patients in whom advanced primary renal cell carcinoma has been diagnosed	Tivozanib (AV-951) is a quinoline-urea–derived vascular endothelial growth factor (VEGF) receptor (VEGFR) inhibitor that inhibits several tyrosine kinases. The theoretical basis for VEGFR inhibitors in treating solid tumors is that VEGF is a key mediator of normal and tumor-induced angiogenesis, or the proliferation and survival of endothelial cells, and vascular permeability. When VEGFRs are activated by VEGF, endothelial cells migrate and proliferate, resulting in the formation of new tumor vasculature. If the VEGF pathway is disrupted, a tumor can no longer trigger the development of its own blood supply, thereby impeding the tumor's growth and dissemination. It is given orally. AVEO Pharmaceuticals, Inc., Cambridge, MA Phase III trial ongoing; in Jan 2012, the company reported that tivozanib met its primary endpoint of improving progression-free survival; FDA new drug application filed Sept 2012	EverolimusInterleukin-2 Sorafenib Sunitinib Temsirolimus	Increased overall survival Increased progression-free survival Improved quality of life
Tivozanib (AV-951) for treatment of metastatic nonsmall cell lung cancer	Patients in whom recurrent advanced or metastatic nonsmall cell lung cancer (NSCLC) has been diagnosed that is refractory to standard chemotherapy	Tivozanib is a quinoline-urea–derived vascular endothelial growth factor (VEGF) receptor (VEGFR) inhibitor that inhibits several tyrosine kinases. It is being investigated for treating NSCLC. The theoretical basis for VEGFR inhibitors in treating solid tumors lies in the fact that VEGF is a key mediator of normal and tumor-induced angiogenesis, or the proliferation and survival of endothelial cells, and vascular permeability. When VEGFRs are activated by VEGF, endothelial cells migrate and proliferate, resulting in the formation of new tumor vasculature. If the VEGF pathway is disrupted, a tumor can no longer trigger the development of its own blood supply, thereby impeding the tumor's growth and dissemination. The agent is given in oral formulation, dosed in cycles of once daily for several weeks, followed by 1 week off treatment. AVEO Pharmaceuticals, Inc., Cambridge, MA Phase I/II trial complete	Palliative care	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Toll-like receptor 9 agonist (MGN1703) maintenance therapy after 1st -line therapy for metastatic colorectal cancer	Patients with metastatic colorectal cancer (CRC) whose disease has responded to 1st -line chemotherapy	Although many patients with metastatic CRC 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 are purported to promote immune system activation, possibly through dendritic cell maturation and/or differentiation of B cells into antibody-secreting plasma cells. Immune-response activation by MGN1703 could overcome immune tolerance to tumor associated antigens, potentially leading to an anticancer immune response. MOLOGEN AG, Berlin, Germany Phase II/III trial ongoing	Bevacizumab Chemotherapy-free interval Leucovorin plus 5-fluorouracil	Increased overall survival Increased progression-free survival Improved quality of life
Topoisomerase I inhibitor-polymer conjugate (NKTR-102) for treatment-resistant, metastatic 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 metastatic breast cancer that has progressed on anthracycline-, taxane-, and capecitabine-containing regimens have few treatment options and a poor prognosis. NKTR-102 is a novel formulation of the topoisomerase I inhibitor irinotecan. Although approved for treating colorectal cancer, irinotecan is not currently indicated for treating breast cancer. NKTR-102 is a modified version of irinotecan in which the drug is linked to a macromolecule core. The linkage is purported to render the drug inert in the bloodstream and allow 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. Nektar Therapeutics, San Francisco, CA Phase III trial ongoing	Eribulin Gemcitabine Ixabepilone Pemetrexed Vinorelbine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Transferrin targeted anticancer agent (NKP-1339) for treatment of metastatic cancer	Patients in whom metastatic cancer has been diagnosed	Many metastatic cancers are unresponsive to current treatments, and new treatments are needed. NKP-1339 is a novel cancer drug that targets the body's natural iron transporter (transferrin), the receptor for which is highly expressed on cancer cells because of these cells' elevated iron requirements. NKP-1339 is injected in an inert form that mimics transferrin and binds to the transferrin receptor. Upon binding, the receptor/drug complex is internalized and the drug becomes activated upon exposure to the redox state of the cytosol. The activated drug leads to the production of free radicals, which potentially lead to apoptosis. Niiki Pharma, Inc., Hoboken, NJ Phase I portion of phase I/II trial complete	Various anticancer therapies	Increased overall survival Increased progression-free survival Improved quality of life
Trastuzumab emtansine for treatment of breast cancer	Patients in whom metastatic HER2-positive breast cancer has been diagnosed	Trastuzumab emtansine (formerly trastuzumab-DM1) is a combination of a 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. F. Hoffmann-La Roche Ltd., Basel, Switzerland Phase III trials ongoing; company reported that trastuzumab emtansine met its primary endpoint of improving progression-free survival in the 2nd-line setting; full results from this trial anticipated in late 2012; FDA Biologics License Application filed late Aug 2012	Lapatinib-based chemotherapy regimens Trastuzumab-based chemotherapy regimens	Increased overall survival Increased progression-free survival Improved quality of life
TroVax for treatment of hormone-refractory prostate cancer	Patients in whom metastatic, hormone-refractory prostate cancer has been diagnosed	Novel cancer therapies for hormone-refractory prostate cancer that may increase treatment efficacy and survival are needed. TroVax® is a modified vaccinia Ankara virus vector encoding the oncofetal antigen 5T4 intended to induce cellular immune responses to tumors; oncofetal antigen 5T4 is expressed by many solid tumors. In current trial, TroVax is given in combination with the chemotherapy drug docetaxel. Oxford BioMedica, Oxford, UK Phase II trial ongoing (was halted in development for renal cell carcinoma in 2009)	Docetaxel alone	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
TRU-016 for treatment of chronic lymphocytic leukemia	Patients in whom chronic lymphocytic leukemia (CLL) has been diagnosed	Many patients with CLL do not achieve an initial treatment response, and most patients eventually relapse, demonstrating the need for new and effective treatments. TRU-016 is a CD37-directed small modular immunopharmaceutical protein intended to treat CLL; TRU-016 uses a different mechanism of action from currently available monoclonal antibodies used to treat CLL (e.g., rituximab, alemtuzumab) and may be used alone or in combination with chemotherapy (bendamustine) and/or other targeted therapeutics. Emergent BioSolutions, Inc., Rockville, MD Phase I/II trials ongoing	Combination chemotherapies, such as: Alemtuzumab plus or minus rituximab Bendamustine/rituximab Cyclophosphamide/ doxorubicin/vincristine/ prednisone/rituximab Fludarabine/ cyclophosphamide/ rituximab/ofatumumab Pentostatin/ cyclophosphamide/ rituximab	Increased overall survival Increased progression-free survival Improved quality of life
Tryptophan hydroxylase inhibitor (telotristat etiprate, 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 (LX1032) is intended to reduce systemic serotonin levels by inhibiting an enzyme involved in the synthesis of serotonin, tryptophan hydroxylase. Lexicon Pharmaceuticals, Inc., The Woodlands, TX Phase II trials completed; FDA granted fast track status	Chemotherapy (e.g., capecitabine, dacarbazine, 5-fluorouracil, temozolomide) Interferon alpha Octreotide	Decreased rate of bowel movements Decreased 5-HIAA levels Decreased rate of flushing episodes Improved quality of life (e.g., less pain, discomfort)
Tumor-treating fields therapy (NovoTTF-100L device) for nonsmall cell lung cancer	Patients in whom stage IIIb–IV nonsmall cell lung cancer has been diagnosed	The system delivers tumor-treating fields (local alternating electrical fields) to the target tumor site. Electrical fields are purported to interfere with charged molecules that are involved the cell's mitotic processes. The therapy is delivered in conjunction with chemotherapy. NovoCure Ltd., Haifa, Israel Phase I/II trial complete; company states it is preparing a phase III trial program to obtain FDA approval for investigational device exemption status to conduct the trial	Chemotherapy alone Radiation therapy/ chemotherapy Surgical resection/ chemotherapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tumor-treating fields therapy (NovoTTF-100L device) for recurrent glioblastoma	Patients in whom recurrent glioblastoma has been diagnosed	The system delivers tumor-treating fields (local alternating electrical fields) to the target tumor site. Electrical fields are purported to interfere with charged molecules that are involved the cell's mitotic processes. The therapy is delivered in conjunction with chemotherapy. NovoCure Ltd., Haifa, Israel FDA approved for recurrent glioblastoma Apr 2011; phase III trial in newly diagnosed glioblastoma ongoing	Bevacizumab Bevacizumab plus irinotecan, BCNU/CCNU, temozolomide Combination PCV (CCNU, procarbazine, and vincristine) Cyclophosphamide Nitrosourea Nitrosourea wafer Platinum-based chemotherapy Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life
Urine test (PSP94) for prostate cancer screening	Men undergoing routine prostate cancer screening (generally men older than 50 years of age)	PSP94 (microseminoprotein-beta, inhibin-like peptide, prostate secretory protein) is expressed in normal prostate tissue; however, studies have shown that its levels are reduced in cancerous prostate cells; test kit is an enzyme-linked immunosorbent assay-based urine assay to detect reduced levels of PSP94. Miraculins, Inc., Winnipeg, Manitoba, Canada Kit was made available as a research-use-only reagent in Aug 2010; company plans to develop a commercially available diagnostic test kit	Digital rectal examination Prostate-specific antigen screening	Increased sensitivity and specificity for screening Improved predictive values Avoided unnecessary biopsies Better treatment planning 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	Urocidin™ is a mycobacterial cell wall/DNA preparation proposed to create a localized immune response (mechanism of action unclear). Administered by transurethral catheter directly into the bladder. Bioniche Life Sciences, Inc., Belleville, Ontario Endo Pharmaceuticals, Chadds Ford, PA (licensee in U.S.) Phase II/III trial complete	Bacillus Calmette-Guérin treatment Cystectomy	Increased overall survival Increased progression-free survival Avoidance of cystectomy Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
trVandetanib (Caprelsa) for treatment of metastatic medullary thyroid cancer	Patients in whom metastatic medullary thyroid cancer has been diagnosed	No treatments are currently approved for metastatic medullary thyroid cancer, which has a 28% rate of survival for 5 years. Vandetanib (Caprelsa®) is a tyrosine kinase inhibitor with activity against various growth factors: vascular endothelial growth factor receptor, epidermal growth factor receptor, and recombined in transfection (RET); about 25% of medullary thyroid cancer is caused by a mutation in the RET proto-oncogene. Taken orally, once daily. AstraZeneca, London, UK FDA approved Apr 2011	Chemotherapy (off label) Radiotherapy Surgery	Increased overall survival Increased progression-free survival Improved quality of life
VGX-3100 for treatment of high-grade cervical dysplasia	Patients in whom human papillomavirus (HPV) 16 or 18-attributed high-grade cervical dysplasia (cervical intraepithelial neoplasia [CIN] 2 or 3) has been diagnosed	Current HPV preventive vaccines do not treat women already infected with HPV 16/18, the main cause of cervical cancer, or who have confirmed CIN; surgical excision is the usual treatment and noninvasive alternatives are needed. VGX-3100 is a therapeutic DNA vaccine encoding regions of HPV 16 and 18, E6 and E7 proteins, which are believed to be important in oncogenesis; intended to elicit cellular immune responses against the 2 most common HPV types associated with cervical cancer to lead to regression of high-grade precancerous lesions. VGX-3100 is given as a 1 mL intramuscular injection followed by electroporation at day 0, week 4, and week 12. Inovio Pharmaceuticals, Inc., Blue Bell, PA Phase II trial ongoing	Colposcopy/excision Imiquimod	Increased CIN regression rate Increased HPV clearance rate Reduced incidence of cervical cancer
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 that is not amenable to surgical resection have few treatment options. Activation of the hedgehog signaling pathway, which is normally silenced following early development, has been implicated in the development and survival of a large percentage of basal cell carcinomas. Vismodegib (GDC-0449) is an inhibitor of the protein Smoothened, which is essential for transducing hedgehog signaling. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland 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 of death or severe birth defects to unborn fetus	No other currently approved systemic treatment option available	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vismodegib (GDC-0449) for treatment of chondrosarcoma	Patients in whom metastatic or unresectable locally advanced chondrosarcoma has been diagnosed	Aberrant hedgehog pathway activation has been implicated in the development of chondrosarcomas, a cancer with few treatment options. No hedgehog pathway inhibitors are currently available. Vismodegib (GDC-0449) is an inhibitor of the protein Smoothened, which is essential for transducing hedgehog signaling. If trials are successful, this could be the 1st hedgehog pathway inhibitor to be approved for this condition. National Cancer Institute, Bethesda, MD, and Institute Bergonié, Bordeaux Cèdex, France Phase II trial ongoing	Doxorubicin	Increased overall survival Increased progression-free survival Improved quality of life
Vismodegib (GDC-0449) for treatment of gastric or gastroesophageal junction cancer	Patients in whom advanced gastric cancer or gastroesophageal junction cancer that is not amenable to surgical resection has been diagnosed	Hedgehog signaling is involved in normal gut epithelial homeostasis; however, aberrant hedgehog signaling may lead to carcinogenesis of the gut epithelium. No hedgehog pathway inhibitors are currently available. Vismodegib (GDC-0449) is an inhibitor of the protein Smoothened, which is essential for transducing hedgehog signaling. If trials are successful, this could be the 1st hedgehog pathway inhibitor to be approved for this condition. In an ongoing gastric cancer trial, vismodegib is administered in combination with the FOLFOX (folinic acid [leucovorin], 5-fluorouracil, oxaliplatin) cytotoxic chemotherapy regimen. National Cancer Institute, Bethesda, MD, and New York Cancer Consortium Phase II trial ongoing	FOLFOX chemotherapy alone	Increased overall survival Increased progression-free survival Improved quality of life
Vismodegib (GDC-0449) for treatment of locally advanced prostate cancer	Patients with locally advanced prostate cancer who are undergoing neo-adjuvant hormone therapy prior to radical prostatectomy	Aberrant hedgehog signaling has been implicated in the development of some prostate adenocarcinoma; however, no hedgehog pathway inhibitors are currently available. Vismodegib (GDC-0449) is an inhibitor of the protein Smoothened, which is essential for transducing hedgehog signaling. If trials are successful, this could be the 1st hedgehog pathway inhibitor to be approved for this condition. National Cancer Institute, Bethesda, MD Phase II trial ongoing	Neoadjuvant hormone therapy alone	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vismodegib (GDC-0449) for treatment of medulloblastoma	Patients in whom recurrent or treatment refractory medulloblastoma has been diagnosed	Activation of the hedgehog signaling pathway, which is normally silenced following early development, has been implicated in the development and survival of up to a 3rd of medulloblastomas; however, no hedgehog pathway inhibitors are currently available. Vismodegib (GDC-0449) is an inhibitor of the protein Smoothened, which is essential for transducing hedgehog signaling. If trials are successful, this could be the 1st hedgehog pathway inhibitor to be approved for this condition. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Curis Pharmaceuticals, Lexington, MA National Cancer Institute, Bethesda, MD Phase II trials ongoing	Various chemotherapy regimens (high-dose cyclophosphamide plus or minus etoposide; etoposide; temozolomide plus or minus 13-cis retinoic acid) High-dose chemotherapy plus autologous stem cell reinfusion	Increased overall survival Increased progression-free survival Improved quality of life
Vismodegib (GDC-0449) for treatment of multiple myeloma	Patients with multiple myeloma who have previously been treated by autologous stem cell transplant	The hedgehog signaling pathway has been implicated in the maintenance of a population of cells (“cancer stem cells”) that drive the proliferation of lymphocytes that underlies the multiple myeloma phenotype. No hedgehog pathway inhibitors are currently available. Vismodegib (GDC-0449) is an inhibitor of the protein Smoothened, which is essential for transducing hedgehog signaling. If trials are successful, this could be the 1st hedgehog pathway inhibitor to be approved for this condition. National Cancer Institute, Bethesda, MD, and Johns Hopkins Medicine’s Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD Phase Ib trial ongoing	Bortezomib Lenalidomide/ thalidomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vismodegib (GDC-0449) for treatment of pancreatic cancer	Patients in whom recurrent or metastatic pancreatic cancer has been diagnosed or in whom pancreatic ductal adenocarcinoma has been diagnosed and who are undergoing surgical resection	Aberrant hedgehog signaling has been implicated in the development of pancreatic cancer. hedgehog signaling may promote tumor growth in a paracrine manner through signaling to the tumor stroma or may play a role in the maintenance of pancreatic "cancer stem cells." Vismodegib (GDC-0449) is an inhibitor of the protein Smoothened, which is essential for transducing hedgehog signaling. If trials are successful, this could be the 1st hedgehog pathway inhibitor to be approved for this condition. National Cancer Institute, Bethesda, MD, and University of Chicago, Chicago, IL Johns Hopkins Medicine's Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK National Cancer Institute, Bethesda, MD, and University of Michigan Cancer Center, Ann Arbor Phase II trials ongoing	Gemcitabine Gemcitabine plus cisplatin or oxaliplatin Gemcitabine plus erlotinib Gemcitabine plus a fluoropyrimidine	Increased overall survival Increased progression-free survival Improved quality of life
Vismodegib (GDC-0449) for treatment of recurrent glioblastoma multiforme	Patients with recurrent glioblastoma multiforme who have undergone surgical resection of the recurrent tumor	Aberrant hedgehog pathway activation has been implicated in maintaining the features of glioblastoma multiforme that resemble "cancer stem cells," which are largely resistant to conventional chemotherapy treatments. No hedgehog pathway inhibitors are currently available. Vismodegib (GDC-0449) is an inhibitor of the protein Smoothened, which is essential for transducing hedgehog signaling. If trials are successful, this could be the 1st hedgehog pathway inhibitor to be approved for this condition. National Cancer Institute, Bethesda, MD Phase II trial ongoing	Bevacizumab Bevacizumab plus irinotecan, BCNU/CCNU, temozolomide Combination PCV (CCNU, procarbazine, and vincristine) Cyclophosphamide Nitrosourea Nitrosourea wafer Platinum-based chemotherapy Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 is purported to intercalate into DNA and inhibit topoisomerase II activity that results in replication-dependent, site-selective double-strand breaks in DNA leading to G2 arrest and apoptosis; compared with other topoisomerase II inhibitors, vosaroxin is not a P-glycoprotein substrate, evading the most common mechanism for multidrug resistance. It may be used in combination with cytarabine. It is given as an intravenous infusion, 90 mg/m^2 for days 1 and 4 for induction and 70 mg/m^2 for all other cycles. Sunesis Pharmaceuticals, Inc., South San Francisco, CA Phase III trial ongoing	Cladribine, cytarabine, and granulocyte colony-stimulating factor (GM-CSF) plus or minus mitoxantrone or idarubicin Clofarabine, cytarabine, and GM-CSF Etoposide and cytarabine plus or minus mitoxantrone Fludarabine, cytarabine, and GM-CSF plus or minus idarubicin High-dose cytarabine and GM-CSF plus or minus anthracycline	Increased overall survival Increased progression-free survival Improved quality of life
Zanolimumab for treatment of cutaneous T-cell lymphomas	Patients in whom treatment-refractory cutaneous T-cell lymphoma (mycosis fungoides or Sezary syndrome) has been diagnosed	Patients whose disease has progressed following 2nd-line treatment have a poor prognosis and few treatment options. The malignant T cells of the majority of cutaneous T-cell lymphomas express CD4. Zanolimumab is a CD4-specific monoclonal that acts by downregulating T-cell activation/proliferation to deplete these malignant T cells from the patient. In trials, eligible patients must have disease that progressed following treatment with bexarotene and 1 additional systemic therapy. Emergent BioSolutions, Rockville, MD (acquired from TenX BioPharma, Philadelphia, PA) Phase II trials complete	Denileukin diftitox Photopheresis Vorinostat	Increased overall survival Increased progression-free survival Improved quality of life

Table 3. AHRQ Priority Condition: 03 Cardiovascular Disease: 99 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Adenosine diphosphate receptor antagonist (ticagrelor, Brilinta) for treatment of acute coronary syndrome	Adults in whom acute coronary syndrome has been diagnosed	The efficacy of clopidogrel varies because it is a pro-drug. It must be metabolized to become active, which can lead to variable platelet inhibition, and that in turn can increase a patient's risk of bleeding, stent thrombosis, and ischemia. Ticagrelor (Brilinta™) is an orally administered blood thinner (to reduce clumping of platelets and clotting, prevent heart attacks, prevent strokes). Potentially the 1st reversibly binding oral adenosine diphosphate (ADP) receptor antagonist, and similar to the action of the thienopyridines prasugrel, clopidogrel, and ticlopidine, ticagrelor blocks ADP receptors of subtype P2Y12. It differs from other antiplatelet drugs because it has a different binding site from ADP; it is an allosteric antagonist, and the blockage is reversible. Also, the drug is not activated by the liver, so, researchers believe, it might work better for patients with genetic variants of the enzyme cytochrome P-450 2C19. AstraZeneca, London, UK FDA approved for acute coronary syndrome Jul 2011; approval included labeled warning that states not to take it with a daily aspirin dose of more than 100 mg	Clopidogrel Prasugrel Ticlopidine	Reduced incidence of heart attacks and strokes Increased overall survival Reduced side effects compared with other antiplatelet drugs
Allogeneic mesenchymal precursor stem cell therapy (Revascor) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	Current therapy for HF is not disease-modifying and addresses only symptoms; stem cell therapy is proposed as a potential treatment to regenerate the heart muscle, and thereby its function, in several ways. Revascor™ is an allogeneic, adult mesenchymal precursor stem cell product intended to be an off-the-shelf product that can be administered as a single injection delivered through a minimally invasive cardiac catheterization procedure; intended effects include rebuilding blood vessels and heart muscle. Cephalon, Inc., acquired by Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, in Oct 2011 Mesoblast Ltd., Melbourne, Australia Phase II trial ongoing	Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics) Implantable medical devices (cardiac rhythm therapy devices, implantable cardioverter defibrillators, left ventricular assist devices) Surgery	Slowed, halted, or reversed HF progression Improved left-ventricular ejection fraction Increased survival Reduced hospital admissions for HF treatment Improved activities of daily living Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Allogeneic precultured adult bone marrow–derived mesenchymal stem cells (Prochymal) for cardiac repair after myocardial infarction	Patients in whom recent myocardial infarction (MI) has been diagnosed	No regenerative therapies are currently approved for MI. Prochymal® consists of allogeneic bone marrow–derived human mesenchymal stem cells intended to preserve and improve cardiac function following an acute MI; manufacturer has developed a specific “expansion” process for these cells, which are intended to be used “off the shelf,” and delivered intravenously within 10 days of a patient's 1st MI. Osiris Therapeutics, Inc., Baltimore, MD Phase II trial ongoing; available in U.S. under Expanded Access Program; approved in Canada for treating acute graft-vs-host disease in children.	Pharmaceutical therapy (e.g., beta blockers)	Increased ejection fraction Increased left ventricular volume Improved cardiac function Decreased cardiovascular events Improved quality of life
Allogeneic stem cells (MultiStem) for repair of myocardial tissue postinfarction	Patients with tissue damage after recent myocardial infarction (MI)	MI is a major cause of death and disability in the U.S. The ability to repair damaged heart tissue after MI remains an unmet need. MultiStem® is a proprietary allogeneic stem cell product made from nonembryonic stem cells obtained from bone marrow donors. The cells are intended to exert their effects by producing therapeutic proteins and other molecules in response to "signals" of inflammation and tissue damage in the heart. In the case of MI, the company suggests the product may promote tissue repair and functionally improve cardiac output and other functional parameters. The company states that MultiStem is designed for “off-the-shelf” use without the need for tissue matching or immunosuppressive drugs. The company states that the product is injected via a micro-infusion catheter into the damaged region of the heart 2–5 days following percutaneous coronary intervention. Athersys, Inc., Cleveland, OH Phase I trial completed; phase II trial planned	Mechanical intervention Pharmaceutical management	Improved cardiac function Reduced morbidity and mortality Improved quality of life
Altitude training using a portable altitude simulation chamber for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	Despite medical therapy, many patients with HF often experience suboptimal quality of life, exercise performance, and skeletal-muscle strength. Clinicians use a portable altitude simulation chamber to expose patients to normobaric hypoxia for 10 sessions over several weeks. The machine filters oxygen molecules from the air to mimic the oxygen level at an altitude of 1,500 meters, which is intended to help the body acclimatize, making delivery of oxygen to muscle tissue more efficient. In a pilot clinical trial, researchers used simulators manufactured by Hypoxico, Inc. (New York, NY), which are currently available for purchase by consumers. Montefiore Medical Center, Bronx, NY Pilot trial complete	High altitude environment Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics)	Improved oxygen-delivery efficiency Improved exercise performance Decreased morbidity and mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anacetrapib for lipid management in coronary artery disease	Patients in whom coronary artery disease has been diagnosed or who are at risk of developing the disease	Cholesterol ester transfer protein inhibitor intended to raise high-density lipoprotein by 100% and reduce low-density lipoprotein, improving lipid profile; precursor was torcetrapib; stopped development because of high rate of cardiovascular adverse events; anacetrapib has been reported to not raise blood pressure of subjects in clinical trials thus far. Merck & Co., Inc., Whitehouse Station, NJ Phase III trials ongoing; company anticipates filing new drug application with FDA after 2015	Lifestyle changes Pharmacotherapy (e.g., statins)	Reduced risk of heart attack Improved cardiovascular outcomes
Apo-B synthesis inhibitor (mipomersen, Kynamro) for treatment of familial hypercholesterolemia	Patients in whom heterozygous or homozygous familial hypercholesterol-emia (FH) has been diagnosed	Outcomes with current medication for FH are suboptimal; mipomersen represents a new mechanism-of-action/drug class for this disease state. Mipomersen (Kynamro™) is a 1st-in-class apolipoprotein (Apo)-B synthesis inhibitor; intended to decrease production of apo-B (structural protein for atherogenic lipids, such as low-density lipoprotein C [LDL-C]), and reduce LDL-C (bad cholesterol) by preventing its formation. Drug is delivered via weekly self-administered injection. Genzyme Corp., a subsidiary of Sanofi, Paris, France ISIS Pharmaceuticals, Inc., a unit of Johnson & Johnson, New Brunswick, NJ Phase III trials completed; Oct 2012, FDA advisory panel voted 9-6 to recommend approval; final decision date is Jan 29, 2013	Extracorporeal apheresis Pharmacotherapy (e.g., statins)	Reduced LDL levels Improved cardiovascular outcomes Improved long-term health outcomes Improved quality of life
$APOCIII_{Rx}$ for treatment of hypertriglyceridemia	Patients in whom hypertriglycerid-emia has been diagnosed	$APOCIII_{Rx}$ is an antisense drug that inhibits production (liver) of apolipoprotein C-III (apo-C-III); lower production of apo-C-III is linked to lower triglycerides and low-density lipoprotein-cholesterol levels, increased high-density lipoprotein levels and a lower risk of cardiovascular disease. The new drug is intended to avoid side effects of current triglyceride-lowering medications. ISIS Pharmaceuticals, Inc., a unit of Johnson & Johnson, New Brunswick, NJ Phase II trial ongoing	Pharmacotherapy (e.g., fenofibrates)	Reduction in triglycerides Reduced cardiovascular risk Improved metabolic syndrome

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Apolipoprotein-B synthesis inhibitor (SPC4955) for treatment of hypercholesterolemia	Patients in whom hypercholesterol-emia has been diagnosed	Despite available therapies, cholesterol levels of some patients with severe hyperlipidemia are not adequately managed, and their cardiovascular risk remains high. This drug represents a new mechanism of action for this condition. SPC4955 is an apolipoprotein-B-100 (apoB-100) synthesis inhibitor that is involved in forming low-density lipoprotein (LDL-C, the "bad" cholesterol), and its inhibition is known to lower LDL and triglyceride levels. This drug is being developed as an injection-administered agent. Santaris Pharma a/s, Hørsholm, Denmark Phase I trial completed	Bile acid sequestrants Ezetimibe Fibrates Niacin Omega-3 fatty acids Statins, alone or in combination with other agents	Reduced LDL and triglyceride levels Reduced cardiovascular morbidity and mortality
Autologous bone marrow–derived cells (Ixmyelocel-T) for treatment of critical limb ischemia	Patients in whom critical limb ischemia (CLI) has been diagnosed	Outcomes for patients with CLI are poor, and many patients require amputation. This intervention represents a novel treatment modality for this condition. Tissue repair cell (Ixmyelocel-T) technology consists of bone marrow extracted from the patient, expanded over the course of 12 days at the manufacturer's facility using the company's proprietary process, and reinfused into the patient 14 days after extraction. The formulation includes monocytes, macrophages (intended to destroy dead tissue, stimulate regeneration, and reduce inflammation), mesenchymal stem cells (intended to promote angiogenesis), and endothelial progenitor cells (intended to promote blood vessel lining and generate cardiovascular tissue). Aastrom Biosciences, Inc., Ann Arbor, MI Phase III trial ongoing	Percutaneous angioplasty and stenting Pharmacotherapy (e.g., cilostazol and pentoxifylline) Surgery	Tissue regeneration Improved circulation Reduced need for amputation Reduced morbidity and mortality
Autologous bone marrow–derived mesenchymal stem cells for myocardial repair after infarction	Patients who need cardiac repair after myocardial infarction (MI)	No regenerative therapies are available for patients experiencing cardiac damage secondary to MI; 20% of MIs are severe enough to cause ventricular remodeling, which leads to heart failure. Autologous mesenchymal (or mononuclear, which includes mesenchymal and hematopoietic cells) stem cells are harvested from patient's own bone marrow, enriched, then injected/infused into patients (e.g., transendocardial or arterial delivery) at some point after their MI. Under development by several entities including University of Miami, FL; Amorcyte, Allendale, NJ; and National Heart Lung and Blood Institute, Bethesda, MD Phase I/II trials ongoing	Pharmaceutical management (e.g., beta blockers)	Myocardial tissue regeneration Improved cardiac function Reduced cardiovascular events Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous heart stem cell transplantation for postmyocardial infarction revascularization	Patients who have experienced a heart attack within the past month	A biopsy performed under local anesthesia is done to harvest cardiac cells from the patient. The harvested heart stem cells are cultured and reintroduced to the patient's coronary arteries. Various cardiovascular research institutions in U.S. and Europe More than 30 randomized controlled trials complete and published worldwide as of 2012	Coronary artery bypass surgery Percutaneous coronary interventions Medical management	Reduced mortality and morbidity (major adverse cardiac events) Improved activities of daily living Reduced need for coronary reintervention Improved quality of life
Autologous stem cell therapy (C-Cure) for heart failure	Patients in whom severe heart failure has been diagnosed	Stem cell product (C-Cure®) is derived from the patient's own bone marrow and (in vitro, before transplantation) cultured to become cardiac lineage cells intended to improve heart function. Cardio3 BioSciences, Mont-Saint-Guibert, Belgium Phase III trial planned for 1st half of 2012	Cardiac rhythm therapy devices Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics) Implanted cardioverter defibrillator Surgery	Increased left ventricular ejection fraction and other heart function outcomes Improved activities of daily living Improved quality of life
Biased angiotensin II type 1 receptor ligand (TRV120027) for treatment of acute heart failure	Patients in whom acute heart failure (HF) has been diagnosed	Current drugs for acute HF are associated with life-threatening safety risks. TRV120027 is a beta-arrestin biased angiotensin II type 1 receptor ligand with a new mechanism of action; it stimulates beta-arrestin recruitment and activates several kinase pathways, potentially eliciting a different pharmacologic effect from unbiased agonists; intended to have minimal effects on heart rate and reduced mean arterial pressure, while increasing the slope of end-systolic pressure-volume relationship and preserving cardiac stroke volume; 1st in biased ligand class to be tested in humans. Administered intravenously. Trevena, Inc., King of Prussia, PA Phase I/II trial complete	Diuretics Inotropic agents Vasodilators	Improved symptoms Improved hemodynamics Improved clinical status Improved long-term outcomes Increased survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Biodegradable scaffold (IK-5001) for support postmyocardial infarction	Patients at risk of heart failure (HF) or ventricular remodeling after acute myocardial infarction	IK-5001, also called a bioabsorbable cardiac matrix, is a partially cross-linked, alginate-based, liquid polymer intended to provide physical support to the heart. It is being investigated to prevent ventricular remodeling and congestive heart failure after an acute myocardial infarction. It is intended to dissipate and be excreted through kidney after 6 weeks. Injected at site of occlusion or distal to site after revascularization of occluded vessel. BioLineRx, Ltd., Jerusalem, Israel, licensed to Ikaria, Hampton, NJ Phase II multicenter international trial ongoing	Pharmacotherapy (to prevent HF)	Improved left ejection fraction Slowed progression of HF Improved activities of daily living Improved survival
Bioresorbable vascular scaffold (Absorb) for treatment of critical limb ischemia	Patients in whom below-the-knee critical limb ischemia (CLI) has been diagnosed	Outcomes for patients with CLI are poor, and many patients require amputation. This intervention represents a novel approach to treatment. Absorb bioresorbable vascular scaffold is made of a biocompatible polylactide polymer scaffold that elutes everolimus. It is intended to provide support to the vessel, then dissolve over the course of 2 years. The company purports that because the device is not permanent, natural vessel function may be restored. Abbott Laboratories, Abbott Park, IL U.S. trial ongoing; approved in Europe in 2011; available also in parts of Asia Pacific and Latin America.	Other bioabsorbable scaffolds in development Percutaneous angioplasty and stenting Pharmacotherapy (e.g., cilostazol and pentoxifylline) Surgery	Decreased pain Improved circulation and mobility Reduced need for amputation Improved quality of life
Bromodomain inhibitor (RVX-208) for treatment of dyslipidemia	Patients with sub-optimal high-density lipoprotein (HDL) levels (dyslipidemia)	Treatment of HDL as a single target is not available. RVX-208 is an orally available small molecule, 1st-in-class inhibitor of the bromodomain and extraterminal domain (BET) proteins. RVX-208 is said to act on BET proteins, including BRD4, which leads to increased transcription of the ApoA-I gene followed by production of more ApoA-I protein. Resverlogix, Calgary, Alberta, Canada Phase IIb trials completed	Pharmacotherapy (e.g., statins)	Improved HDL levels Decreased plaque burden Improved cardiovascular outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cardiac contractility modulation (Optimizer III Implantable Pulse Generator system) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	Optimizer III™ system is a device implant intended to treat patients with chronic heart failure who are unable to achieve desired goals with optimal medical therapy 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 three 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. Impulse Dynamics, N.V., Willemstad, Netherlands Antilles Pivotal investigational device exemption trial completed; FIX-HF-5B confirmatory trial ongoing; CE marked for distribution in Europe	Implanted pacemakers and/or defibrillators Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics)	Symptom relief Improved 6-minute walk test Fewer hospital admissions Delayed progression of HF Delayed need for ventricular assist devices Improved quality of life
Cardiac pacing system (Revo) for patients who may require future magnetic resonance imaging	Patients with pacemakers who need to undergo MRI scanning	Revo MRI™ SureScan® pacing system is intended for patients who may need to undergo MRI in the future. Pacemaker implants had previously been a contraindication for MRI because of potential risks of malfunction during MRI. Revo includes hardware modifications that are designed to reduce/eliminate pacemaker hazards produced by MRI environment. Pacemaker includes a feature that sets device into appropriate mode for MRI environment. Medtronic, Inc., Minneapolis, MN FDA approved Feb 2011	Other pacemakers might be safe for use with MRI, under certain conditions	Ability for physicians to use MRI for patients who require pacemaker therapy

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Catheter-based renal denervation (Symplicity System) for treatment-resistant hypertension	Patients in whom uncontrolled hypertension has been diagnosed	The Symplicity® catheter system is intended to accomplish renal denervation through a minimally invasive procedure. The device is used to affect 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. Renal sympathetic nerves are believed to often cause chronic hypertension. Medtronic, Inc., Minneapolis, MN Phase III trial SYMPLICITY HTN-3 ongoing	Pharmacotherapy (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers) Renal artery stents	Controlled hypertension without medications Controlled blood pressure to reduce incidence of blindness, heart attacks, kidney failure, and stroke
Catheter-based ultrasound renal denervation system (Paradise) for treatment-resistant hypertension	Patients in whom treatment-resistant hypertension has been diagnosed	Many pharmacotherapies are available for treating hypertension, but many cases of hypertension are not controlled with these interventions. Because uncontrolled hypertension is associated with high morbidity (e.g., end-organ damage) and mortality, novel interventions are warranted. This product might offer a therapeutic intervention for patients whose hypertension remains uncontrolled, despite pharmacotherapy. The Paradise™ Percutaneous Renal Denervation System is a catheter-delivered procedure that uses a cylindrical transducer to emit ultrasound energy circumferentially to the renal nerves. The manufacturer states that hyperactivity of the afferent and efferent sympathetic nerves from and to the kidneys are thought to play a role in blood pressure regulation and the pathophysiology of hypertension and that deactivating these nerves might reduce this hyperactivity, potentially lowering blood pressure. ReCor Medical, Inc., Ronkonkoma, NY First-in-human trial completed	Alpha agonists Alpha blockers Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers Beta blockers Calcium channel blockers Combination medications Diuretics Other catheter-based renal denervation systems (in development) Renal artery stents Renin inhibitors	Controlled hypertension without medications Reduced rates of blindness, heart attack, kidney failure, and stroke

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Catheter-based ventricular restoration implant (Parachute) for treatment of heart failure	Patients in whom ischemic heart failure (HF) has been diagnosed	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 the condition. 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. CardioKinetix, Inc., Menlo Park, CA Mid-phase trials ongoing	Heart transplant Pharmacotherapy (e.g., beta blockers) Surgical ventricular revision	Improved HF symptoms Increased cardiac output Increased survival Reduced left ventricular volume Reduced morbidity
Catheter-delivered biodegradable adhesive (Sapheon Closure System) for treatment of varicose veins	Patients with varicose veins who are eligible for treatment	Although many options exist for treating varicose veins, treatments are sought that offer shorter intervention time than other methods and offer faster recovery phase than surgery, thermal, or chemical treatments. Sapheon Closure System™ consists of a catheter to deliver biodegradable adhesive that is intended to treat varicose veins by closing off and destroying the target vein or veins. Sapheon, Inc., Santa Rosa, CA Pilot trial complete in U.S.; Conformité Européene (CE) marked Sept 2011	Laser Radiofrequency ablation Sclerotherapy Support stockings Surgery (vein stripping)	Improved healing of wounds Improved blood flow Prevention of blood clots Reduced pain Restored functional capacity (walking)
CER-001 for treatment of acute coronary syndrome	Patients in whom acute coronary syndrome has been diagnosed	Treatment for high-density lipoprotein (HDL) levels alone (as a single target) is not available. CER-001 is an HDL mimetic that consists of a recombinant human apolipoprotein A (Apo-A-I, the major structural protein of HDL) and phospholipids; HDL is responsible for reverse cholesterol transport, and the drug is intended to mobilize cholesterol, thus reducing atherosclerotic plaque burden. Administered as a weekly infusion for 6 weeks in clinical trials. Cerenis Therapeutics, Inc., Ann Arbor, MI Phase II trial ongoing	Pharmacotherapy (e.g., statins)	Improved HDL levels Improved heart function Fewer cardiac events

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cholesteryl ester transfer protein inhibitor (evacetrapib) 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 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 is purported to differ from other CETP inhibitors in development. CETP is a plasma protein responsible for lipid transport. Also known as LY2484595. Eli Lilly and Co., Indianapolis, IN Phase II trial complete	Pharmacotherapy Sclerotherapy	Improved HDL profile Reduced cardiovascular morbidity and mortality Improved quality of life
Dual natriuretic peptide receptor agonist (Cenderitide) for treatment of postacute decompensated heart failure	Patients in whom acute decompensated heart failure (ADHF) has been diagnosed	According to the American Heart Association, more than 1.2 million patients are admitted for ADHF annually; about 40% of these patients are re-admitted within 90 days, so novel interventions are needed to prevent a recurrence of acute symptoms. Cenderitide is a chimeric natriuretic peptide receptor agonist that is intended to offer dual mechanisms of action, which may provide a unique therapeutic window to relieve symptoms of heart failure (HF). Intended to be administered in a continuous subcutaneous pump for 90 days to provide symptomatic relief in the outpatient setting, which could contribute to a reduction in postacute hospitalizations and persistent improvement in cardio-renal functions. Nile Therapeutics, Inc., San Mateo, CA Phase I trial ongoing, expected completion in 1st quarter 2012; FDA granted fast track status; company is seeking “post-ADHF” indication with this drug	Diuretics Natrecor	Reduced hospital readmissions Reduced HF symptom burden Improved cardiovascular outcomes
Electrical stimulation of carotid baroreceptors (Rheos System) for treatment of drug-resistant hypertension	Patients in whom severe, drug-resistant hypertension has been diagnosed	Electrical stimulation of carotid baroreceptors through a pulse generator inserted subcutaneously (CVRx Rheos® System), which delivers electrical signals to baroreceptors in both carotid arteries in the neck through carotid sinus leads. CVRx, Inc., Minneapolis, MN Phase II/III trials ongoing	Pharmacotherapy (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers)	Reduced hypertension Reduced stoke incidence Reduced cardiovascular events Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Elinogrel for prevention of heart attack and stroke and treatment of acute coronary syndrome	Patients in whom acute coronary syndrome has been diagnosed	Elinogrel is a reversible, direct-acting oral and intravenous P2Y12 ADP receptor antagonist. It is a novel small-molecule, antiplatelet compound that inhibits the ADP receptor (P2Y12) on platelets to block platelet aggregation and prevent thrombosis. It is the only compound in this class with both oral and intravenous (IV) formulations, and it could potentially be used for acute and chronic indications. The IV formulation is intended to provide immediate onset and high levels of platelet inhibition. Elinogrel requires no metabolism for activation (similar to Brilinta™); as a result, elinogrel avoids the issue of delayed action and wide interpatient variability seen with thienopyridines (e.g., clopidogrel [Plavix®] and prasugrel [Effient®]). The developer claims that elinogrel's ability to compete directly with ADP for the P2Y12 binding site may favorably affect the balance of its influence on thrombosis (low ADP state) versus hemostasis/bleeding (high ADP state), leading to a better risk-benefit ratio. Portola Pharmaceuticals, Inc., South San Francisco, CA Novartis International AG, Basel, Switzerland Phase II trial for IV and oral formulations complete; phase III trials planned to begin 2012	Pharmacotherapy (e.g., prasugrel)	Fewer side effects from anticlotting medication regimen Reduced stroke incidence Reduced heart attack incidence Increased survival Improved quality of life
Excimer laser-assisted nonocclusive anastomosis (Elana) procedure for intracranial vascular bypass	Patients older than age of 13 years with an aneurysm or skull base tumor affecting a large (>2.5 mm), intracranial artery that failed balloon test occlusion, cannot be sacrificed, or cannot be treated with conventional means	In some patients, aneurysms or skull base tumors cannot be treated with conventional means (e.g., coiling). For these patients, a surgical bypass of the lesion may be indicated. However, traditional surgical bypass procedures require shutting off blood flow to the target artery, which can put patients at high risk of stroke. The Excimer laser-assisted nonocclusive anastomosis (Elana) procedure purportedly allows clinicians to perform a bypass without shutting off blood flow to the target artery. The system consists of a ring, which is placed around the donor vessel, and a laser catheter system, which is placed through the donor vessel and used to cut holes in the target vessel. One-half of the donor vessel is then sutured to the target vessel, clamped, and eventually attached to the other donor vessel. Elana bv, Utrecht, The Netherlands FDA approved in Mar 2011 under a humanitarian device exemption	Traditional surgical artery bypass grafting	Decreased morbidity Increased survival Reduced stroke incidence

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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 to be used in patients with more advanced HF stages. This intervention represents a novel device for treating 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). Sunshine Heart, Inc., Eden Prairie, MN Feasibility trials completed; pivotal trial planned	Intra-aortic balloon pumps Left ventricular assist devices	Decreased morbidity Increased cardiac output Increased survival Reduced cardiac workload Reduced risk of stroke or thrombi
Factor IXa inhibitor and active control agent (REG2 System) for prevention of venous thromboembolism	Patients in whom risk of venous thromboembolism (VTE) has been diagnosed	Treatment for VTE is associated with limitations, including limited oral treatment alternatives to warfarin for patients with severe renal impairment and the inability to fully reverse the effects of available pharmacotherapy. The REG2 system is intended to be used prophylactically to prevent VTE. According to its developer, the system "comprises a nuclease-stabilized RNA aptamer, the therapeutic effect of which can be reversed partially or completely in real time by its specific and complementary oligonucleotide active control agent." This approach technology is being studied in acute and sub-acute care cardiovascular settings. It consists of a subcutaneously administered direct coagulation factor IXa inhibitor, called RB006, and an intravenous bolus formuation of RB007. RB006 is purported to be a "potent highly selective Factor IXa inhibitor" and RB007 is said to be RB006's complementary active control agent. Regado Biosciences, Inc., Basking Ridge, NJ Phase I trial complete	Available pharmacotherapy (e.g., warfarin)	Reversal of anticoagulation Increased survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Factor Xa inhibitor (apixaban; Eliquis) for prevention of stroke, and systemic embolism	Patients with nonvalvular atrial fibrillation (AF) at risk of deep vein thrombosis (DVT), pulmonary embolism (PE), or stroke	Apixaban (Eliquis™, BMS-562247-01) is an oral, highly selective coagulation factor Xa inhibitor intended to reduce the risk of stroke in patients with AF and to prevent or treat venous thromboembolism (VTE). Bristol-Meyers Squibb, New York, NY, in joint development with Pfizer, Inc., New York, NY New drug application filed and granted priority review; Jun 26, 2012, FDA issued a complete response letter (CRL) for preventing stroke and systemic embolism in patients with nonvalvular AF. In the CRL, the agency asked for more information on data management and verification from the phase III Aristotle study. Approved May 2011 by European Medicines Agency for VTE prevention after knee or hip replacement surgery	Available pharmacotherapy (e.g., warfarin)	Reduced DVT events Reduced stroke incidence Reduced PE events
Factor Xa inhibitor (betrixaban) for prevention of deep vein thrombosis or pulmonary embolism	Patients at high risk of thrombosis	Betrixaban is a direct coagulation factor Xa inhibitor and has the potential to be used in patients with severe renal impairment (excluding dialysis patients); betrixaban keeps prothrombin from converting to thrombin to decrease clot formation; it is primarily eliminated unchanged in the bile so it is metabolized through cytochrome 450 enzyme system. Portola Pharmaceuticals, San Francisco, CA Phase III trial planned for 2012	Available pharmacotherapy (e.g., warfarin)	Prevention of thrombosis Prevention of pulmonary embolism Decreased stroke events
Factor Xa inhibitor (edoxaban) for prevention of thrombosis	Patients at risk of venous thromboembolism (VTE) or with atrial fibrillation (AF)-related stroke	Edoxaban is an agent in a new class of anticoagulants designed to inhibit coagulation factor Xa (FXa), which is known to be an important component of the coagulation cascade. It is intended to be administered orally, once daily. Daiichi Sankyo Co., Ltd., Tokyo, Japan Phase III trial ongoing for VTE indication; phase II trial complete for AF indication; received approval in Japan in Apr 2011 for preventing VTE after major orthopedic surgery; in the U.S., manufacturer is seeking indications only for VTE and preventing stroke in patients with AF	Available pharmacotherapy (e.g., other FXa inhibitors, dabigatran, warfarin)	Reduced thrombosis rate Reduced stroke incidence Reduced pulmonary embolism incidence

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Factor Xa inhibitor (otamixaban) for treatment of acute coronary syndrome	Patients in whom acute coronary syndrome (ACS) has been diagnosed	Otamixaban is a reversible, direct selective coagulation factor Xa (FXa) inhibitor that the manufacturer purports has a fast onset of action and a short half-life and may not require anticoagulation monitoring or dose adjustments for certain populations. Sanofi, Paris, France Phase III trial ongoing	Available pharmacotherapy (e.g., other FXa inhibitors, dabigatran, warfarin)	Reduced morbidity and mortality Reduced need for monitoring or adjusting anticoagulant dose
Factor Xa inhibitor (rivaroxaban, Xarelto) for prevention of deep vein thrombosis	Patients who have undergone hip or knee replacement	Rivaroxaban (Xarelto®) is a member of a new class of anticoagulants that are designed to inhibit factor Xa (FXa), which is known to be an important component of the coagulation cascade. It is administered orally, once daily at 10 mg dose for 35 days after hip replacement and 12 days after knee replacement for preventing deep vein thrombosis. Janssen Pharmaceuticals Inc., a unit of Johnson & Johnson, New Brunswick, NJ FDA approved Jul 2011	Available pharmacotherapy (e.g., other FXa inhibitors, dabigatran, warfarin)	Reduced morbidity and mortality Reduced thrombotic events
Factor Xa inhibitor (rivaroxaban, Xarelto) for prevention of stroke in patients with nonvalvular atrial fibrillation	Patients in whom with non-valvular atrial fibrillation (AF) has been diagnosed	Rivaroxaban (Xarelto®) is a member of a new class of anticoagulants that are designed to inhibit factor Xa (FXa), which is known to be an important component of the coagulation cascade. It is administered orally, once daily, and is approved to reduce the risk of stroke in people who have abnormal heart rhythm (nonvalvular atrial fibrillation). Janssen Pharmaceuticals Inc., a unit of Johnson & Johnson, New Brunswick, NJ FDA approved Nov 2011	Available pharmacotherapy (e.g., other FXa inhibitors, dabigatran, warfarin)	Reduced stroke incidence Reduced morbidity and mortality
Factor Xa inhibitor (rivaroxaban, Xarelto) for treatment of acute coronary syndrome	Patients in whom acute coronary syndrome has been diagnosed	Rivaroxaban (Xarelto®) is a coagulation factor Xa (FXa) inhibitor; keeps prothrombin from converting to thrombin, decreasing clot formation. Compared with previously available pharmaceuticals, it might offer fewer drug interactions, and might not require frequent blood checks. It is an oral medication taken daily. Janssen Pharmaceuticals Inc., a unit of Johnson & Johnson, New Brunswick, NJ In Jun 2012, FDA denied approval and issued a complete response letter requesting more data; Janssen is considering its next steps	Available pharmacotherapy (e.g., other FXa inhibitors, dabigatran, warfarin)	Reduced morbidity and mortality Reduced thrombotic events

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Factor XI inhibitor (ISIS-FXIRX) for anticoagulation	Patients at risk of aberrant blood clot formation	Some currently available anticoagulation agents carry a high risk of bleeding, or require ongoing monitoring and dose adjustments. This agent represents a novel mechanism of action for patients at risk of aberrant blood clot formation. ISIS-FXIRX is intended to inhibit factor XI, a clotting factor that is a component of the coagulation pathway. High levels of factor XI are a risk factor for clots. Because of its position in the coagulation pathway, this agent may be associated with minimal risk of bleeding. ISIS Pharmaceuticals, Inc., a unit of Johnson & Johnson, New Brunswick, NJ Phase I trial completed; phase II study planned for 2012	Available pharmacotherapy (e.g., dabigatran, factor Xa inhibitors, warfarin)	Reduced incidence of aberrant clot formation Reduced thrombosis rate Reduced stroke incidence Reduced pulmonary embolism incidence Reduced morbidity and mortality
Fibrin-specific plasminogen activator (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 1 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 timeframe. Desmoteplase is a chemical derived from the saliva of vampire bats that catalyzes the conversion of plasminogen to plasmin, the enzyme responsible for breaking down fibrin blood clots. Structurally, the chemical is similar to tPA, but has much higher fibrin selectivity and, therefore, does not cause systemic plasminogen activation and fibrinogen depletion. H. Lundbeck a/s, Valby, Denmark One phase III trial complete; other phase III trials ongoing	tPA therapy	Increased blood flow to the brain Reversed damage Improved stroke-related outcomes
Freedom driver system for Total Artificial Heart as bridge to heart transplantation	Patients with nonreversible biventricular failure who are candidates for heart transplantation	The temporary Total Artificial Heart (TAH) functions in place of ventricles/valves by pumping blood to both the pulmonary and systemic circulation. This TAH is distinguished from prior TAHs by its portable driver (Freedom® driver) that is intended to allow patients to recover and remain at home, rather than remaining hospitalized. SynCardia Systems, Inc., Tucson, AZ TAH was FDA approved in 2004; clinical trial investigating use of Freedom driver system ongoing under FDA investigational device exemption trial status; expected to be complete in 2012	TAH used with in-hospital driver	Restored mobility Possible recovery at home (reduction in hospitalization costs) Extended survival for patients awaiting heart transplantation

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Frontal near-infrared spectroscopy for monitoring stroke recurrence	Hospitalized patients who are being treated for stroke	About 1/3 of patients who are hospitalized for stroke treatment experience another stroke while in the hospital. Current methods for monitoring whether another stroke is occuring require either a computed tomography (CT) scan with a contrast medium or an invasive procedure that requires an oxygen probe to be inserted into the brain. Frontal near-infrared spectroscopy is a patch-like device that is placed onto the patient's forehead. According to researchers, it acts similarly to a pulse oximeter (used on a finger to monitor patient's oxygen saturation during surgery), measuring blood oxygen in the brain by emitting near-infrared light that penetrates the scalp and underlying brain tissue. Mayo Clinic, Jacksonville, FL Small pilot trial complete	CT perfusion scan Oxygen probe	Reduced exposure to radiation Reduced need for invasive monitoring procedures Timelier stroke intervention Reduced morbidity from stroke
Gene therapy (Mydicar) for heart failure	Patients in whom heart failure (HF) has been diagnosed (additional trials needed to identify appropriate candidate population)	Genetically targeted enzyme replacement therapy (Mydicar®) as adjunct to treat HF. Intended to correct or replace faulty genes, restore levels of key proteins, and restore the heart's pumping capacity. Celladon Corp., La Jolla, CA Targeted Genetics Corp., Seattle, WA Phase II trial ongoing; received FDA fast track status Dec 2011	Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics)	Improved left ventricular ejection fraction Improved cardiovascular outcomes (reduction in cardiovascular events) Improved quality of life
Glial growth factor 2 for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	Existing medications for HF treatment primarily aim to modify the workload of the heart, rather than promote ventricular repair. Glial growth factor 2 is a neuregulin (part of a family of proteins) believed to act directly on cardiomyocytes to repair tissue damage from heart disease, thereby improving contractility. Administered as single intravenous infusion. Acorda Therapeutics, Hawthorne, NJ Phase I trial ongoing	Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics)	Increased ventricular repair Improved cardiac output Improved cardioprotection Improved long-term cardiac outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Human monoclonal antibody (BI-204) for treatment of coronary artery disease	Patients in whom coronary artery disease (CAD) has been diagnosed	BI-204 is a human monoclonal antibody that specifically targets oxidized form (apoB100) of a low-density lipoprotein that has been linked to increased inflammatory processes leading to plaque formation in blood vessel walls, leading to CAD. BioInvent International AB, Lund, Sweden Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase II trial ongoing	Pharmacotherapy (e.g., statins)	Prevent plaque formation Reduced existing plaques Prevent breakdown of unstable plaques Reduced cardiac events in high-risk patients
Icatibant (Firazyr) for treatment of acute hereditary angioedema	Patients 18 years of age or older in whom acute hereditary angioedema (HAE) has been diagnosed	HAE is a genetic disorder caused by dysfunction or deficiency of the plasma protein C1 inhibitor (C1INH). C1INH is an inhibitor of the C1 protease that is responsible for activating the complement pathway in the immune system. If C1INH is deficient, the immune system reacts with an inflammatory response that leads to swelling. Unlike bradykinin beta-receptor-1, bradykinin beta-2 receptors do not appear to be involved in chronic inflammatory diseases but may mediate acute inflammatory processes. Icatibant (Firazyr®) is a peptidomimetic drug consisting of 10 amino acids and is a selective and specific antagonist of bradykinin beta-2 receptors. Administered by subcutaneous injection. Shire Pharmaceuticals, plc, Dublin, Ireland FDA approved Aug 2011 for treating acute attacks of HAE	Antihistamines C1-INH (concentrate from donor blood) Fresh-frozen plasma Pain relievers and fluids given intravenously	Faster symptom relief of primary symptom Reduced severity of symptoms Reduced mortality
Implantable cardiac monitor for detecting myocardial infarction	Patients at high risk of myocardial infarction (MI)	Implantable electronic device designed to warn patients of an impending MI; measures electrical changes in the heart. Angel Medical Systems, Shrewsbury, NJ Phase III trial ongoing	Conventional, external MI detection technologies Patient report	Earlier detection of impending heart attack Prevention of heart damage Increased overall survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Injectable biopolymer (Algisyl-LVR) for prevention or treatment of heart failure	Patients in whom an enlarged left ventricle (from mitral valve regurgitation, ischemia, dilated cardiomyopathy and/or other disorders) has been diagnosed	No treatments are available to reverse the progression of heart failure (HF). 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; intended to thicken heart muscle wall, reduce chamber size, decrease local muscle wall stress, allow for reshaping of dilated ventricle; material is inert (i.e., does not interact with the human immune system). Cardio Polymers, now part of LoneStar Heart, Inc., Laguna Hills, CA Phase II/III trial ongoing	Drug therapy to prevent HF	Increased left ejection fraction Reduced progression of HF Reduced regression of HF Improved cardiovascular outcomes Improved quality of life
Intravenous methamphetamine HCl for neuroprotection during stroke	Patients experiencing an acute ischemic stroke	Only 1 drug, tissue-plasminogen activator (tPA) is approved for this indication, but is effective only when administered within the 1st 3 hours of symptom onset, and only a very small percentage of patients experiencing an acute stroke receive tPA. Methamphetamine is currently marketed in pill form for attention deficit disorder with hyperactivity. Abuse of methamphetamine is known to cause arterial injury, stroke, brain hemorrhage and death at high doses. The manufacturer has created new low-dose version and new route of administration (intravenous injection). The company claims that preclinical models have shown neuroprotection for up to 12 hours. It is believed to exert its effects by inhibiting apoptosis (programmed cell death) and upregulating anti-inflammatory cytokines, as well as downregulating proinflammatory cytokines, through dopaminergic pathways. Sinapis Pharma, Inc., Jacksonville, FL Phase I trial completed; company stated phase II trial planned to begin by late 2011, but no trial is yet registered	tPA	Improved poststroke neuron survival Improved patient outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ivabradine for treatment of heart failure	Patients with symptomatic (New York Heart Association class II–IV) chronic heart failure (HF) and systolic dysfunction who are on stable background therapy and in a normal sinus rhythm	Ivabradine is an oral selective inhibitor of hyper-polarization-activated cyclic-nucleotide-gated funny current involved in pacemaking and responsiveness of the sinoatrial node; intended to slow heart rate and allow more time for blood to flow to the heart. Servier, Neuilly sur Seine, France Phase III trial (sponsored by IRCCS San Raffaele) ongoing; approved in EU in 2005 as Procoralan for treating stable angina; approved in EU in 2012 for treating heart failure.	Beta blockers Calcium channel blockers	Reduced HF hospitalizations Reduced coronary events Reduced incidence of myocardial infarction Improved quality of life
JVS-100 for treatment of critical limb ischemia	Patients in whom critical limb ischemia has been diagnosed	No regenerative or disease-modifying therapies are available to treat this condition, and this drug has that potential. JVS-100 is an agent that encodes stromal-cell derived factor 1 (SDF-1). SDF-1 recruits endothelial progenitor cells to site of injury, thereby potentially inducing neovascularization and angiogenesis (sustained vessel formation necessary for adult tissue to become fully revascularized, particularly after ischemia); natural SDF-1 expression lasts for less than a week so natural stem cell homing signals fade quickly. Juventas Therapeutics, Cleveland, OH Phase II trial ongoing	Endovascular intervention Medication to reduce contributing factors (e.g., cholesterol) or pain Surgical intervention	Reduced pain Improved blood flow Reduced need for amputation Improved functional ability Improved quality of life
Lecinoxoid anti-inflammatory agent (VB-201) for treatment of atherosclerosis	Patients in whom atherosclerosis has been diagnosed	C-reactive protein (CRP) is an established biomarker for cardiovascular disease. However, current agents used to prevent cardiovascular disease do not always effectively control CRP levels, allowing patients to remain at high risk of cardiovascular events. VB-201 is a member of a new drug class, called Lecinoxoids, that act as anti-inflammatory agents. Although the drug's specific mechanism of action has not been described, the manufacturer states that the agent acts as a specific, targeted, oral controller medication for inflammatory diseases. The agent is intended to reduce CRP levels, potentially reducing patient risk of cardiovascular events. VBL Therapeutics, Tel Aviv, Israel Phase II trial completed	Pharmacotherapy (e.g., statins)	Reduced risk of cardiovascular events Reduced morbidity Reduced mortality from heart attack

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Left ventricular assist device (HVAD) as bridge to transplantation for end-stage heart failure	Patients with end-stage heart failure (HF) who are eligible for heart transplantation	HeartWare is developing a left ventricular assist device (LVAD) for treating advanced HF. The device (HVAD™) propels blood centrifugally from the center of a spinning disc, which is suspended by magnetics and blood; smaller than currently marketed devices, it can be implanted directly in left ventricle and surrounding space (does not require abdominal surgery to create pocket). The device is implanted with less invasive surgery which could enable more patients to be candidates for the devices and at earlier stages of disease progression. HeartWare International, Inc., Framingham, MA U.S. multicenter late-phase clinical trial under FDA investigational device exemption status ongoing; Conformité Européene (CE) marked in 2009	Optimal medical management Other LVADs Total artificial heart	Improved survival Improved quality of life prior to transplant Reduced incidence of internal bleeding compared with continuous-flow devices
Low-dose tPA for treatment of intraventricular hemorrhage	Patients in whom intraventricular hemorrhage has been diagnosed	The agent tissue plasminogen activator (tPA) is a thrombolytic (clot-busting drug) long used for treating stroke; it may be useful to treat intraventricular hemorrhage clots that form once bleeding has been stopped; current strategy is to remove the clots with intraventricular catheter, which can clog and take days. Use of tPA could offer a less invasive, faster treatment option. Johns Hopkins University, Baltimore, MD Phase III trial ongoing	Intraventricular catheter alone	Improved clot evacuation Decreased time to clot evacuation Improved cardiovascular outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Membrane active chelator (DP-b99) for neuroprotection during acute stroke	Patients experiencing an acute ischemic stroke	Only 1 drug, tissue plasminogen activator (tPA), is FDA approved for this indication, but tPA is effective only when administered within the 1st 3 hours of symptom onset, and only a very small percentage of patients experiencing an acute stroke receive tPA. When a cell is deprived of oxygen, the ability of membranes to control ion flux is disrupted, resulting in the loss of metal ion homeostasis, which can significantly impair cell or organ function and eventually lead to cell death. DP-b99 is a lipophilic chelator of calcium, zinc, and copper ions; it is intended to sequester metal ions only within and near cell membranes. The manufacturer claims it can bind to pathological levels of metal ions, making it useful for the suppression of cell damage in stroke patients. The technology is based on lipid modification of metal ion chelators, which sequester metal ions in all aqueous environments, causing potential toxic effects. The modified version binds metal ions selectively, which makes it potentially safer and is intended to increase treatment window to 9 hours. DP-b99 is delivered via intravenous infusion. D-Pharm, Ltd., Rehovot, Israel Phase III trial suspended by trial steering committee in Jan 2012; investigations are being performed to determine whether study will continue; FDA granted fast track status	tPA	Improved poststroke neuron survival Faster recovery Reduced need for rehabilitation services
Metabolic regulator (ETC-1002) for treatment of dyslipidemia	Patients with cardiovascular disease (CVD), or in whom a risk of CVD has been diagnosed	Despite available treatments, CVDs are still a leading cause of morbidity and mortality. Current therapies for these conditions primarily target an individual risk factor (e.g., low-density lipoprotein levels [LDLs]). According to its manufacturer, ETC-1002 is a small-molecule, metabolic regulator of imbalances in lipid and carbohydrate metabolism and inflammation. The manufacturer states that the agent is intended to inhibit fatty acid and cholesterol synthesis, as well as enhance fatty acid oxidation. Therefore, it may improve multiple risk factors (potentially addressing the underlying causes of metabolic diseases). It is taken orally, once daily. Esperion Therapeutics, Inc., Plymouth, MI Phase II trial completed	Pharmacotherapy (e.g., statins)	Improved LDL profile Reduced incidence of cardio-metabolic disease Increased overall survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mitochondrial pore modulator (TRO-40303) to prevent reperfusion injury after heart attack	Patients receiving cardiac reperfusion after heart attack or coronary bypass surgery	Experimental studies show that reperfusion injury accounts for as much as 50% of the final size of a myocardial infarct in patients having a heart attack; protecting the heart during reperfusion of ischemic areas is therefore, important; as oxygen is reintroduced into an ischemic area after heart attack or heart bypass surgery, oxygen free radicals are generated, resulting in cellular damage in the form of swelling and/or contracture; this leads to what is termed a “no-reflow phenomenon”; this effect limits recovery of some heart cells and is believed to contribute to irreversible injury of other heart cells. TRO-40303 targets mitochondria to protect cells from apoptosis; intended to prevent reperfusion injury that occurs in virtually all patients when ischemic tissue in the heart is reperfused after a heart attack or coronary artery bypass surgery. It is administered intravenously. Trophos S.A., Marseille, France Phase II ongoing	Angioplasty and stenting Fibrinolytic therapy	Reduced myocardial cell death Improved cardiovascular function Increased survival
Mitochondrial-targeted compound (Bendavia) for treatment of ischemia reperfusion injury	Patients experiencing ischemia reperfusion injury during reperfusion post-myocardial infarction and coronary bypass surgery	As oxygen is reintroduced into an ischemic area after heart attack or heart bypass surgery, oxygen free radicals are created, resulting in cellular damage in the form of swelling and/or contracture. This leads to what is termed a "no-reflow phenomenon.” This effect limits recovery of some heart cells and is believed to contribute to irreversible injury of other heart cells. Bendavia™ is a compound that targets mitochondria to protect cells from undergoing cellular death. It is intended to prevent reperfusion injury that occurs in virtually all patients as ischemic tissue in the heart is being reperfused after a heart attack or coronary artery bypass surgery. Stealth Peptides, Inc., Newton Centre, MA Phase II ongoing	Angioplasty and stenting Fibrinolytic therapy	Improved electron transport efficiency Maintained mitochondrial respiration and adenosine triphosphate levels Prevented mitochondrial swelling and depolarization Reduced apoptosis Improved cardiovascular outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mobile phone electrocardiography (iPhoneECG)	Patients in need of an electrocardiogram (ECG) who have access to a mobile device	Access to ECG machines is limited in some rural or emergency rescue locations; patients are required to visit health care facilities for ECG readings, and "portable" ECG machines still require 12 leads. The iPhoneECG is a slim device in a case that fits over an iPhone (also available as the iCard, which sticks to the back of any mobile device, including iPads) and has low-power electrodes on the case that are pressed against the fingers or chest of a patient to display full ECG and heart rate. Device is intended to record and upload the reading onto a server, which converts it to a PDF for analysis by a medical professional; manufacturer intends device to be used to aid diagnosis of heart blockage or unstable heartbeat, or to monitor heart rate during exercise or stress reduction techniques. The manufacturer claims that the device will work in any location with wireless coverage. AliveCor, Seattle, WA Premarket notification for 510(k) clearance from FDA in progress	Standard ECG machines Portable ECG machines	Increased access to ECG technology Reduced morbidity from heart conditions monitored by ECG Reduced health disparities
MTP inhibitor (lomitapide) for treatment of homozygous familial hypercholesterolemia	Patients in whom homozygous familial hyper-cholesterolemia (HoFH) has been diagnosed	Outcomes with current medication 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. Taken orally. Aegerion Pharmaceuticals, Inc., Cambridge, MA FDA granted orphan drug status; Oct 2012 FDA advisory panel voted 13-2 in favor of approving; final FDA decision scheduled for Dec 29, 2012	Extracorporeal apheresis Liver transplant Pharmacotherapy (e.g,. statins)	Reduced low-density lipoprotein levels Improved cardiovascular outcomes Improved quality of life Improved long-term health outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Myosin activator (omecamtiv mecarbil) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	Currently available ionotropic pharmacotherapy for HF increases contractility without prolonging systole, which increases oxygen demand, thereby exacerbating myocardial ischemia and the risk of adverse events. Omecamtiv mecarbil is a myosin activator intended to prolong systole in the heart. The manufacturer claims the agent can increase the duration of systole without changing the rate of left ventricular pressure development, thereby increasing stroke volume and cardiac output. The agent is being developed as both oral and intravenous formulations, for use as both inpatient and outpatient therapy. Cytokinetics, Inc., South San Francisco, CA Phase II trials ongoing	Pharmacotherapy (e.g., beta blockers)	Prolonged systole Improved heart efficiency Reduced adverse events Improved quality of life Reduced morbidity and mortality
Nitroxyl donor (CXL-1020) for treatment of acute decompensated heart failure	Patients in whom acute decompensated heart failure (HF) has been diagnosed	CXL-1020 is a proprietary nitroxyl donor intended to enhance heart contractility (inotropy) and relaxation (lusitropy) and peripheral vasodilation without increasing heart rate or myocardial oxygen consumption. Administered intravenously. Cardioxyl Pharmaceuticals, Inc., Chapel Hill, NC Phase II completed.	Diuresis (for fluid removal) Vasodilation (for preload and afterload reduction) Other intravenous inotropic agents (dobutamine, milrinone)	Improved symptoms, hemodynamics, and clinical status of patients with acute decompensated HF
Off-label minocycline with tPA for treatment of stroke	Patients in whom acute ischemic stroke has been diagnosed	Minocycline, a tetracycline antibiotic, is given with tissue plasminogen activator (tPA) to reduce stroke-associated inflammatory factors and bleeding. Georgia Health Sciences University, Augusta Phase I/II trial completed	tPA alone	Reduced bleeding in stroke Improved overall outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label sildenafil (Viagra) to improve pediatric exercise tolerance after Fontan surgery for heart defect	Pediatric patients with exercise intolerance after undergoing Fontan operation to correct heart defect	No medical therapies have demonstrated a benefit in improving exercise tolerance in patients who have undergone a Fontan operation. The Fontan procedure is a palliative surgery for patients who have a single pumping ventricle; a staged reconstruction of the heart and the major blood vessels whereby the veins that usually bring blood back to the heart are connected directly to the pulmonary arteries; this creates a “new” circulatory system, in which blood from the body bypasses the heart and flows directly to the lungs; importantly, blood flow through the lungs is passive (not pumped) and the efficiency of flow through the cardiovascular system is related to the resistance to blood flow in the vessels of the lungs, or pulmonary vascular resistance (PVR). Sildenafil (Viagra®) is a phosphodiesterase type 5 inhibitor that has potent selective vasodilatory effects on pulmonary vasculature; may decrease PVR, resulting in increased pulmonary blood flow. It does not appear that company that makes this drug is seeking a labeled indication change. Pfizer, Inc., New York, NY (manufacturer) Pennsylvania State University, Pennsylvania State Hershey Medical Center, Hershey (investigator) Phase IV trial ongoing; in Aug 2012, FDA recommended against off-label sildenafil for the pediatric population due to high risk of death with high doses and no improved exercise tolerance with low doses.	Exercise training	Improved PVR Improved pulmonary blood flow Improved cardiac filling Increased stroke volume Improved cardiac output response to exercise Increased exercise tolerance Increased time to transplant Improved quality of life
Oxygenated pegylated hemoglobin (MP4OX) for treatment of hemorrhagic shock	Patients in whom trauma-related oxygen deprivation (hemorrhagic shock) has been diagnosed	Standard of care for hemorrhagic shock is limited because treatments do not reach capillaries or ischemic tissues; many patients treated with optimal care for traumatic injuries still experience organ dysfunction and failure; treatments are needed to improve the perfusion and oxygenation capabilities of standard of care. MP4OX is oxygenated, pegylated hemoglobin that is intended to prevent the premature release of oxygen in the vascular system and to open capillary beds for perfusion and targeted oxygen delivery; it is designed to be at a certain optimal oxygen affinity, diffusion potential, and molecular size so it has the potential to perfuse capillaries and delivery oxygen to tissues at risk of ischemia; intended for use as an adjunctive treatment to standard of care (transfused blood or packed red blood cells). Sangart, Inc., San Diego, CA; MP40X’s development is part of a Dec 2010 cooperative research and development agreement (CRADA) with the U.S. Navy Phase IIb trial ongoing	Fluid replacement alone	Improved perfusion of capillaries and oxygenation of ischemic tissues Resolution of hemorrhagic shock Reduced rate of organ failure Improved survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
PAR-1 antagonist (atopaxar) for prevention of atherothrombosis	Patients in whom a risk of atherothrombosis has been diagnosed	Current standard of care, DAPT, for reducing ischemic events in patients with atherothrombotic disease is associated with limitations, including the risk of bleeding and the possibility of recurrent thrombotic events. These agents do not modulate thrombin, a potent receptor for platelet activation. Atopaxar (E555) represents a new mechanism of action for this disease state and is a protease-activated receptor 1 (PAR-1) antagonist. Thrombin mediates its effects through PAR-1 on the platelet surface, so inhibition of PAR-1 may represent a viable approach for reducing platelet activation, without causing prolongation of bleeding time (because other thrombin-mediated effects associated with hemostasis are not affected). Administered orally, once daily. Eisai, Inc., Tokyo, Japan Phase II trials completed	Aspirin Clopidogrel	Reduced platelet aggregation Fewer ischemic events Improved bleeding rates Reduced mortality
PCSK9 inhibitor (REGN727/ SAR236553) for treatment of hypercholesterol-emia	Patients in whom hypercholesterol-emia has been diagnosed	This drug represents a new mechanism of action for hypercholesterolemia treatment. REGN727/SAR236553 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. Intended to be administered subcutaneously. Sanofi, Paris, France Regeneron Pharmaceuticals, Inc., Tarrytown, NY Phase III trial ongoing	Pharmacotherapy (e.g., statins)	Improved lipid levels Reduced morbidity Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pediatric ventricular assist device (Excor) for pediatric end-stage heart failure	Pediatric patients in whom heart failure (HF) has been diagnosed, and 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. Berlin Heart GmbH, Berlin, Germany FDA approved Dec 2011; designated an orphan product	ECMO	Increased recovery of native heart (when used as destination therapy) Increased overall survival Reduced adverse events compared with ECMO
PerClot blood-clotting agent for perioperative and postoperative hemostasis	Surgical patients at risk of perioperative and postoperative hemorrhage	Hemostatic agent (PerClot®) in form of absorbable powder used adjunctively when control of bleeding from capillary, venous, or arteriolar vessels by pressure, ligature, and other conventional means is either ineffective or impractical. Cryolife, Inc., Atlanta, GA Company filed investigational device exemption application with FDA in Apr 2011 to begin U.S. trials ongoing; has marketing approval in Europe	Conventional hemostatic techniques (e.g., fibrin sealants, mechanical hemostasis) used during surgery	Adequate, timely hemostasis

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Percutaneous annuloplasty (Carillon Mitral Contour System) for functional mitral valve repair	Patients in whom functional mitral regurgitation has been diagnosed	Percutaneous annuloplasty for functional mitral valve repair is a surgical approach intended to achieve the therapeutic result of open surgical annuloplasty through a less-invasive, catheter-based technique. The Carillon® Mitral Contour System™ comprises a thin, flexible metal bridge or tether with a self-expanding anchor at each end. The device is delivered to the coronary sinus by a catheter inserted in the jugular vein at the neck. This tension around the mitral valve annulus is intended to squeeze the mitral leaflets together to close the gap that may have developed due to heart enlargement. Typically, the entire catheter is removed if the placement of nitinol tension rods does not reduce mitral regurgitation. Cardiac Dimensions, Inc., Kirkland, WA Several trials ongoing, FDA granted investigational device exemption status for clinical trial in 2005; trial ongoing, but not registered with National Clinical Trials database. Approved for marketing in Europe in 2009	Optimal medical management Minimally invasive surgery Open surgery	Reduced risk of cardiac events Reduced mitral regurgitation Reduced operative morbidity Reduced mortality Improved quality of life
Percutaneous left atrial appendage occlusion (Watchman) for prevention of atrial fibrillation-associated stroke	Patients with atrial fibrillation who are not good surgical candidates	Intended to block left atrial appendage opening and prevent clots from entering general circulation. Atritech, Inc., Plymouth, MN, acquired by Boston Scientific Corp., Natick, MA Phase III trial ongoing	Long-term anticoagulation therapy	Reduction in stroke risk
Phospholipase A2 inhibitor (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 that is being investigated as a treatment for 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. GlaxoSmithKline, Middlesex, UK Phase III trials ongoing	Pharmacotherapy (e.g., statins)	Improved plaque stability Reduced atherosclerosis Reduced morbidity and mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pipeline Embolization Device for treatment of brain aneurysms	Patients in whom giant or wide-necked brain aneurysms, in the internal carotid artery from the petrous to the superior hypophyseal segments, have been diagnosed	Pipeline™ Embolization Device is a self-expanding, microcatheter-delivered, cylindrical mesh "flow diversion" device intended to divert blood flow away from the aneurysm sac and assist in reconstruction of the parent artery while leaving the side vessels open. Approved for the "endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments." ev3 Neurovascular, Menlo Park, CA FDA approved Apr 2011; continued followup for 5 years of individuals in the pivotal clinical cohort and continued access cohort required	Endovascular coiling Stent-assisted coiling Surgical clipping or bypass	Prevented rupture of brain aneurysms Reduced mortality form aneurysm
Placenta-derived cell therapy (PLX-PAD) for critical limb ischemia	Patients with critical limb ischemia (CLI) including pain at rest and tissue necrosis, Fontaine class III–IV	Treatment is needed for patients with CLI whose CLI is not responding to medical or surgical interventions; these patients are at risk of amputation. Placenta-derived cell therapy (PLX-PAD) for peripheral artery disease consists of mesenchymal-like stromal cells derived from a full-term placenta; PLX-PAD cells originate from the human placenta harvested after a caesarean section and cultured in a bioreactor (PluriX™). Delivered by intramuscular injection to a patient's limb with the intent to improve blood flow. Pluristem Therapeutics, Inc., Haifa, Israel Phase I trial completed; phase II/III trial planned	Pharmacotherapy (e.g., cilostazol and pentoxifylline) Percutaneous angioplasty and stenting Surgery	Less pain Increased amputation-free survival rate (amputations and death) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 associated with 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 currently available options because they (conventional tourniquets, knee pressing, clamps) 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. Compression Works, LLC., Birmingham, AL (manufacturer) Speer Operational Technologies, LLC, Greenville, SC (distributor) FDA granted 510(k) clearance Oct 2011, after expedited review	Clamps Conventional tourniquet Knee pressing	Improved bleeding control Reduced morbidity Reduced mortality
Point-of-care autologous bone marrow for treatment of critical limb ischemia	Patients with critical limb ischemia (CLI) who are not eligible for revascularization surgery	Treatment is needed for patients with CLI whose disease is not responding to medical or surgical interventions; these patients are at risk of amputation. The Magellan ® MAR01™ system enables the production of a concentrate of aspirated bone marrow at the patient's bedside that yields an injectable tissue rich in platelets, hematopoietic stem cells, and mesenchymal stem cells (key cells in tissue repair); intervention will evaluate administration of concentrated bone marrow injections (using the 510[k] cleared Magellan MAR01 technology) at the bedside; injected concentrate intended to improve perfusion in ischemic tissue in affected limbs of patients with CLI who are not candidates for revascularization surgery. Arteriocyte, Inc., Cleveland, OH Phase I trial ongoing under investigational device exemption status	Percutaneous angioplasty and stenting Pharmacotherapy (e.g., cilostazol and pentoxifylline) Surgery	Increased amputation-free survival rate (amputations and death) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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. The increase is thought to be 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 because it is associated 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 following 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. Spartan Bioscience, Inc., Ottawa, Ontario, Canada Phase II/III trial complete; received Conformité Européene (CE) mark in Europe; intending to file for FDA 510(k) clearance	No genetic testing Genetic testing performed in a clinical laboratory	Decreased cardiovascular death Decreased stent thrombosis Decreased nonfatal myocardial infarction Decreased high reactivity on DAP
Polymer strands (cPAX system) for treatment of giant and wide-neck cerebral aneurysms	Patients 22 years of age or older with a wide-necked large and giant sized cerebral aneurysm 10 mm or larger that requires use of adjunctive assist-devices such as stents or balloons	Large, giant and wide-neck cerebral aneurysm remain the most difficult to treat, and conventional platinum coils have been suboptimal. CPAX is polymeric strand delivered into the aneurysm using a technique similar to currently available platinum coil technologies (endovascular embolization); the difference is that cPAX is a soft polymeric material designed to achieve more complete filling of the giant or wide-neck aneurysm than is possible with currently available platinum coils; translucency of its polymeric material allows for noninvasive computed tomography and MRI scans with little or no artifact for more accurate patient assessment and followup. NeuroVasx, Inc., Maple Grove, MN FDA approved under humanitarian device exemption in Apr 2011	Endovascular embolization-detachable coils (spirals of platinum wire) Microvascular clipping (clothespin-like clip on the aneurysm's neck) Occlusion of artery that leads to the aneurysm	Decreased incidence of ruptured aneurysm (about 27,000 individuals per year in the U.S.) Reduced incidence of hemorrhagic stroke, vasospasm (the leading cause of disability or death following a burst aneurysm) Short-term and/or permanent brain damage Decreased mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Positron emission tomography imaging agent (11C-metomidate) for diagnosis of hyperaldosteronism	Patients with diagnosed hypertension that may be secondary to hyperaldosteron-ism	Up to 9% of patients with hypertension have a condition called hyperaldosteronism (Conn's syndrome). In these patients, adenomas on the adrenal glands release excessive amounts of aldosterone, a hormone that is known to raise blood pressure. The gold standard for diagnosing hyperaldosteronism is an invasive and technically challenging procedure called adrenal vein sampling. 11C metomidate is a radiopharmaceutical intended for use with positron emission tomography (PET) as a noninvasive option to diagnose this condition. Because 11C-metomidate has been shown to accumulate in Conn's adenomas and nowhere else, researchers think it can be used with PET imaging to help identify patients with hyperaldosteronism adenomas. This radiopharmaceutical is used with PET imaging in the U.S. to aid diagnosis of adrenal tumors. University of Cambridge, Cambridge, UK Pilot trial completed	Adrenal vein sampling	Improved hyperaldosteronism diagnosis Improved management of hyperaldosteronism-associated hypertension Decreased morbidity
Potassium binder (RLY5016) for prevention of hyperkalemia	Patients in whom heart failure (HF) or HF with underlying renal impairment has been diagnosed	Renin-angiotensin-aldosterone-system-inhibitor drugs cannot be used in HF patients and renal impairment because of concerns about hyperkalemia; an effective drug therapy would allow better management of patients with HF; current agents are poorly tolerated and cause bowel necrosis. RLY5016 is a novel potassium binder (orally absorbed resin; high capacity cation binder) that is intended to lower serum potassium, thereby preventing hyperkalemia in patients with HF or HF and renal impairment; appears to be better tolerated and potentially has twice the potassium-binding capacity compared with current agents. Relypsa, Santa Clara, CA Phase II trial completed	Other potassium binders (e.g., sodium polystyrene sulfonate)	Improved side effect profile Decreased incidence of hyperkalemia Optimal medical management of HF Improved long-term cardiac outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Recombinant neuregulin-1 (Neucardin) for treatment of chronic heart failure	Patients in whom heart failure (HF) has been diagnosed	No disease-modifying treatments for HF exist; only the symptoms are treated. Neucardin™ (rhNRG-1) represents a potential disease-modifying approach to treatment; it is a recombinant peptide fragment of human neuregulin-1 (NRG-1); NRG1 is a tyrosine kinase receptor agonist (member of the endothelial growth factor [EGF] family) and is known to activate multiple intracellular signaling pathways in cardiomyocytes, including mitogen-activated protein kinase pathway (associated with protein synthesis and muscle hypertrophy) and PI3K-Akt-mTOR (mammalian target of rapamycin) pathway (associated with prosurvival effects and activation of cellular metabolism); the NRG signaling cascade is challenged by stress factors and has limited ability to compensate for myocardial cell loss, so rhNRG-1 is intended to aid in development, differentiation, and function of myocardial cells. Zensun (Shanghai) Sci & Tech Co., Ltd., Shanghai, China Phase III terminated; Zensun to replace with another study design; phase II trial ongoing	Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics)	Increased cell survival Improved cell metabolism Increased cell proliferation Improved symptoms Improved morbidity and decreased mortality
Robotic system (CorPath 200) for remotely controlled percutaneous coronary intervention	Patients undergoing percutaneous coronary intervention (PCI)	PCI, as it is currently performed, is associated with procedural challenges, radiation exposure, and spinal strain for interventional cardiologists. CorPath™ 200 is a console or cockpit with radiation shielding placed several feet from patient that allows the physician to use robotic-assisted tools to place coronary guidewire and stent/balloon catheters. The physician does not have to wear a lead shield apron during PCI; system is intended to fixate and hold devices to enable the cardiologist (while seated) to control contrast injection and manipulate the guidewire; intended to enhance visualization, minimize fatigue, and protect against exposure to radiation and back strain. According to manufacturer, improved control of contrast injection and visualization of angiography may also reduce the volume of contrast media and radiation dose administered to the patient. Corindus Vascular Robotics, Inc., Natick, MA Phase II completed; company received FDA 510(k) marketing clearance Jul 2012	Manually performed PCI	Improved procedural visualization Reduced radiation exposure Reduced physician spinal strain Reduced physician fatigue Increased number of PCI procedures performed Improved patient safety

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
School-wide electrocardiogram screening (Young Hearts for Life) for cardiac abnormalities in students	Students in high school or college, who may or may not participate in organized sports	More than 1,000 young adults die from sudden cardiac death annually in the U.S. The Young Hearts for Life Cardiac Screening Program is intended to provide free electrocardiograms (ECGs) to all high school students (who choose to participate) to identify students at risk of sudden cardiac death; screenings are conducted during the school day, usually during physical education classes, and echocardiograms are available on site at no cost for selected students who have an inconclusive screening ECG (intended to give additional information regarding whether further evaluation is necessary); ECGs are interpreted by volunteer cardiologists; parents receive test results about 3 weeks after the screening and are instructed to follow up with primary care physician if necessary. Midwest Heart Foundation, Lombard, IL As of Oct 2012, screenings had been provided to more than 74,000 students.	American Heart Association-recommended screening that includes physical examination and family and personal medical history	Increased detection of potential cardiac abnormalities Earlier diagnosis of abnormalities Reduced incidence of sudden cardiac death Increased costs from screening general student population who would otherwise not be screened by ECG
Selective serotonin-4 antagonist (RO1160367, SER101) for treatment of heart failure	Patients in whom heart failure has been diagnosed	SER101 is a 5-HT4 (serotonin) antagonist; 5-HT4 receptors have been discovered on muscle cells in failing cardiac ventricles and failing cardiac ventricle expresses 5-HT4 receptors as a response to the serious condition. Serodus ASA, Oslo, Norway (licensee) F. Hoffmann-La Roche, Basel, Switzerland (developer) Phase I trial completed	Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics)	Increased cardiac output Improved cardioprotection Improved long-term cardiac outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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, and primary percutaneous coronary intervention (PCI) within 90 minutes, of symptom onset, 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: 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). 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: 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: leaving patient on the original stretcher and creating system-compatible intravenous (IV) tubing and pumps, and/or eliminating the need for IV pumps (e.g., through administration of IV bolus of unfractionated heparin). Sponsored by North Carolina Chapter of the American College of Cardiology Pilot study with 436 patients at 55 hospitals completed; data available	Current STEMI practices (vary between hospitals)	Reduced door-in-to-door-out time Reduced time to treatment Improved cardiovascular morbidity Improved mortality outcomes
Stromal cell–derived factor-1 (JVS-100) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	About 5.4 million Americans have HF, and because of the lack of regenerative treatments, the vast majority of patients will die within 8 years of 1st diagnosis. JVS-100 (also called ACRX-100) is an agent that encodes stromal-cell derived factor 1 (SDF-1); SDF-1 recruits endothelial progenitor cells to site of injury or ischemia, thereby potentially inducing neovascularization and angiogenesis (sustained vessel formation necessary for adult tissue to become fully revascularized, particularly after ischemia). Natural SDF-1 expression lasts for less than a week, so natural stem cell homing signals fade quickly. In clinical trial, agent is being injected directly into the myocardium as a single dose at multiple sites through a percutaneous, left ventricular approach using a needle injection catheter. Juventas Therapeutics, Inc., Cleveland, OH Phase II trial ongoing	Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics)	Increased neovascularization and angiogenesis Reduced symptom burden Disease regression or slowed disease progression

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy	Patients with cardiomyopathy who are at risk of sudden cardiac arrest	This subcutaneous implantable cardioverter defibrillator's (S-ICD®) wires do not connect to the heart and reduce risk of wires bending and causing unnecessary shocks; no imaging equipment required for placement. Cameron Health, Inc., San Clemente, CA (Boston Scientific Corp., Natick, MA, announced in Mar 2012 it was exercising its option to acquire Cameron Health) Premarket approval application submitted to FDA Jan 2012; FDA granted expedited review status; Conformité Européene (CE) marked in 2009. FDA approved Sept 2012 to provide defibrillation therapy for treating 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 anti-tachycardia pacing	Other implantable defibrillators	Quicker recovery after implantation Reduced risk of unnecessary shocks Reduced risk of failures to shock Improved quality of life
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/or 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. Medtronic, Inc., Minneapolis, MN Two pivotal U.S. trials begun in 2011 under FDA investigational device exemption status; late-phase and postmarket international trials completed; Conformité Européene (CE) marked in 2007; available outside U.S. in 34 countries	Open surgery Optimal medical management Other transcatheter aortic valves	Improved cardiac function Increased survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Transcatheter aortic valve implantation (Lotus) for treatment of severe aortic stenosis	Patients with severe, symptomatic aortic stenosis who are unable to undergo open-heart 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/or 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. Transcatheter aortic valves that are available in the U.S. (Sapien) or in development (CoreValve®) for transcatheter aortic valve implantation (TAVI) cannot be repositioned or retrieved after deployment. If these valves are inappropriately placed, unintended events can occur, such as paravalvular regurgitation or coronary artery obstruction. The Lotus™ Aortic Valve System is intended to address these limitations. According to its manufacturer, the valve can be both retrieved and repositioned and is designed to minimize aortic regurgitation. The valve is a bovine tissue trileaflet bioprosthesis with a self-expanding nitinol frame. The company states that the valve is designed to conform to the patient's native valve anatomy, which might minimize valve leakage. Sadra Medical, Inc., subsidiary of Boston Scientific Corp., Natick, MA Phase I trial completed; phase II trial planned to begin in 2012	Other transcatheter aortic valves	Increased survival Reduced surgical complications Reduced paravalvular leakage Improved quality of life
Transcatheter aortic valve (Sapien) implantation for treatment of severe aortic stenosis	Patients with severe calcific aortic stenosis who are considered to be high-risk or non-operable 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/or 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. Edwards Lifesciences, Irvine, CA 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 Jun 2012, FDA’s Circulatory System Devices Panel voted 12-0 to recommend an expanded indication for patients with symptomatic severe aortic stenosis who are at high operative risk.	Optimal medical management Open surgery Other transcatheter aortic valves	Accurate valve replacement Avoided open surgery Decreased rehospitalization for heart failure Decreased mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	Minimally invasive transcatheter approach requires transseptal puncture to access the left heart chambers; in lieu of sutures, a flexible metal clip covered in polyester fabric (MitraClip®), is used. Intended for patients whose valve disease originates mainly from the center of the valve. Evalve, Inc., Menlo Park, CA (being acquired by Abbott Laboratories, Abbott Park, IL) Phase III trial ongoing; Conformité Européene (CE) marked in 2008	Open surgical mitral valve repair Pharmacotherapy	Improved quality of life for patients who are not good surgical candidates Reduction in mitral regurgitation and associated cardiovascular outcomes Decreased cost because of slowing disease progression Decreased cost compared with open surgery
Transcatheter pulmonary valve (Sapien) implantation for treatment of pulmonary valve disease	Pediatric patients in whom a malformed pulmonary valve has been diagnosed	Interventional cardiac catheterization procedure using the Sapien stent valve to replace a defective or worn-out pulmonary valve. Edwards Lifesciences, Irvine, CA Clinical trial ongoing under FDA investigational device exemption status; company intends to seek humanitarian device exemption from FDA	Open heart surgery	Accurate deployment of valve Avoided open surgery Reduced hospital stay Reduced pain Reduced bleeding/transfusion Quicker recovery and return to normal activity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ultrasound (ClotBust-ER) for treatment of acute ischemic stroke	Patients in whom acute ischemic stroke has been diagnosed	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, which are 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. Cerevast Therapeutics, Inc., Redmond, WA Phase I/II trial completed; phase III trial registered, but not yet recruiting	Sonographer-administered ultrasound Tissue plasminogen activator therapy	Improved clot lysis Reduced stroke-related morbidity and mortality
Urocortin 2 for treatment of heart failure	Patients in whom heart failure has been diagnosed	Urocortin 2 (infusion) is intended to mimic the effect of the newly discovered protein urocortin 2, which selectively stimulates the corticotropin-releasing factor receptor, thereby improving cardiac output with minimal increase in heart rate; new mechanism of action for cardioprotection by regulating calcium cycling enzymes/channels in heart muscle cells. Neurocrine Biosciences, Inc., San Diego, CA Trials ongoing (conducted by Centre for Cardiovascular Sciences at The University of Edinburgh, UK, through a British Heart Foundation grant)	Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics)	Increased cardiac output Improved cardioprotection Improved long-term cardiac outcomes
Vagus nerve stimulation (CardioFit) for treatment of congestive 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. BioControl Medical, Yehud, Israel Phase III trial ongoing	Heart transplantation Minimally invasive heart surgery Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics) Ventricular assist devices	Improved left ventricular ejection fraction Improved 6-minute walk test Reduced need for medication Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vasoactive intestinal peptide analog injection (Vasomera) for treatment of hypertension	Patients in whom hypertension has been diagnosed	Many factors contribute to patient nonadherence with hypertension treatment; therefore, hypertension often remains uncontrolled or poorly controlled, contributing to a patient's risk of cardiovascular events. Also, current hypertension medications are associated with undesirable side effects and safety concerns. Vasomera™ is an analog of vasoactive intestinal peptide, a naturally occurring 28-amino-acid peptide that acts as a vasodilatory neuropeptide. This agent is delivered via injection, and the manufacturer purports that its long-acting properties may allow for once-weekly dosing. PhaseBio Pharmaceuticals, Inc., Malvern, PA Phase I trial ongoing	Pharmacotherapy (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers)	Improved control of hypertension Reduced risk of cardiovascular events Reduced morbidity Reduced mortality from hypertension
Wireless cardiac resynchronization therapy (WiCS) for treatment of heart failure	Patients in whom heart failure has been diagnosed	Currently approved cardiac resynchronization therapy (CRT) using pacemakers or defibrillators requires implantation of leads, 1 of which is threaded to the heart's left ventricle in a technically challenging process associated with risk of lead failure and infection. Because of these limitations, many patients who are appropriate candidates for CRT do not receive the therapy. The WiCS® Wireless Cardiac Stimulation device is intended to deliver CRT wirelessly to address some of this risk and also pace the left ventricle in a way that better mimics the natural activation and mechanical contraction pattern of the heart. EBR Systems, Inc., Sunnyvale, CA Cambridge Consultants, Ltd., Cambridge, UK Phase I/II trial ongoing	Biventricular pacing with leads	Improved cardiac pacing Reduced need for reoperation because of lead failure Shortened implantation procedure time Reduced morbidity Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 electronics 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 potentially give clinicians more timely access to changes in symptoms and/or 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. CardioMEMS, Inc., Atlanta, GA 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 has issued no information regarding status since that time	Weight monitoring (for fluid retention) Symptom monitoring	Improved clinician access to changes in patient symptoms Earlier medical intervention Reduced HF-related hospitalizations Improved morbidity and mortality

Table 4. AHRQ Priority Condition: 04 Dementia (including Alzheimer's: 22 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anavex 2-73 for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	Anavex 2-73 acts as a sigma-1 receptor agonist and has muscarinic cholinergic effects and affects modulation of endoplasmic reticulum stress to prevent oxidative stress and apoptosis; intended to alleviate neurotoxicity and cognitive deficits. Anavex Life Sciences Corp., Hoboken, NJ Phase I trial completed; phase IIa trial planned for late 2012	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Delayed memory loss Delayed cognitive decline Longer maintenance of independent living

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti-a-beta monoclonal antibody for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	Currently, no disease-modifying agents for AD are available, although several are in development. Anti-a-beta (also known as MABT5102A) is a humanized monoclonal antibody intended to be used for passive immunotherapy against beta amyloid (a-beta, main constituent of a-beta plaques); it is intended to promote clearance of a-beta protein from damaged sites of the brain; according to the manufacturer, the agent binds both monomeric and oligomeric forms of a-beta, inhibits a-beta aggregation, and promotes a-beta disaggregation. In clinical trials, being administered in both subcutaneous and intravenous formulations. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase II trials ongoing	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Reduced a-beta load in brain Slowed progression of AD Increased survival Improved quality of life
Antiamyloid monoclonal antibody (ponezumab) for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	Current drug therapy for AD has nonspecific antibodies that interact with many other brain processes; a need exists for therapy to reduce toxicity or presence of beta amyloid (a-beta) without creating other side effects. Ponezumab is a human monoclonal antibody intended to promote clearance of a-beta protein from damaged sites of the brain while minimizing adverse effects that may result from less-specific binding (i.e., monoclonal antibody to bind specifically to a-beta, but not to amyloid precursor protein also); it recognizes and binds to the free carboxy terminal amino acids 33–40 of the a-beta 1-40 peptide; also called PF-04360365. Pfizer, Inc., New York, NY Phase II trials completed	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Decreased a-beta 40 load in brain Slowed disease progression Improved cognitive function Improved memory Increased ability to live independently longer Improved quality of life
AZD1446 for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	AZD1446 is a selective modulator of alpha4beta2. Targacept, Inc., Winston-Salem, NC, licensed to AstraZeneca, London, UK Phase II trial completed; additional phase II trial terminated due to poor recruitment according to trial listing Oct 2012; AstraZeneca listed in its 2nd quarter pipeline update Jul 2012; 3rd quarter pipeline update not yet available	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Delayed progression of AD symptoms Delayed need for intensive assistance with activities of daily living Improved quality of life Improved functional capacity

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Beta-amyloid immunotherapy (CAD-106) for Alzheimer's disease	Patients in whom mild to severe Alzheimer's disease (AD) has been diagnosed	No disease-modifying treatments for AD are approved or available. CAD-106 is an active immunization targeting beta amyloid (a-beta), which is thought to contribute to AD progression. CAD-106 is intended to induce a-beta-specific antibodies without stimulating a-beta-reactive T cells. The stimulation effect has been a safety concern with earlier attempts at immunotherapy for this population. In preclinical studies, the vaccine was shown to reduce amyloid burden in the brain. Administered via subcutaneous injection. Novartis International AG, Basel, Switzerland Phase II clinical trials ongoing; filing planned for after 2015	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Reduced a-beta load in brain Regression or slowing of disease progression Reduced morbidity and mortality Improved quality of life
Beta-amyloid monoclonal antibody (RG1450, gantenerumab) for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	No disease-modifying treatments for AD are currently available. 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 amyloid plaques in the brain. The drug purportedly binds to amyloid plaques to clear them by a process called phagocytosis. In clinical trials, gantenerumab is given as an intravenous infusion every 4 weeks up to 7 times. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase II trial ongoing	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Slowed disease progression, or regression Reduced morbidity Improved quality of life
Beta-amyloid monoclonal antibody (solanezumab) for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	Current treatments for AD treat symptoms only and are not effective for many patients. Current treatments also have no effect on disease progression. Solanezumab is a fully humanized anti-beta-amyloid (a-beta) antibody that binds specifically to soluble a-beta and is intended to draw the peptide away from the brain through the blood to promote clearance of a-beta 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. Eli Lilly and Co., Indianapolis, IN Phase III trials completed (EXPEDITION 1 and 2 trials); EXPEDITION-EXT ongoing; Aug 2012 report of top line results indicated drug failed to reach its goals in either of 2 phase III studies, but showed improvement in pooled results; next steps being discussed with FDA	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Decreased a-beta load in brain Slowed or halted disease progression Improved memory and cognition Improved survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Beta-amyloid precursor protein site cleaving enzyme inhibitor (MK-8931) for treatment of Alzheimer's disease	Patient in whom Alzheimer's disease (AD) has been diagnosed	No disease-modifying treatments for AD are approved or available. MK-8931 is an oral beta-amyloid precursor protein site cleaving enzyme (BACE) inhibitor that is being investigated for treating AD. The company states that the drug is intended to inhibit BACE, an enzyme that is known to play a role in the initiation of synthesis of beta amyloid peptide. Because abnormal accumulation of beta amyloid peptide is thought to play a role in AD's progression, the company states, this agent may have the potential to improve outcomes in AD. Merck & Co., Inc., Whitehouse Station, NJ Phase I trial ongoing	Pharmacotherapy that is not disease modifying (e.g., donepezil, galantamine, memantine, rivastigmine)	Reduced amyloid beta load in brain Regressed or slowed disease progression Reduced morbidity and mortality Improved quality of life
Exebryl-1 for treatment of Alzheimer's disease	Patients in whom mild to moderate Alzheimer's disease (AD) has been diagnosed	No disease-modifying treatments for AD are approved or available. Exebryl-1 inhibits beta amyloid (a-beta) protein aggregate formation in the brain and disaggregates amyloid plaques already present; it targets both a-beta and tau protein (specificity toward tau protein aggregates) and is intended to slow AD progression. ProteoTech, Inc., Kirkland, WA Tasly Pharmaceuticals, Inc., Rockville, MD Phase I trial ongoing	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Delayed or halted progression of AD Preservation of cognitive ability and memory
Gamma secretase inhibitor (BMS-708163) for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	Currently, no disease-modifying treatments for AD exist. BMS708163 inhibits cutting of amyloid precursor protein by gamma secretase, which in turn prevents the creation of beta amyloid (a-beta) 42, thought to contribute to the pathophysiology of AD. According to the manufacturer, does not disrupt the Notch signaling pathway. Administered as oral capsules. Bristol-Myers Squibb, New York, NY One phase II trial completed, 1 phase II trial ongoing for different AD stage	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Reduced a-beta load Slowing of disease progression, or regression Improved long-term outcomes Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gamma secretase inhibitor (EVP-0962) for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	No disease-modifying treatments for AD are approved in the U.S. EVP-0962 is a selective gamma secretase modulator with potential disease-modifying capability. Gamma secretase is an enzyme involved in the processing of beta amyloid, which contributes to amyloid plaques in the brain, which are believed by some to have a role in the pathophysiology of AD. According to the manufacturer, it does not affect the Notch signaling pathway and, therefore, may offer a better safety profile than other gamma secretase modulators. EnVivo Pharmaceuticals, Watertown, MA Phase I trial ongoing	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Slowed disease progression, or regression Improved long-term outcomes Improved quality of life
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 means are available to definitively diagnose AD (prior to autopsy), and a significant gap exists between AD onset and the point at which treatment begins. An unmet need exists for diagnostic/screening tools that can detect the condition before significant loss of memory, cognition, and activities of daily living occur. 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 into central data bank, which analyzes data and classifies the patient's brainwaves based on similarities to known neurologic risk profiles. Neuronetrix, Inc., Louisville, KY Trial ongoing (no phase listed)	Cerebrospinal fluid tests Neuropsychological test battery Positron emission tomography scans	Improved ability to diagnose, rule out, and/or screen for AD Earlier intervention Improved outcomes Improved quality of life
Insulin sensitizer (MSDC-0160) for treatment of Alzheimer's disease	Patients in whom mild Alzheimer's disease (AD) has been diagnosed	No disease-modifying treatments for AD are approved or available.MSDC-0160 is a novel insulin sensitizer that modulates mitochondrial metabolism. Research has suggested that that loss of mitochondrial function and decline in brain glucose metabolism may contribute to the pathology of AD. Intended to be administered orally, 150 mg/daily. Metabolic Solutions Development Co., LLC, Kalamazoo, MI Phase II trial completed; the manufacturer received a $773,000 grant from the Alzheimer's Drug Discovery Foundation to conduct a pilot phase IIa trial for this indication: Phase IIa trial registered and currently recruiting participants.	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Delay or halt in progression of AD Improved long-term outcomes Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Intravenous Immunoglobulin for treatment of Alzheimer's disease	Patients in whom mild to moderate AD has been diagnosed	No effective treatments for slowing the progression of AD are available. Intravenous immunoglobulin (IVIG) infusion is approved for treating many immune disorders; in patients with AD, IVIG is intended to clear beta amyloid (a-beta) from the brain, thereby blocking a-beta's detrimental effects on the brain. Dosing is still being determined, but will be administered as an infusion, every 2 or 4 weeks, depending on physician recommendation. Baxter International, Inc., Deerfield, IL Phase III trial ongoing	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Reduced a-beta load in brain Halted or slowed disease progression Improved quality of life
Nicotine patch 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 medications are approved for MCI, and treatments approved for AD are not encouraged in this population. Nicotine replacement therapy has been shown to improve outcomes in patients with AD, and now researchers are looking at it to improve outcomes in patients with MCI. The rationale for using this treatment in this population is that patients with AD have a reduced number of nicotinic receptors. University of Vermont, Burlington Trial completed	No approved medications	Improved cognitive performance Improved clinical status Delayed progression to AD Reduced morbidity Reduced mortality
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 medications are approved for MCI. Atomoxetine (Strattera®) is an oral 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 does not appear that Strattera's manufacturer is seeking a labeled indication change. Eli Lilly and Co., Indianapolis, IN (manufacturer) Emory University, Atlanta, GA, with the National Institute on Aging, Bethesda, MD (investigators) Phase II trial ongoing	No approved medications	Improved cognitive performance Delayed progression to AD Reduced morbidity

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label bexarotene (Targretin) for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	No disease-modifying treatments for AD are approved or available. Bexarotene is a retinoid X receptor agonist that is approved for treating cutaneous T-cell lymphoma, under the brand name Targretin®. The drug acts to induce, via transcription, apolipoprotein E (Apo-E) expression. Apo-E is known to facilitate beta-amyloid (a-beta) clearance from the brain (a-beta is a substance associated with AD). For this off-label use, researchers have administered the drug orally in a murine model of AD. Targretin's manufacturer does not appear to be seeking a labeled indication change. Eisai Co., Ltd., Tokyo, Japan (manufacturer) Case Western Reserve University School of Medicine, Cleveland, OH (investigator) Preclinical trial completed; drug can be prescribed off label in the U.S.	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Reduced a-beta load in brain Regression or slowing of disease progression Reduced morbidity and mortality Improved quality of life
Off-label intranasal insulin for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	No disease-modifying interventions for AD are currently available. 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 (a-beta), and providing neuroprotection for synapses against a-beta. 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 IU or 40 IU total dose, twice daily. It does not appear that the insulin manufacturers are pursuing a labeled indication change. HealthPartners Research Foundation, Minneapolis, MN University of Kansas, Lawrence University of Washington, Seattle Phase II trials ongoing	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Slowed disease progression, or regression Improved memory Improved long-term outcomes Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Positron emission tomography imaging agent (AZD4694) to aid diagnosis of Alzheimer's disease	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. AZD4694 is a fluorine-18 labeled precision radiopharmaceutical candidate intended for use as a contrast agent during PET scans. Because the agent binds to beta amyloid, it may aid clinicians in diagnosing AD. Some researchers believe amyloid plaques in the brain have a role in the pathophysiology of AD. AstraZeneca, London, UK Phase II trial completed; Phase I trial ongoing	Blood tests and other biomarkers Clinical exam and history Other F18 agents (e.g., florbetapir, flutemetamol, Pittsburgh Compound B)	More accurate diagnosis Earlier intervention for care planning Delayed disease progression Improved quality of life
Positron emission tomography imaging agent (florbetapir F18, Amyvid) for detecting beta-amyloid plaques	Patients suspected of having beta amyloid (a-beta) - associated disease	No definitive method exists for diagnosing AD in a living person. Florbetapir F18 (Amyvid™) is a radiopharmaceutical that binds specifically to a-beta and is visualized by positron emission tomography (PET) imaging. Contrast agent would be indicated for visualization of a-beta aggregates; a negative result could help to rule out presence of pathologically relevant levels of a-beta plaques. Avid Radiopharmaceuticals, a subsidiary of Eli Lilly and Co., Indianapolis, IN FDA approved Apr 2012 for detecting beta-amyloid plaques	Blood tests and other biomarkers Clinical exam and history Other F18 agents (e.g., florbetapir, flutemetamol, Pittsburgh Compound B)	Increased sensitivity and specificity of a-beta plaque detection
Positron emission tomography imaging agent (flutemetamol) for detecting beta-amyloid plaques	Patients in whom Alzheimer's disease (AD) is suspected	A positron emission tomography (PET) imaging agent intended to detect normal or raised beta-amyloid plaques in the brain to confirm a diagnosis of AD. General Electric Co., Fairfield, CT (GE Healthcare, Chalfont St. Giles, UK) Phase III trials completed and met primary endpoints; company expects to file new drug application with FDA by end of 2012	Blood tests and other biomarkers Clinical exam and history Other F18 agents (e.g., florbetapir, flutemetamol, Pittsburgh Compound B)	Sensitivity and specificity of PET for diagnosing AD Improved positive and negative predictive values Earlier diagnosis of AD Earlier intervention for management of early AD

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Viral delivery of nerve growth factor (CERE-110) for treatment of Alzheimer's disease	Patients in whom mild to moderate Alzheimer's disease (AD) has been diagnosed	CERE-110 uses a deactivated virus (i.e., one that cannot replicate on its own) to transfer a gene to nerve cells in the brain to make nerve growth factor; nerve growth factor is a protein shown to be neuroprotective in the brain by maintaining nerve cell survival in brain tissue; injected into brain during surgical procedure. Ceregene, Inc., San Diego, CA Phase II trial ongoing	Available pharmacotherapy (e.g., donepezil, galantamine, memantine, rivastigmine)	Reduced cell apoptosis Reduced brain degeneration Preserved cognition Preserved memory Preserved independence Reduced need for caregivers Improved quality of life

Table 5. AHRQ Priority Condition: 05 Depression and Other Mental Health Disorders: 34 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Acupuncture for treatment of posttraumatic stress disorder	Patients in whom posttraumatic stress disorder (PTSD) has been diagnosed	Many patients with PTSD do not adequately respond to available treatments, which include pharmacotherapy (e.g., antidepressants) and psychotherapy; additional efficacious treatments are needed. Acupuncture is a type of Traditional Chinese Medicine in which needles are inserted into specific points along meridians of the body. From a Western medicine perspective, acupuncture's efficacy may be related to its regulatory effects on the nervous system, which increases the activity of biochemicals (such as endorphins and immune system cells) at specific sites in the body, or related to its effect on brain chemistry and the release of neurotransmitters and neurohormones, which affect immune reactions and processes that regulate a person's blood pressure, blood flow, and body temperature. It is being investigated for use in patients with PTSD to reduce anxiety, sleep disruption, and other signs and symptoms. Department of Veterans Affairs Trials completed	Pharmacotherapy	Reduced symptoms Improved quality of life
Bright-light therapy for nonseasonal major depressive disorder	Patients in whom nonseasonal major depressive disorder (MDD) has been diagnosed	Many pharmacologic and psychotherapeutic options are available for major depression, yet fewer than half of patients achieve remission, and antidepressant drugs have undesired side effects for many patients. 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. It would likely be used as an adjunct to other treatments. National Institute of Mental Health, Bethesda, MD Trial completed	Pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, etc.) Psychotherapy	Improved depression rating scale scores Improved sleep patterns Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Citizen soldier peer support outreach program (Buddy-to-Buddy) for returning veterans	Returning veterans in whom mental health or substance abuse conditions have been, or may be, diagnosed	Twenty-five to 40% of citizen soldiers (National Guard, Reserves) develop posttraumatic stress disorder, clinical depression, sleep disturbances, or suicidal thoughts, but when veterans return home, barriers exist to receiving appropriate care, and about half of those needing medical or psychological intervention are not receiving care. The Buddy-to-Buddy is a veteran outreach peer support program; according to the program's developers, returning soldiers are assigned a "Buddy One," who is a veteran who has received training in peer support and systematically makes contact (via telephone) with each of his or her assigned veterans to try to identify those who may benefit from further evaluation or referral; "Buddy Two" volunteers receive more intensive training in motivational interviewing approach, local resources, and they also receive weekly telephone supervision; these Buddies visit armories during drill weekends and are available by telephone to all soldiers. Currently available only to veterans in Michigan, but intending to scale up nationally. Developed by Michigan Army National Guard (MI ARNG); Michigan State University, East Lansing; University of Michigan, Ann Arbor; Buddy One funded by MI ARNG and the National Guard Bureau (NGB); Buddy Two funded by Major League Baseball charities, New York, NY; and McCormick Foundation, Chicago, IL Fully implemented in Michigan; outcomes evaluation is ongoing	Peer support group programs (e.g., Vet-to-Vet)	Increased access for veterans to medical and psychological support resources Improved mental health outcomes Improved substance abuse outcomes Improved quality of life
Cortisol antagonist (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, in tablet form, once daily. Corcept Therapeutics, Menlo Park, CA Phase III trial ongoing; FDA granted fast track status for this indication; FDA approved for a different indication (Cushing's syndrome) in Feb 2012	Antipsychotics in combination with antidepressants Electroconvulsive therapy	Improvement in psychotic symptoms Reduced suicide rate Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Deep brain stimulation of Brodmann's area 25 (Libra System) for treatment of major depressive disorder	Patients in whom treatment-resistant major depressive disorder (MDD) has been diagnosed	Once multiple medications, psychotherapy, and electroconvulsive therapy have failed, no proven treatment options exist for MDD; many patients do not respond to initial therapy. The Libra™ Deep Brain Stimulation System sends mild pulses of current from an implanted device to stimulate the brain. Deep brain stimulation (DBS) leads are surgically placed within a target area in the brain and connected to a neurostimulator that is usually implanted under the skin near the collarbone. For depression, the manufacturer is investigating placement of the leads in Brodmann's area 25 (high concentration of serotonin). St. Jude Medical, Inc., St. Paul, MN Pilot trial completed, pivotal trial ongoing	DBS (with other systems, or in other brain areas) Deep transcranial magnetic stimulation Repetitive transcranial magnetic stimulation Vagus nerve stimulation	Reduced symptom burden Improved quality of life
Deep brain stimulation (Reclaim system) therapy for treatment-resistant depression	Patients in whom treatment-resistant depression has been diagnosed	Neurostimulator (Reclaim system) implanted subcutaneously in chest; intended to deliver controlled electrical stimulation to targeted parts of the brain via thin wire electrodes. Medtronic, Inc., Minneapolis, MN Phase III trial ongoing	DBS (with other systems, or in other brain areas) Deep transcranial magnetic stimulation Repetitive transcranial magnetic stimulation Vagus nerve stimulation	Reduced scores on depression scales Improved quality of life
Deep brain stimulation (thalamic or globus pallidus stimulation) for Tourette's syndrome	Patients in whom Tourette's syndrome (TS) has been diagnosed	About 200,000 people in the U.S. have been diagnosed with TS; however, many people with debilitating cases do not respond to currently available pharmacotherapy. Deep brain stimulation (DBS) involves implanting a battery-operated medical device (neurostimulator) in the brain to deliver electrical stimulation to targeted areas that control movement (e.g., subregions of the globus pallidus internus, centromedian-parafascicular, and ventralis oralis complex of the thalamus). The type of DBS device being used was not indicated. Medtronic, Inc., Minneapolis, MN One U.S. trial completed, several ongoing trials: 1 in U.S.; 2 in Israel, 2 in Europe	Botulinum toxin type A (Botox®) injections Pharmacotherapy (antidepressants, central adrenergic inhibitors, fluphenazine, pimozide, stimulant medications)	Reduced symptom burden Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Dextroamphet-amine prodrug (lisdexamfetamine, Vyvanse) for treatment of binge-eating disorder	Patients in whom binge-eating disorder (BED) has been diagnosed	No pharmacotherapies are approved for treating binge-eating disorder, and off-label pharmacotherapies are associated with limited efficacy, undesirable side effects, and low compliance. Lisdexamfetamine (Vyvanse®) is a prodrug of dextroamphetamine; it is indicated 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. Shire, plc, Dublin, Ireland Phase III trial ongoing	Antiepileptics (off label) Selective norepinephrine reuptake inhibitors (off label) Selective serotonin/ norepinephrine reuptake inhibitors (off label)	Decreased morbidity Fewer binge-eating episodes Improved quality of life
Dimethoxy-benzylidene anabaseine for treatment of schizophrenia	Patients in whom schizophrenia has been diagnosed	Dimethoxybenzylidene anabaseine is an alpha-7 neural nicotinic receptor (NNR) agonist, which is a novel target for schizophrenia because no drugs are currently indicated for treating cognitive symptoms of the disorder; patients with schizophrenia have poor psychosocial/cognitive functioning (e.g., cognitive symptoms), which has been associated with decreased expression of the alpha-7 NNR. Department of Veterans Affairs Phase II trial ongoing	Pharmacotherapy (e.g., atypical antipsychotics)	Improved cognitive function Improved clinical schizophrenia rating scales Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gamma-aminobutyric acid agonist (BL-1020) for treatment of schizophrenia	Patients in whom schizophrenia has been diagnosed	BL-1020 may address cognitive and negative symptoms, an unmet need in this population for which no therapies exist. Negative symptoms may be more common and detrimental on quality of life than positive symptoms and can be difficult to recognize; negative symptoms are an absence of normal responses, including blank stares, monotone and monosyllabic speech, few gestures, and disengagement or disinterest; these often persist in the lives of people with schizophrenia during periods of low (or absent) positive symptoms. BL-1020 has a novel mechanism of action (i.e., 1st in class) as a gamma aminobutyric acid (GABA) ester of perphenazine (Trilafon, typical antipsychotic, no efficacy in negative or cognitive symptoms); it blocks dopamine and serotonin while increasing GABA activity (lowered levels of GABA participate in the pathogenesis of schizophrenia). BioLineRx, Ltd., Jerusalem, Israel Cypress Bioscience, Inc., San Diego, CA Phase II/III trial ongoing	Pharmacotherapy (e.g., atypical antipsychotics)	Improved cognition Decreased negative symptoms Improved social functioning Improved quality of life
Glutamate positive allosteric modulator (ADX71149) for treatment of schizophrenia	Patients in whom schizophrenia has been diagnosed	About 1/3 of patients with schizophrenia do not respond adequately to currently available treatments and almost all currently available pharmacotherapies for schizophrenia cause extrapyramidal side effects (EPSs) to some degree. ADX71149 has a novel mechanism of action as a positive allosteric modulator of glutamate receptor 2 (mGluR2) that is intended to fine-tune glutamate transmission, presumably by increasing the activity of the mGluR2; glutamate (specifically, mGluR2 activation) acts on the N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and is known to play a role in schizophrenia; clinical data suggests EPSs are not associated with this drug, which is being investigated as both a monotherapy and adjunctive treatment. Addex Pharmaceuticals, Geneva, Switzerland Ortho-McNeil-Janssen Pharmaceuticals, Inc., Titusville, NJ Phase IIa trial ongoing	Pharmacotherapy (e.g., atypical antipsychotics)	Decreased positive symptoms of schizophrenia Decreased EPSs Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Glycine reuptake inhibitor (RG1678) for treatment of schizophrenia	Patients with schizophrenia who present with predominantly negative symptoms (e.g., flat affect, unable to experience pleasure, blank gaze)	Most drugs for schizophrenia treat the positive symptoms (e.g., hallucinations) and treatments are needed for the negative symptoms; RG1678 is a 1st-in-class glycine reuptake inhibitor; normalizes glutamate neurotransmission by increasing synaptic levels of glycine, an essential cofactor for N-methyl-D-aspartate receptors (NMDARs), which likely have a role in the pathophysiology of schizophrenia; without it, receptor does not work properly. Chugai Pharmaceutical subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials ongoing; filing anticipated in 2013	Pharmacotherapy (e.g., atypical antipsychotics)	Meaningful reduction in negative symptoms of schizophrenia, as measured by clinical rating scales (e.g., Positive and Negative Syndrome Scale) Improved personal and social functioning
Glycine-site functional partial agonist selective modulator of NMDAR (GLYX-13) for treatment-resistant depression	Patients in whom treatment-resistant depression has been diagnosed	Glycine-site functional partial agonist selective modulator of N-methyl-D-aspartate receptors (NMDAR; GLYX-13) that is an oral medication intended for treatment-resistant depression. Naurex, Inc., Evanston, IL Phase II trials ongoing	Pharmacotherapy (e.g., selective serotonin reuptake inhibitors Psychotherapy	Improved score on standardized depression measures Reduced side effects Improved quality of life
Lisdexamfetamine (Vyvanse) for treatment of negative symptoms in schizophrenia	Patients in whom schizophrenia has been diagnosed	Currently, no therapies exist for the effective treatment of negative symptoms in schizophrenia; they might be more common and detrimental on quality of life even than positive symptoms. Negative symptoms include an absence of normal responses such as blank stares, monotone and monosyllabic speech, few gestures, disengagement or disinterest. Lisdexamfetamine is a prodrug of dextroamphetamine; indicated to treat attention deficit hyperactivity disorder; induces release of dopamine and norepinephrine, which contribute to maintaining alertness, focus, thought, effort, and motivation. Shire Pharmaceuticals, plc, Dublin, Ireland Phase II trial completed	Pharmacotherapy (e.g., atypical antipsychotics)	Reduced negative symptoms Improved social functioning Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lisdexamfetamine (Vyvanse) for treatment-resistant major depressive disorder and bipolar depression	Patients in whom treatment-resistant major depressive disorder has been diagnosed	Lisdexamfetamine (Vyvanse®) is a prodrug of dextroamphetamine; currently indicated to treat attention-deficit/hyperactivity disorder; induces release of neurotransmitters dopamine and norepinephrine, which are known to contribute to maintaining alertness, focus, thought, effort, and motivation. Shire Pharmaceuticals, plc, Dublin, Ireland Phase III trials ongoing	Pharmacotherapy (e.g., selective serotonin reuptake inhibitors) Psychotherapy	Improved symptoms on major depression scales Improved quality of life
Mobile phone psychotherapy applications as alternative care-delivery model for mental health conditions	Patients in whom mental health conditions (e.g., major depressive disorder, anxiety) have been diagnosed	Psychotherapy traditionally involves in-person meetings between a therapist and patient or client. This method has limitations, including 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, some researchers have created mobile phone applications ("apps") that purport to provide some psychotherapeutic benefit to patients even if they don't attend traditional therapy. These apps range in their capabilities and intended benefits. For example, the Mobilyze app is designed to use data from sensors already embedded in the phone (e.g., GPS, Bluetooth, Wi-Fi, accelerometers) to identify patient states, without requiring patient self-reporting. This automated system for detecting mood-related states is intended to address nonadherence and other treatment difficulties as they occur in real time. For example, if the app detects that an individual is becoming isolated, it will recommend that he or she calls a friend. Another app is intended to decrease social anxiety and excessive worrying by reducing the tendency of anxious people to focus on threatening items around them. The app purports to train people to divert attention away from negative stimuli that appear on the screen. Various research institutions, including Northwestern University, Evanston, IL, and McNally Laboratory at Harvard University, Cambridge, MA Clinical trials ongoing	In-person psychotherapy Internet-delivered (nonmobile phone) psychotherapy	Improved performance on mental health rating scales Reduced morbidity Reduced mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multimodal antidepressant (Lu AA21004) for treatment of major depressive disorder	Patients in whom major depressive disorder (MDD) has been diagnosed	Patients in whom MDD has been diagnosed have high rates of inadequate response to currently available medications, and available pharmacotherapies are associated with undesirable side effects, including sexual dysfunction. Lu AA21004 is a 5-HT3 and 5-HT7 receptor antagonist, 5-HT1A receptor agonist, 5-HT1B 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 currently available products. Planned oral dosages include 10, 15, and 20 mg. Takeda Pharmaceutical Co., Ltd., Osaka, Japan, jointly with H. Lundbeck a/s, Valby, Denmark Phase III trials completed	Pharmacotherapy (e.g., selective serotonin reuptake inhibitors) Psychotherapy	Improved scores on validated depression instruments Reduced side effects including sexual dysfunction Improved quality of life
Nicotinic alpha-7 agonist (EVP-6124) for treatment of cognitive symptoms of schizophrenia	Patients in whom schizophrenia has been diagnosed	No effective agents are available to treat the cognitive symptoms of schizophrenia. EVP-6124 is a selective, potent, oral 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 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. EnVivo Pharmaceuticals, Watertown, MA Phase II trial completed; phase III trials planned for 2012	Pharmacotherapy (e.g., atypical antipsychotics)	Improved cognitive symptoms Improved social functioning Improved quality of life
Nicotinic receptor (TC-5619) agonist for treatment of schizophrenia	Patients in whom schizophrenia has been diagnosed	No therapies exist to treat the cognitive symptoms of schizophrenia. TC-5619 is an alpha-7 neural nicotinic receptor (NNR) partial agonist and novel target for schizophrenia; patients with schizophrenia have poor psychosocial/cognitive functioning (e.g., cognitive symptoms), which has been associated with decreased expression of the alpha-7 NNR. Targacept, Winston-Salem, NC Phase II trial completed, additional phase II trial ongoing	Pharmacotherapy (e.g., atypical antipsychotics)	Improved cognitive symptoms Improved social functioning Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label armodafinil (Nuvigil) for treatment of binge-eating disorder	Patients in whom binge-eating disorder has been diagnosed	No pharmacotherapies are approved by FDA for binge-eating disorder, and currently used off-label pharmacotherapies are associated with limited efficacy, undesirable side effects, and low adherence. 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 the relationship between narcolepsy and obesity, so researchers are investigating the off-label use of armodafinil in patients with binge-eating disorder. In a clinical trial, the drug is being dosed in oral form, at a variable dosage of 150–250 mg/day. Cephalon, Inc., acquired by Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, in Oct 2011 (manufacturer) Lindner Center of Hope, Mason, OH (investigator) Phase III trial ongoing	Off-label pharmacotherapy (e.g., antiepileptics, selective norepinephrine reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors)	Improved symptoms of binge eating Decreased morbidity and mortality
Off-label ketamine for treatment-resistant severe depression	Patients in whom treatment-resistant major depressive disorder or bipolar depression has been diagnosed	Oral N-methyl-D-aspartate (NMDA; ketamine, a recreational drug) for rapid (within 40 minutes) relief of severe treatment-resistant depression. National Institutes of Health, Bethesda, MD Phase II trial ongoing	Pharmacotherapy (e.g., selective serotonin reuptake inhibitors) Psychotherapy	Rapid response Improved treatment adherence Reduced symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label mifepristone (Mifeprex) for treatment of anxiety-associated cognitive impairment	Patients in whom cognitive impairment, secondary to anxiety, has been diagnosed	Cognitive impairment associated with anxiety can lead to disability, reduced treatment response, and dementia. No treatments are approved for treating cognitive impairment. Although cholinesterase inhibitors are sometimes prescribed when the main symptom is memory loss, they are not recommended for routine use because they do not provide lasting benefit, and currently used antianxiety medications do not improve cognitive impairment. Mifepristone blocks the effects of elevated cortisol levels on glucocorticoid receptors in the brain. Because elevated cortisol and glucocorticoid levels have been associated with cognitive impairment, this may improve cognitive function. For this indication, the drug is dosed orally, 300 mg per day, for 28 days. Mifepristone is approved by FDA for use in ending early pregnancy and is marketed under the brand name Mifeprex® (Danco Laboratories, New York, NY); the manufacturer does not appear to be seeking a labeling change for this indication. Washington University School of Medicine, St. Louis, MO Phase I/II trial ongoing	Pharmacotherapy (e.g., cholinesterase inhibitors)	Improved memory and executive function Improved morbidity (dementia, disability) Improved quality of life
Off-label oxytocin for treatment of social cognition deficits associated with schizophrenia	Patients in whom schizophrenia has been diagnosed	Currently, no pharmacotherapies exist for treating social cognition deficits in patients with schizophrenia. Psychotherapeutic interventions are limited by suboptimal efficacy and availability. Release of oxytocin is associated with bonding, empathy, and trust. Given oxytocin's importance in social behavior, researchers purport it may have utility in improving social cognition deficits in patients with schizophrenia. Researchers have administered this agent intranasally over varying periods of time. Several institutions, including University of California, Los Angeles, and University of North Carolina, Chapel Hill Clinical trials completed	Psychotherapeutic intervention	Improved social cognition Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label riluzole (Rilutek) for treatment of major depressive disorder	Patients in whom treatment-resistant major depressive disorder (MDD) has been diagnosed	Fewer than half of patients with MDD achieve remission with currently approved antidepressant therapy. The mechanism of action of riluzole (Rilutek®) would be novel for this disease state. Riluzole is a glutamatergic modulator currently 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. Sanofi, Paris, France (manufacturer) National Institute of Mental Health, Bethesda, MD (investigator) Phase II trials ongoing; 1 phase II trial completed	Pharmacotherapy (e.g., selective serotonin reuptake inhibitors) Psychotherapy	Glutamatergic modulation Improved MDD symptoms Improved quality of life
Off-label sodium oxybate for treatment of binge-eating disorder	Patients in whom binge-eating disorder has been diagnosed	No pharmacotherapies are approved for binge-eating disorder, and currently used off-label pharmacotherapies are associated with limited efficacy, undesirable side effects, and low adherence. This intervention represents a novel mechanism of action for the condition. The active ingredient in sodium oxybate is gamma hydroxybutyrate, a compound endogenously synthesized in the central nervous system, which is known to modulate neurotransmitters (e.g., gamma aminobutyric acid [GABA], dopamine, serotonin, opioids, glutamate) that regulate feeding behavior. This agent is marketed under the trade name Xyrem® for treating daytime sleepiness and cataplexy in patients with narcolepsy. Some investigators have suggested that binge-eating disorder may mediate the relationship between narcolepsy and obesity. This agent is administered orally, in liquid form, twice every night. Jazz Pharmaceuticals, Inc., Palo Alto, CA (manufacturer listed as a collaborator on clinical trials, but does not list active development for this indication on its Web site) Lindner Center of Hope, Mason, OH (primary investigator) Phase II/III trial completed; regulated as a Class III controlled substance by FDA and U.S. Drug Enforcement Agency	Off-label pharmacotherapy (e.g., antiepileptics, selective norepinephrine reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors)	Improved symptoms of binge eating Improved morbidity and mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 1 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 better tolerated and more effective in treating patients with 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. It does not appear that Effexor's manufacturer is seeking a labeled indication change. Pfizer, Inc., New York, NY (manufacturer) University of California, San Diego (investigator) Clinical trial completed	Psychotherapy SSRIs	Improved scores on hoarding rating scales Reduced morbidity Reduced mortality Improved quality of life
Reversible inhibitor of monoamine oxidase A (TriRima) for treatment-resistant depression	Patients in whom treatment-resistant depression has been diagnosed	Reversible and selective inhibitors of monoamine oxidase A (MAO-A; TriRima™, CX157) represent a novel class of drugs. If approved, it would be the 1st monotherapy indicated for treatment-resistant depression. CeNeRx BioPharma, Inc., Cary, NC Phase II trials completed	Pharmacotherapy (e.g., selective serotonin reuptake inhibitors) Psychotherapy	Improved score on validated depression scales Reduced serious cardiovascular side effects associated with other MAO-A inhibitors
RO4917838 for treatment of negative symptoms of schizophrenia	Patients in whom schizophrenia has been diagnosed	Glycine transporter type 1 inhibitor (RO4917838); elevation of extracellular synaptic glycine concentration by blockade of glycine transporter type 1 has been hypothesized to potentiate N-methyl-D-aspartate receptor (NMDAR) 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. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials ongoing	Pharmacotherapy (e.g., atypical antipsychotics)	Symptom improvement Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Serotonin-norepinephrine-dopamine reuptake inhibitor (EB-1010) for treatment of depression	Patients with major depressive disorder who do not respond adequately to selective serotonin reuptake inhibitors	A novel, unbalanced, triple serotonin-norepinephrine-dopamine reuptake inhibitor (EB-1010) antidepressant that acts simultaneously as a reuptake inhibitor for the 3 monoamines; demonstrates greatest affinity for transporters that inhibit serotonin reuptake, half as much against norepinephrine reuptake, and 1/8 as much against dopamine reuptake. Euthymics Biosciences, Inc., Cambridge, MA Phase II/III trial ongoing	Pharmacotherapy (e.g., selective serotonin reuptake inhibitors) Psychotherapy	Increased serotonin, norepinephrine, and dopamine neurotransmission Improvement in symptoms, as measured by standard depression rating scales Improved quality of life
Synthetic neurosteroid (Ganaxolone) for treatment of posttraumatic stress disorder	Patients in whom posttraumatic stress disorder (PTSD) has been diagnosed	Despite pharmacotherapy and psychotherapy, many patients have treatment-resistant PTSD. Ganaxolone (3 alpha-hydroxy-3 beta-methyl-5 alpha-pregnan-20-one) is a 3beta-methylated synthetic analog of allopregnanolone (a naturally occurring neuromodulator that is a neurosteroid metabolite of progesterone); researchers believe that neurosteroid (allopregnanolone) levels play a role in the severity and outcomes for patients with PTSD. Ganaxolone is intended to regulate inhibitory gamma aminobutyric acid (GABA) as a positive allosteric modulator. Marinus Pharmaceuticals, Inc., Branford, CT, in public-private collaboration with INTRuST Consortium (group of clinical study centers in the U.S. funded by U.S. Department of Defense) Phase II trial ongoing	Pharmacotherapy Psychotherapy	Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Text-messaging 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 behavioral therapy approaches are needed that engage participant. With this text messaging approach, participants send a nightly text message to clinicians to report the number of binge eating and purging episodes and rate their urges to binge and purge. Participants receive automatic feedback message 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. University of North Carolina at Chapel Hill Trial completed (phase not reported)	Antidepressant medication Nutritional counseling Psychological counseling	Reduced number of binge eating and purging episodes Improved symptoms of depression, eating disorder, and night eating Enhanced self-monitoring and treatment, leading to improved attendance, adherence, and engagement in treatment Increased remission
Trigeminal nerve stimulation (eTNS) for treatment of major depressive disorder	Patients in major depressive disorder (MDD) has been diagnosed	Available pharmacotherapies for MDD are characterized by limitations, including lack of efficacy for many patients and unwanted side effects; options for treatment-resistant MDD (e.g., deep brain stimulation [DBS], vagus nerve stimulation [VNS], transcranial magnetic stimulation, or repetitive transcranial magnetic stimulation [rTMS]) are surgically invasive and must be performed in a hospital setting. Trigeminal nerve stimulation (eTNS) is a noninvasive therapy in which mild electrical signals pass through electrodes placed on the forehead. It is intended to transcutaneously stimulate the various branches of the trigeminal nerve (the largest cranial nerve), which projects to the amygdala (mood regulation). The stimulation is controlled by an external pulse generator worn by patient during 8 hours of sleep. Researchers are also developing sTNS version (subcutaneous electrodes and implantable pulse generator). University of California, Los Angeles, and NeuroSigma, Inc., Los Angeles, CA Phase II trial ongoing	DBS Electroconvulsive therapy Pharmacotherapy rTMS VNS	Improved depression symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Trigeminal nerve stimulation (eTNS) for treatment of posttraumatic stress disorder	Patients in whom posttraumatic stress disorder (PTSD) has been diagnosed	Many patients with PTSD do not adequately respond to pharmacotherapy and psychotherapy; additional efficacious treatments are needed. eTNS™ is a noninvasive therapy in which mild electrical signals pass through electrodes placed on the forehead. It is intended to transcutaneously stimulate the various branches of the trigeminal nerve (the largest cranial nerve), which projects to the amygdala (mood regulation). The stimulation is controlled by an external pulse generator and worn by patient during 8 hours of sleep. Researchers are also developing sTNS version (subcutaneous electrodes and implantable pulse generator). University of California, Los Angeles, and NeuroSigma, Inc., Los Angeles, CA Phase I trial completed; phase II trials being planned	Pharmacotherapy Psychotherapy	Improved symptom burden Improved quality of life
Wisdom therapy for posttraumatic embitterment disorder	Patients in whom posttraumatic embitterment disorder (PTED) has been diagnosed	PTED is an emerging condition and does not have an established therapeutic regimen. Wisdom therapy is a relatively young field of psychology; somewhat related to motivational interviewing; based on the concept that cognition and reflection (central aspects of wisdom) may help one to overcome bitterness. Embitterment is the outcome of a particular way of handling life experiences, as is wisdom, so wisdom therapy may provide an avenue for growth while dealing with negative life experiences. First described by Michael Linden, Charité University Hospital, Berlin, Germany Pilot trial completed	Pharmacotherapy (e.g., selective serotonin reuptake inhibitors)	Improved symptoms Improved quality of life

Table 6. AHRQ Priority Condition: 06 Developmental Delays, Attention-Deficit Hyperactivity Disorder, and Autism: 13 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
AFQ056 for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	No cure exists for FXS; medications and behavioral interventions alleviate individual symptoms but do not address the cause of FXS. 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), may potentially normalize the excessive protein synthesis and control symptoms associated with FXS. Dose range will be 25, 50, and 150 mg twice a day. Drug is also under study for Parkinson's disease and Huntington's disease. Novartis International AG, Basel, Switzerland Phase II/III trials ongoing in adults and adolescents; company plans new drug application filing in 2013	Physical and behavioral 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 baseline in behavioral symptoms using the Aberrant Behavior Checklist
Functional magnetic resonance imaging for differentiating autism from bipolar and other behavioral disorders in children	Children suspected of having autistic spectrum disorder	Certain psychiatric, behavioral, and developmental disorders, such as bipolar disorder and autism, can have similar signs and symptoms in young children and differentiating between the 2 when making a diagnosis can be very difficult. Functional MRI is being investigated as a means of differentiating the 2 conditions by observing patterns of activity in the brain during MRI. Twenty individuals previously diagnosed with autism spectrum disorder were studied; next goal is to test in children suspected of having autism. Institute of Psychiatry, King's College, London, UK Phase I trial completed on autism and bipolar disorder; other trials ongoing	Assessments based on interviews and behavior observation	Early diagnosis Early intervention and treatment Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ganaxolone for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	No cure exists for FXS; medications and behavioral interventions alleviate individual symptoms but do not address the cause of FXS. 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. Pharmacologic treatments that address FXS social deficits are needed because impairments in social function are a core feature of FXS. Ganaxolone is synthetic neurosteroid, the 3beta-methylated synthetic analog of allopregnanolone, a metabolite of progesterone. Reduced gamma aminobutyric acid A (GABA-A) receptor expression in FXS includes heightened sensitivity to sensory stimuli, anxiety, and seizures in some patients. Developers theorize that ganaxolone, which demonstrates high affinity for GABA-A/delta receptors, could increase signaling at existing receptors to normalize GABA-mediated inhibition to reduce anxiety, hyperactivity, and learning disabilities associated with FXS. Marinus Pharmaceuticals, Inc., Branford, CT Company stated in 2011 that U.S. Dept of Defense awarded a $3 million grant to University of California, Davis, for an early phase trial planned to start in 2012; no FXS trials yet registered in the National Clinical Trials database as of Oct 2012	Physical and behavioral 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)	Improved behavior and cognitive measures Increased sociability and communication Improved scores on scales of sociability
Mecasermin (Increlex) for treatment of Rett syndrome	Children aged 2–12 years in whom Rett's syndrome has been diagnosed	Mecasermin (Increlex®) is a synthetic form of insulin-like growth factor-1 intended to stimulate synaptic maturation and used to improve cognitive function in children with Rett's syndrome. Ipsen (acquired developer Tercica, Inc.), Paris, France; investigated by Children's Hospital of Boston, Boston, MA, in collaboration with International Rett Syndrome Foundation, Cincinnati, OH, and Autism Speaks, New York, NY Phase I/II trial ongoing	Physical and behavioral interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Pharmacotherapy (e.g., antiepileptics)	Improved neurodevelopmental symptoms (severe cognitive, motor, and language problems and autistic behaviors)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
N-acetylcysteine for treatment of autism	Children receiving a diagnosis of autism	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 behavioral programs, devices, and pharmacotherapies. N-acetylcysteine (NAC) is a glutamate modulator and antioxidant known to increase glutathione in children diagnosed with autism. For children in whom autism has been diagnosed, NAC is administered orally, 900 mg twice daily, or 900 mg 3 times daily, in 1 study; in another study evaluating NAC for treating autism spectrum disorders, NAC is being administered orally, 600 mg 3 times daily, with a maximum dose of 4,200 mg/day. Stanford University School of Medicine, Stanford, CA, and Indiana University School of Medicine, Indianapolis, in collaboration with National Alliance for Autism Research, Princeton, NJ Stanford University School of Medicine: phase II trial completed Indiana University School of Medicine: phase II trial completed	Physical and behavioral interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Off-label pharmacotherapy (e.g., acetylcholinesterase inhibitors, alpha-2 adrenergic agonists, carnitine) Pharmacotherapy (e.g., risperidone, anti-inflammatories, melatonin, naltrexone, oxytocin, tetrahydrobiopterin)	Improved Clinical Global Rating Scale results Improved Repetitive Behavioral Scale score Improved social responsiveness Improved speech and language Improved metabolic measures Improved quality of life
Off-label donepezil (Aricept) for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	No cure exists for FXS; medications and behavioral interventions alleviate individual symptoms but do not address the cause of FXS. FXS is a neurodevelopmental disorder caused by mutations of the *FMR1* gene; it is the most common known heritable cause of cognitive and behavioral disability. Abnormalities of cholinergic pathway function and neurochemistry observed with functional magnetic resonance imaging (fMRI) in FXS patients makes researchers believe that functional cholinergic deficits contribute to cognitive-behavioral dysfunction in FXS. Donepezil HCl (Aricept®) is a cholinesterase inhibitor that is intended to improve memory, attention, social interaction, reasoning and language abilities, and ability to perform activities of daily living by increasing the amount of acetylcholine in the brain by reversibly inhibiting its hydrolysis by acetylcholinesterase; may potentially augment the cholinergic system in adolescents affected by FXS. The drug is approved to treat mild, moderate, and severe Alzheimer's disease and is under study for various other types of cognitive impairment, including Down syndrome. Under study by Autism Speaks, New York, NY; National Institute of Mental Health, Rockville, MD; and Stanford University, Stanford, CA Phase II trial ongoing	Physical and behavioral 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)	Improvements in specific measures of behavior and cognition Improved scores on behavior assessments Improved scores on working memory tests

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label intranasal oxytocin for treatment of social dysfunction in autism spectrum disorders	Patients in whom autistic spectrum disorder (ASD) or Asperger's syndrome has been diagnosed	Most individuals with ASD are treated through highly structured behavioral programs to try to improve social cognition and functioning; pharmacologic therapies address symptoms of hyperactivity and depression; 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 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; potential improvements in social function and quality of life and reductions in certain types of repetitive behaviors may be realized with oxytocin therapy. This treatment is administered intranasally at a 12 unit puff per nostril twice daily, totaling 48 IU daily. Montefiore Medical Center, Bronx, NY Phase II trials ongoing	Physical and behavioral interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Off-label pharmacotherapy (e.g., acetylcholinesterase inhibitors, alpha-2 adrenergic agonists, carnitine) Pharmacotherapy (e.g., risperidone, anti-inflammatories, melatonin, naltrexone, oxytocin, tetrahydrobiopterin)	Improved Diagnostic Analysis of Nonverbal Accuracy results Improved Social Responsivity Scale scores Improved Clinical Global Impressions Scale - Improvement scores
Off-label minocycline for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	Medications and behavioral interventions alleviate individual symptoms but do not address the cause of FXS. 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. In FXS, synaptic protein synthesis is excessive and connections do not develop normally. Minocycline is an antibiotic used in children for infection and is being investigated for treating FXS; minocycline lowers matrix metalloproteinase 9 levels, which are high in FXS, and it also strengthens brain connections according to animal models of FXS; potential benefits include improved language, behavior and/or cognition in children with FXS. Administration is orally, once a day, for 3 months. University of California, Davis; FRAXA Research Foundation (in collaboration with Fragile X Foundation of Canada), Toronto, Ontario, Canada Pilot trial ongoing; unphased trial completed	Physical and behavioral 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)	Improved behavior, perceptual and cognitive development Improved daily living skills Improved gross motor skill development Increased sociability and communication Improved speech and language

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
RO4917523 for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	No cure exists for FXS; medications and behavioral interventions alleviate some individual symptoms, but do not address the underlying cause of FXS. 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. RO4917523, an antagonist of 1 type of mGluR, mGluR5, may potentially normalize the excessive protein synthesis and control symptoms associated with FSX. F. Hoffmann-La Roche, Ltd., Basel, Switzerland One phase II trial completed; 1 Phase II trial ongoing	Physical and behavioral 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)	Improved behavioral and cognitive measures Improved daily living skills Improved gross motor skill development Increased sociability and communication Improved sensory system Improved speech and language skills
STX107 for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	No cure exists for FXS; medications and behavioral interventions alleviate individual symptoms but do not address the cause of FXS. 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. STX107 selectively inhibits 1 type of mGluR, mGluR5, and may potentially normalize the excessive protein synthesis that may give rise to symptoms associated with FXS. Seaside Therapeutics, Inc., Cambridge, MA Phase II trial ongoing	Physical and behavioral 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)	Improved behavioral and cognitive measures Improved daily living skills Improved gross motor skill development Increased sociability and communication Improved sensory system Improved speech and language skills

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
STX209 (arbaclofen) for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	No cure exists for FXS; medications and behavioral interventions alleviate some individual symptoms, but do not address the underlying cause of FXS. 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. Pharmacologic treatments that address FXS social deficits are needed because impairments in social function are a core feature of FXS. Research suggests that individuals with FXS have abnormalities in synaptic transmission. STX209 (arbaclofen) is a selective gamma aminobutyric acid type B (GABA-B) receptor agonist; through the GABA-B receptor, STX209 may serve to restore the normal balance at the synapse and correct abnormalities associated with FXS. Seaside Therapeutics, Inc., Cambridge, MA Phase III trials ongoing	Physical and behavioral 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)	Improved behavioral and cognitive measures Increased sociability and communication
STX209 (arbaclofen) for treatment of social withdrawal in autism spectrum disorder	Patients in whom an autism spectrum disorder (ASD) has been diagnosed	Most individuals with ASD are treated through highly structured behavioral programs to try to improve social cognition and functioning; pharmacologic treatments to address ASD-related social deficits are lacking (existing pharmacologic treatments address symptoms such as hyperactivity, irritability, anxiety, or depression, not social deficits); a pharmacologic treatment targeted at the core social deficits in areas of communication or repetitive behaviors and restricted interests is needed. Research suggests an imbalance in gamma aminobutyric acid (GABA)/glutamate transmission underlies behavioral deficits of ASD; arbaclofen is intended to improve synaptic functioning by regulating glutamate and increasing GABA (the main inhibitory neurotransmitter in the central nervous system), an inhibitory transmitter, which counteracts the over-excitability of cells. STX209, a GABA-B agonist, has been proposed as a treatment to normalize this deficiency. Clinical trials dosage: disintegrating tablet 5 or 10 mg, twice a day; 10 or 15 mg, 3 times a day. Seaside Therapeutics, Inc., Cambridge, MA Phase II trials ongoing	Off-label pharmacotherapy (e.g., acetylcholinesterase inhibitors, alpha-2 adrenergic agonists, carnitine) Physical and behavioral interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Pharmacotherapy (e.g., risperidone, anti-inflammatories, melatonin, naltrexone, oxytocin, tetrahydrobiopterin)	Improvement in Aberrant Behavior Checklist-Social Withdrawal Subscale

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Trigeminal nerve stimulation (eTNS) for treatment of attention-deficit/hyper-activity disorder	Patients in whom attention-deficit hyperactivity disorder (ADHD) has been diagnosed	ADHD affects an estimated 5 million children aged 4–17 years in the U.S. Current treatments, especially those involving prescription drugs, are not viable for all patients, the drugs are in short supply currently, and concerns about their side effects worry many patients and their families. Trigeminal nerve stimulation (eTNS) is proposed as a noninvasive therapy during which mild electrical signals pass through adhesive conductive electrode pads placed on the patient's forehead to transcutaneously stimulate the trigeminal nerve branches. University of California, Los Angeles, and NeuroSigma, Inc., Los Angeles, CA Phase I trial ongoing	Behavioral therapies and psychotherapy Pharmacotherapy (e.g. central nervous system stimulants, selective serotonin reuptake inhibitors, antidepressants, clonidine [Catapres®])	Improved behavior and focus Improved quality of life

Table 7. AHRQ Priority Condition: 07 Diabetes Mellitus: 54 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Allogeneic fecal enema for treatment of metabolic syndrome in obese patients	Obese patients with metabolic syndrome (at least 3 of 5 National Cholesterol Education Project metabolic syndrome criteria)	The prevalence of metabolic syndrome is increasing in the U.S., warranting the need for effective therapies aimed to reduce coronary artery disease, stroke, and diabetes mellitus. Fecal matter is harvested from healthy lean donors, processed, and transferred into obese patients with metabolic syndrome in an effort to treat insulin resistance and obesity by populating the lower intestinal tract with the flora of a healthy, lean person. Academic Medical Center/University of Amsterdam, the Netherlands Pilot trial completed	Antiobesity pharmacotherapy Dietary and behavioral modifications Surgical intervention (e.g., bariatric surgery)	Improved fecal flora composition Weight loss Resolution of metabolic syndrome

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Alpha-1 antitrypsin for treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus (T1DM) has been diagnosed	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. Kamada, Ltd., Ness Ziona, Israel National Institute of Allergy and Infectious Disease, Bethesda, MD University of Colorado, Denver, in collaboration with Omni Bio Pharmaceuticals, Inc., Greenwood Village, CO Phase I/II trial and phase II trials ongoing; FDA granted orphan drug designation Aug 2011	Insulin modifications Islet cell transplantation Pancreas transplantation	Reduced daily insulin usage Improved glycosylated hemoglobin (HbA_{1c}) levels Reduced complications of diabetes Improved quality of life
Anakinra interleukin-1 receptor antagonist for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	Research has implicated inflammation in the development of insulin resistance associated with T2DM; however, no anti-inflammatory treatments are currently approved for treating T2DM. Anakinra is a recombinant protein inhibitor of interleukin-1 (IL-1) receptors that has been approved since 2001 for treating rheumatoid arthritis; IL-1 is a proinflammatory cytokine that has been observed in pancreatic sections obtained from patients with T2DM and may play a role in the inflammatory process leading to T2DM progression. Amgen, Inc., Thousand Oaks, CA (manufacturer) Radboud University Nijmegen, the Netherlands; University Hospital, Zurich, Switzerland; and Steno Diabetes Center, Gentofte, Denmark (investigators) Phase II/III trials ongoing	Dietary and lifestyle modifications Exenatide Insulin sensitizers (pioglitazone, rosiglitazone) Insulin Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Achieved target glycosylated hemoglobin (HbA_{1c}) levels Desired fasting glucose level control Resolved insulin sensitivity

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Angiotensin analog (DSC127) for treatment of diabetic foot ulcers	Patients in whom diabetic foot ulcers have been diagnosed	Current treatments for diabetic foot ulcers result in complete healing less than 30% of the time; therefore, effective treatments are intended to accelerate and complete the wound healing process. DSC127 is an analog of the human peptide signaling molecule angiotensin; angiotensin has properties that are believed to improve wound healing, including increasing keratinocyte/mesenchymal stem cell proliferation, extracellular matrix production, and vascularization; DSC127 has been modified from endogenous angiotensin to remove the normal effects of the peptide on blood pressure; applied daily as a topical gel until the wound is healed. Derma Sciences, Princeton, NJ Phase II trial completed; company anticipated phase III trial to commence in 2nd half of 2012	Acellular wound matrices Cellular wound matrices Hyperbaric oxygen therapy Negative pressure wound therapy	Increased percentage of ulcers healed Decrease in ulcer size
Artificial pancreas for treatment of diabetes	Patients with type 1 or type 2 diabetes mellitus who require insulin and are highly motivated to use the system and monitor its function	Artificial pancreas 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 created a total closed loop system. Sixteen systems are in early-phase trials. Various manufacturers Early phase trials completed and ongoing; Dec 2011, FDA issued a 2nd guidance document for artificial pancreas systems to facilitate clinical development of the fully closed-loop system	Insulin modifications Islet cell transplantation Pancreas transplantation	Reliable glycemic control at desired levels Reduced risk of acute and nighttime hypoglycemia Reduction in postprandial (after meal) hyperglycemia Halted or delayed progression of secondary complications Improved quality of life
Atrasentan for treatment of chronic kidney disease in type 2 diabetes	Patients with type 2 diabetes mellitus who have chronic kidney disease (CKD)	Current treatments only modestly slow CKD, and patients ultimately need dialysis. Atrasentan is a highly selective endothelin-A receptor antagonist, which blocks the effect of endothelin-I, a protein that constricts blood vessels and raises blood pressure, thereby decreasing kidney function. In conjunction with renin-angiotensin system inhibitors, Atrasentan may reduce albuminuria (presence of protein in urine) which occurs as kidney function decreases. Abbott Laboratories, Abbott Park, IL Phase II trial completed; additional phase II trials ongoing	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Reduced urine albumin-to-creatinine ratio Improved kidney function Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bariatric surgery for resolution of diabetes in obese and non-obese patients	Obese and non-obese patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	Researchers have theorized that bariatric surgery might resolve diabetes in non-obese patients, in light of evidence of diabetes resolution in obese patients after undergoing successful bariatric surgery and achieving weight loss. Bariatric surgery (gastric bypass, lap banding, sleeve gastrectomy) for resolution of T2DM. Some researchers suggest that bariatric surgery could be used to treat, or possibly "cure," patients with T2DM regardless of body mass index level and independent of weight loss. Various academic research centers and manufacturers Mid-to-late phase trials completed and ongoing	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Resolution of T2DM
Breath analysis for assessing blood glucose levels	Patients in whom type 1 or type 2 diabetes mellitus (T1DM, T2DM) has been diagnosed	About 7 million people in the U.S. have diabetes but do not know it because they have not been screened and diagnosed. Late detection typically leads to secondary complications (i.e. cardiovascular disease, nephropathy, neuropathy) that could otherwise be prevented or delayed with early diagnosis. Late diagnosis can occur for many reasons, including patient nonadherence to recommended screening (blood draw). More novel, noninvasive diabetes screening devices are needed to improve screening compliance and increase diagnosis. Breath analyzer uses proprietary cavity-enhanced absorption spectroscopy technology to measure acetone levels in breath. Intended as a rapid, noninvasive blood glucose test for patients with T1DM or T2DM. Oxford Medical Diagnostics, Oxford, UK Early phase trials planned	Standard blood glucose testing	Improved adherence with blood glucose testing

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Breath analysis (laser-based) for diagnosing diabetes	Patients at risk of type 1 or type 2 diabetes mellitus	About 7 million people in the U.S. have diabetes but do not know it because they have not been screened and diagnosed. Late detection typically leads to secondary complications (i.e. cardiovascular disease, nephropathy, neuropathy) that could otherwise be prevented or delayed with early diagnosis. Late diagnosis can occur for many reasons, including patient nonadherence to recommended screening (blood draw). More novel, noninvasive diabetes screening devices are needed to improve screening compliance and increase diagnosis. Uses laser-based gas analysis; intended to provide a rapid, noninvasive method for diagnosis. Avacta Group, plc, York, UK Oxford Medical Diagnostics, Oxford, UK Unphased trial ongoing	Standard blood glucose testing	More patients screened and diagnosed Diagnosis earlier in disease course Faster, point-of-service diagnosis
Buccal insulin (Oral-lyn) for treatment of type 1 and 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; short duration of activity; intended for dosing before and after meals; intended for use adjunctively with long-acting, injectable or infused insulin and as a substitute for injectable short-acting insulin; not intended to reach the lungs; may pose less risk of respiratory or pulmonary complications associated with inhaled insulin. Generex Biotechnology Corp., Toronto, Ontario, Canada Phase III trial completed; FDA approved in 2009 a treatment investigational new drug (IND) program for the product that 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	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Achieved target glycosylated hemoglobin (HbA_{1c}) levels Reduced glycemic excursions related to meals Prevented onset of T2DM in prediabetic individuals Delayed insulin dependence in T2DM Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Canakinumab interleukin-1 inhibitor for treatment of type 2 diabetes	Patients in whom impaired glucose tolerance or type 2 diabetes mellitus (T2DM) has been diagnosed	Research has implicated inflammation in the development of insulin resistance associated with T2DM; however, no approved anti-inflammatory treatments are availablefor T2DM. Canakinumab is a human monoclonal antibody against interleukin-1 (IL-1)-beta; IL-1 is a proinflammatory cytokine that has been observed in pancreatic sections obtained from patients with T2DM and may play a role in the inflammatory process leading to T2DM progression. Novartis International AG, Basel, Switzerland Phase II/III trial completed	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Glycosylated hemoglobin (HbA_{1c}) level control Desired fasting glucose level control Resolved insulin sensitivity
Chemokine receptor antagonist (CCX140) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	Although many treatments for T2DM help control glucose levels, these treatments often come with significant side effects, including gastrointestinal effects (e.g., nausea, diarrhea), weight gain, hypoglycemia, and edema. Additionally, current treatments may slow progression of renal disease at best, warranting the need for treatments that stop renal disease progression. CCX140 is an antagonist of chemokine receptor 2 (CCR2), which is responsible for the activation and migration of monocytes/macrophages during the inflammatory process. CCX140 is highly selective for CCR2 and does not inhibit migration mediated by other chemokine receptors. It is administered orally, 5 or 10 mg, once daily. ChemoCentryx, Inc., Mountain View, CA Phase II trial completed, with 2 phase II trials ongoing	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Improved glycosylated hemoglobin (HbA_{1c}) levels Reduced hyperglycemic episodes Halted or delayed secondary complications (i.e., nephropathy)
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 biologic 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, which is being studied in treating of various secondary complications of diabetes. Cebix, Inc., La Jolla, CA Phase II trial ongoing; FDA has granted fast track status for diabetic peripheral neuropathy	Analgesics Antiepileptics Duloxetine (antidepressant), Lidocaine patches Pregabalin (anticonvulsant) Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors Tricyclic antidepressants	Reduced patient-reported pain on visual analog scale Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
CTP-499 for treatment of diabetic nephropathy	Patients in whom diabetic nephropathy has been diagnosed	Renal failure is common in patients with long-term diabetes; CTP-499 is an anti-inflammatory, antioxidant, and antifibrotic agent being developed for diabetic nephropathy and other forms of chronic kidney disease. CTP-499 is a deuterium-containing new chemical entity derived from an active metabolite of a drug approved for a different indication; deuterium is a stable, nonradioactive relative of hydrogen that forms strong bonds with carbon; this affinity may affect the drug's absorption, distribution, metabolism and/or excretion properties, and improve drug efficacy, safety, and tolerability. It has potential to preserve kidney function and slow disease progression when added to existing therapy. Concert Pharmaceuticals, Inc., Lexington, MA Phase II trial ongoing	Dialysis (end-stage renal failure) Kidney transplantation (end-stage renal failure) Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors)	Protect kidney function and slow disease progression when added to existing therapy Delay/prevent kidney transplantation
DB 959 (PPAR agonist) delta/gamma for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus has been diagnosed	DB 959 is a peroxisome proliferator-activated receptor (PPAR)-delta/gamma agonist intended to control glucose while raising high-density lipoprotein (HDL) and the ratio of HDL to low-density lipoprotein and lowering triglycerides; purported to not cause weight gain seen with other PPAR agonists. Taken once daily. DARA Biosciences, Inc., Raleigh, NC Phase Ib trial completed; phase IIa planned for 2012	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Achieved target glycosylated hemoglobin (HbA_{1c}) levels Improved lipid profile

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Docosahexaenoic acid and salicylate conjugate (CAT-1004) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	T2DM accounts for about 90% of diabetes cases globally, with incidence and prevalence rising. Many current treatments help control glucose levels, but these treatments often come with significant side effects, which include gastrointestinal effects (e.g., nausea, diarrhea), weight gain, hypoglycemia, and edema. Additionally, many patients have difficulty achieving control of blood glucose with current treatments. CAT-1004 is a conjugate of docosahexaenoic acid (DHA) and salicylate. Several studies reveal the potential therapeutic effects of omega-3 fatty acids in inflammatory and metabolic diseases. DHA exhibits cardioprotective properties and salicylate exhibits anti-inflammatory properties. Studies suggest that this conjugate may improve insulin sensitivity and glucose homeostasis by simultaneously inhibiting proinflammatory pathways and activating endogenous anti-inflammatory pathways. Catabasis Pharmaceuticals, Inc., Cambridge, MA Phase I trial completed	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Decreased inflammation and insulin resistance Near-normal glycosylated hemoglobin (HbA_{1c}) levels Halted or delayed acute and secondary complications
Exenatide (Byetta) continuous subcutaneous (Duros, or ITCA 650 pump) delivery for treatment of type 2 diabetes	Patients with type 2 diabetes mellitus who have not achieved desired blood glucose goals with metformin	Exenatide (Byetta®) is a glucagon-like peptide-1 (GLP1) mimetic delivered continuously with an implantable pump, using Duros® technology; device can be inserted under the skin in a few minutes; intended to improve glucose control and result in less nausea than observed with injected exenatide. Amylin Pharmaceuticals, Inc., San Diego, CA (drug) Intarcia Therapeutics, Inc., Hayward, CA (device) Duros technology is FDA approved for drug delivery; exenatide formulation for use with pump is under study; in Nov 2011, Eli Lily and Co. returned all development rights of exenatide to Amylin; phase II trial completed; phase III trial ongoing	Dietary and lifestyle modifications Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Improved glycosylated hemoglobin (HbA_{1c}) levels Weight loss Reduced side effects (nausea)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) 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	Extended-release exenatide (Bydureon™), a version of Byetta (approved in 2005) is taken by injection, once a week. Amylin Pharmaceuticals, Inc., San Diego, CA Alkermes, Inc., Waltham, MA 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 trail to evaluate the effects of Bydureon on the incidence of major adverse cardiovascular events in T2DM patients; medullary thyroid carcinoma biomarkers; and long-term effects on specific disorders of the thyroid and pancreas. The approval also included a Risk Evaluation and Mitigation Strategy plan.	Dietary and lifestyle modifications Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Blood sugar control Cardiovascular changes (QTc segment prolongation arrhythmias)
Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema	Patients in whom diabetic macular edema has been diagnosed	No FDA-approved drug therapy is available for treating diabetic macular edema. Iluvien® is a tube-shaped implant that releases a steady flow of the corticosteroid fluocinolone acetonide (FAc) into the ocular space for up to 3 years; FAc is a corticosteroid that has both anti-inflammatory and anti-VEGF (vascular endothelial growth factor) activity and has a history of effectiveness in treating ocular disorders. Alimera Sciences, Alpharetta, GA Phase III trials completed; new drug application (NDA) submitted in Jun 2010; FDA issued a complete response letter in Dec 2010 asking for additional safety data; NDA resubmitted May 2011; Nov 2011, FDA issued a complete response letter not approving the drug. The company is considering next steps for the U.S. market; received marketing approval in several EU countries.	Intravitreal triamcinolone acetonide with or without laser photocoagulation Laser photocoagulation Pharmacotherapy (e.g., vascular endothelial growth factor antagonists)	Increased visual acuity Increased contrast sensitivity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
GFT 505 for treatment of prediabetes and diabetes	Patients in whom diabetes, abdominal obesity, or atherogenic dyslipidemia (low levels of high-density lipoprotein cholesterol, high triglycerides) has been diagnosed	Mixed peroxisome proliferator-activated receptor alpha/delta agonist (GFT 505) is based on Genfit's Selective Nuclear Receptor Modulator (SNuRM) platform; GFT 505 simultaneously targets several micro- and macro-vascular risk factors such as hyperglycemia and insulin resistance, dyslipidemia, inflammation, and hepatic steatosis. Genfit Corp., Lille, France Phase II trial completed; Sept 2012, FDA approved phase IIb trial.	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Improved blood glucose levels Improved lipid profiles Halted progression to diabetes Resolution of diabetes
GLP1 analog (ORMD 0901) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	T2DM accounts for about 90% of diabetes cases globally, with incidence and prevalence rising. ORMD 0901 is an oral formulation of the approved injectable glucagon-like peptide-1 (GLP1) analog exenatide. GLP1 analogs stimulate insulin secretion, suppress glucagon release, and slow gastric emptying. An oral formulation would be expected to enhance diabetes control and patient adherence. Oramed Pharmaceuticals, Inc., Jerusalem, Israel Phase II trial ongoing	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Near-normal glycosylated hemoglobin (HbA_{1c}) levels Improved fasting glucose levels Improved insulin sensitivity Reduced acute and secondary complications
Glutamic acid decarboxylase-based vaccine (Diamyd) for treatment of latent autoimmune diabetes of adults	Patients in whom latent autoimmune diabetes of adults has been diagnosed	Subcutaneous injection with Diamyd® vaccine intended to preserve insulin-producing islet cells in pancreas of patients with latent autoimmune diabetes of adults. Diamyd is thought to induce tolerance to GAD65, thereby preventing or reducing autoimmune attack on islet-beta cells and preserving the pancreas's capacity to produce insulin in patients with autoimmune diabetes. Given as 2 injections, administered 1 month apart. Diamyd Medical AB, Stockholm, Sweden Phase II trial completed	Insulin modifications Islet cell transplantation Pancreas transplantation	Preserved islet cell function Reduced need for insulin injections Reduced incidence of diabetes acute and secondary complications

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Glutamic acid decarboxylase-based vaccine (Diamyd) for treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus has been recently diagnosed	Subcutaneous injection with Diamyd® vaccine is intended to preserve insulin-producing islet cells in pancreas of patients with latent autoimmune diabetes of adults. Diamyd is thought to induce tolerance to GAD65, thereby preventing or reducing autoimmune attack on islet-beta cells and preserving the pancreas' capacity to produce insulin in patients with autoimmune diabetes. Given as 2 injections, administered 1 month apart. Diamyd Medical AB, Stockholm, Sweden Phase III trial ongoing; 1 phase III trial (EU) terminated because primary endpoint at 15 months was not met	Insulin modifications Islet cell transplantation Pancreas transplantation	Improved islet cell function Reduced need for insulin therapy Decreased diabetes complications
Hematopoietic stem cell transplantation for treatment of type 1 diabetes	Patients with type 1 diabetes mellitus who have not achieved adequate control of blood glucose levels	Patients are given immunosuppressive drugs and then a stem cell infusion of their own previously harvested blood (hematopoietic) stem cells, which is intended to restore insulin-producing function of beta cells in the pancreas. Various research organizations and companies are developing proprietary versions of stem cell transplants Phase II trials ongoing	Insulin modifications Islet cell transplantation Pancreas transplantation	Decreased or eliminated insulin use Improved glycemic control Normal growth rate for children Restored beta-cell function as measured by C-peptide levels
HPTPbeta inhibitor (AKB-9778) for treatment of diabetic macular edema	Patients in whom diabetic macular edema has been diagnosed	Currently, no pharmacotherapy is approved for treating diabetic macular edema. Patients still experience significant loss of visual acuity when using available diabetic macular edema treatments. Other treatments may stabilize, but not improve vision and are associated with additional loss of clarity, color, and peripheral vision. AKB-9778 is a human protein tyrosine phosphatase beta (HPTPbeta) inhibitor that purportedly increases Tie2 receptor activity to restore vascular integrity and reduce vascular leaks and pathologic angiogenesis. HPTPbeta typically dephosphorylates Tie2, inhibiting its signaling and allowing for Ang2 (a natural Tie2 inhibitor) to destabilize vascular structures. The company began a 28-day phase 1b/2a ascending dose study in Sept 2012 in which the drug was to be delivered as a daily subcutaneous injection in up to 24 patients at 6 sites. Akebia Therapeutics, Inc., Cincinnati, OH Phase Ib/2a trial ongoing	Intravitreal triamcinolone acetonide with or without laser photocoagulation Laser photocoagulation Pharmacotherapy (e.g., vascular endothelial growth factor antagonists)	Improved visual acuity Halted loss of vision Increased contrast sensitivity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Imeglimin for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	Despite available treatments for T2DM, a need exists for more effective treatments. Imeglimin is an oral antidiabetes treatment in a new glimin class that acts by inhibiting mitochondrial oxidative phosphorylation. Researchers believe this mechanism of action decreases hepatic gluconeogenesis and muscle glucose uptake and increases pancreatic glucose-dependent insulin secretion. Imeglimin is also purported to be an indirect activator of adenosine monophosphate–kinase, which is thought to play a role in increasing muscle glucose uptake and lipid oxidation. Poxel S.A., Lyon, France Phase II trial completed	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Improved glycosylated hemoglobin (HbA_{1c}) levels Reduced hyperglycemic episodes Halted or delayed secondary complications
Implantable stimulator (Balance system) for treatment of type 2 diabetes	Patients with type 2 diabetes mellitus who do not have adequate glucose control	The Balance system is implanted to purportedly pace the duodenum to control contractions and change speed of food passage through digestive tract; electrical stimulation closes the pyloric sphincter to stop food from entering the duodenum causing early satiety. It also can speed transit through the duodenum, decreasing absorption, which is purported to lead to a decrease in blood glucose. Beta-Stim Ltd., Caesarea, Israel Phase I trial completed	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Achieved normal blood glucose levels Delayed or halted progression of disease Reduced secondary complications

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Inhaled insulin (Afrezza) for treatment of diabetes	Patients with type 1 or type 2 diabetes mellitus who require insulin injections	Inhaled insulin (Afrezza®) to control blood glucose levels. Afrezza is categorized as an ultra-rapid-acting insulin therapy to be taken at mealtime by individuals with type 1 or 2 diabetes who require exogenous insulin. This combination drug-device product uses a proprietary inhalation powder that has been pre-metered into single-use dose cartridges. The inhaler device is small and fits within the palm of the user's hand. MannKind Corp., Valencia, CA Phase III trials ongoing; in Mar 2010, FDA issued a complete response letter questioning whether the inhaler used in mid-phase trials was comparable to a new-generation inhaler that the company wants to market with the drug. In Jan 2011, company received a 2nd response letter outlining additional trials needed for approval; Aug 2011, 2 phase III trials were planned after manufacturer met with FDA; Oct 2012, manufacturer stated that enrollment has been completed for 2 phase III trials. These trials are not yet registered on National Clinical Trials database.	Dietary and lifestyle modifications Exenatide Insulin modifications Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Decreased blood glucose levels Better glycemic control Delayed or halted progression of complications Improved patient acceptance Improved quality of life
InsuPatch for improving insulin absorption in type 1 diabetes	Patients with type 1 diabetes mellitus who use an insulin pump	InsuPatch™ device is intended to improve insulin delivery into the blood by heating the area of the body around the point of insulin infusion; system includes a catheter that connects to the insulin pump, electrical contacts, and embedded wires. InsuLine Medical, Ltd., Petach-Tikvah, Israel Phase III trial completed; InsuLine intends to file a submission to the FDA for approval late in 2012	Insulin modifications	Improved insulin absorption Decreased frequency and severity of adverse events Avoided glycemic excursions
Leptin analog (Metreleptin) for treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus has been diagnosed	Metreleptin is an analog of human leptin; studied as treatment for obesity, type 2 diabetes mellitus, and severe lipodystrophy; leptin is a hormone secreted by fat cells that plays fundamental role in regulation of glucose metabolism. Preclinical studies indicate metreleptin decreases blood glucose levels, blood fats, and cholesterol. Drug is taken in addition to insulin. University of Texas Southwestern Medical Center, Dallas (in collaboration with Juvenile Diabetes Foundation, New York, NY, and Amylin Pharmaceuticals, Inc., San Diego, CA) Phase I trial ongoing	Insulin modifications Islet cell transplantation Pancreas transplantation	Better blood sugar control Improved lipid and cholesterol profile

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mitoglitazone (MSDC-0160) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	First-generation thiazolidinediones (TZDs) have been used for T2DM by actively binding to PPAR-gamma receptors, most notably decreasing insulin resistance and modifying adipocyte differentiation; however, these pharmacologic therapies have been associated with unwanted cardiovascular adverse effects. If approved, mitoglitazone could potentially replace existing TZDs. Mitoglitazone is a TZD displaying the positive effect of insulin sensitizers on blood glucose, serum lipids, and blood pressure, but it does so through a PPAR-gamma-sparing mechanism. Mitoglitazone does not directly activate these nuclear receptors and therefore may avoid the adverse side effects associated with 1st-generation TZDs, including edema, weight gain, and danger of congestive heart failure. Mitoglitazone has also shown the ability to turn committed precursor cells into functional brown fat, a specialized type of fat in the body that burns rather than stores fat. Metabolic Solutions Development Co., LLC, Kalamazoo, MI Phase IIa trial and phase IIb completed; manufacturer states that upon continued development of MSDC-0602 (in phase IIa development), another insulin sensitizer for T2DM treatment, mitoglitazone may be shifted to neurodegenerative disease treatment	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Decreased HA_{1c} levels Decreased fasting glucose levels Increased insulin sensitivity Decreased acute and secondary complications
Motilin agonist (GSK962040) for treatment of diabetes-related gastroparesis	Patients in whom gastroparesis resulting from type 1 or type 2 diabetes mellitus has been diagnosed	Current treatments for gastroparesis have significant side effects that can preclude long-term use or induce movement disorders; therefore, novel treatments for gastroparesis are needed. GSK962040 is a small-molecule, selective motilin agonist; activation of the motilin receptor is proposed to increase stomach wall contraction and thereby increase the rate of food passage. GlaxoSmithKline, Middlesex, UK Phase II trial completed; other phase II trials ongoing	Pharmacotherapy (e.g., antiemetic agents, erythromycin, metoclopramide)	Faster gastric emptying (as measured by the 13C-octanoic acid breath test) Improved gastric half emptying time

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Noninvasive skin measurement test (Scout DS) for screening for type 2 diabetes	Patients at risk of type 2 diabetes mellitus (T2DM)	About 7 million of the 25.8 million people in the U.S. with diabetes have not been screened and had the disease diagnosed. Late detection typically leads to secondary complications (e.g., cardiovascular disease, nephropathy, neuropathy) that could be prevented or delayed with earlier diagnosis. Late diagnosis may occur for many reasons, including patient nonadherence with recommended screening (blood draw). The Scout DS® 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, the skin fluorescence measurement is said to be converted into a Scout Diabetes Score in less than 4 minutes. This device is intended for individuals 18 years or older who are at risk of prediabetes and/or T2DM. VeraLight, Inc., Albuquerque, NM Late-phase testing completed on 5,000 patients; U.S. testing ongoing in 3,500 patients. Company expects to file for FDA approval in 2012; has Conformité Européene (CE) mark and Health Canada License approval	Standard blood glucose testing	Delayed or prevented secondary complications Increased screening adherence Increased rate of early diagnosis Improved quality of life
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. Joslin Diabetes Center, Boston, MA; various academic research centers Phase II/III trial completed; other phase II/III trials ongoing	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Achieved target glycosylated hemoglobin (HbA_{1c}) levels Desired fasting glucose level control Resolved insulin sensitivity

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oral insulin capsule (ORMD 0801) for treatment of type 1 or type 2 diabetes	Patients in whom type 1 or type 2 diabetes mellitus has been diagnosed	Adherence with insulin injections is suboptimal, leading to poor blood glucose control and acute and secondary complications of diabetes. ORMD 0801 is an oral formulation of insulin. Oramed Pharmaceuticals, Inc., Jerusalem, Israel Phase IIb trial completed	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Near-normal glucose targets Improved glycosylated hemoglobin (HbA_{1c}) levels Improved patient adherence with insulin regimen Reduced acute and secondary complications
Oral neuronalalpha-7 neural nicotinic receptor modulator (TC-6987) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	Inflammation has been implicated in the progression of T2DM following exposure of beta-islet cells to continuously high levels of glucose; however, no anti-inflammatory agents are approved for diabetes treatment. TC-6987 is an orally administered modulator of alpha-7 neural nicotinic receptor (NNR), which has been shown to play a role in controlling inflammation pathways; modulation of alpha-7 NNR has been shown to lead to a reduction in the production and release of proinflammatory cytokines. Administered in trials as a 10 mg daily, hard-gel capsule or as a 20 mg loading dose gel capsule followed by 10-mg daily dosing. Targacept, Inc., Winston Salem, NC Phase II completed	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Improved fasting glucose levels Achieved target glycosylated hemoglobin (HbA_{1c}) levels Decreased insulin sensitivity Delayed disease progression Avoidance of secondary complications of diabetes
Otelixizumab (TRX4) for early treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus has been diagnosed within the past 90 days	Otelixizumab is an anti-CD3 monoclonal antibody that preserves beta cell function if used early in the disease course; CD3-monoclonal antibodies bind to and inactivate cytotoxic T-lymphocytes, the cells that destroy beta cells. Additionally, CD3-monoclonal antibodies activate T cells, which helps control cytotoxic T-lymphocyte action. Tolerx, Inc., Cambridge, MA GlaxoSmithKline, Middlesex, UK Phase III trial completed; GlaxoSmithKline announced Mar 2011 that drug did not meet primary endpoint and stated it will explore additional dosing regimens to inform decisions about future clinical development of the compound	Insulin modifications Islet cell transplantation Pancreas transplantation	Improved C-peptide levels, which indicate beta cell function Improved glycemic control Daily insulin required Reduced side effects

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Peptide immune modulator (DiaPep277) for treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus (T1DM) has recently been diagnosed	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. Would be delivered as a vaccine in a physician's office rather than as a self-administered drug (or self-administered insulin). Andromeda Biotech, Ltd., Yavne, Israel Phase III trial complete; 2nd confirmatory phase III trial ongoing	Insulin modifications Islet cell transplantation Pancreas transplantation	Improved beta-cell function (measured as change from baseline in stimulated C-peptide secretion during a mixed-meal tolerance test) Increased glycemic control
PF-04523655 (PF-655) for treatment of diabetic macular edema	Patients in whom diabetic macular edema has been diagnosed	No therapies are approved drugs for treating diabetic macular edema, and 12% to 15% of patients still experience significant loss of visual acuity when using available diabetic macular edema treatments. PF-04523655 (RTP801I-14) is a small, interfering RNA directed against the *RTP-801* gene, which is believed to be involved in the development of abnormal blood vessels and vessel leakage in the eye and would represent a novel molecular target in diabetic macular edema treatment. Quark Pharmaceuticals, Inc., Fremont, CA, in cooperation with Pfizer, Inc., New York, NY Phase IIb trial completed; 1 phase IIb trial ongoing	Intravitreal triamcinolone acetonide with or without laser photocoagulation Laser photocoagulation Pharmacotherapy (e.g., vascular endothelial growth factor antagonists)	Improved visual acuity Halted loss of vision Improved contrast sensitivity Improved quality of life
Porcine-derived cell transplant (DiabeCell) for treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus (T1DM) has been diagnosed	DiabeCell® is a xenotransplantation therapy (i.e., animal-based transplant) using porcine pancreatic islet cells injected into the patient's abdomen. Because insulin-producing islet cells are destroyed in T1DM by an autoimmune response, replacing islet cells may improve glycemic control and overall disease management. The porcine islet cells in DiabeCell are coated with a biocapsule made of alginate gel that company claims will prevent rejection and eliminate the need for immunosuppressants. Living Cell Technologies, Ltd., Sydney, Australia Phase IIb trial completed late 2010; phase I/IIa trial on 10 patients completed in Russia; phase II trial ongoing in New Zealand	Insulin modifications Islet cell transplantation Pancreas transplantation	Reduced graft rejection Freedom from immunosuppressive drugs posttransplant Reduced insulin independence Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pulsed acoustic pressure device (dermaPACE) for treatment of diabetes-related foot ulcers	Patients in whom diabetic foot ulcers have been diagnosed	About 3 million patients a year develop diabetic foot ulcers; current treatments achieve complete healing less than 30% of cases; therefore, effective treatments are intended to accelerate and complete the wound healing process. The dermaPACE® device is intended to work by use of acoustic pressure waves that are purported to initiate a biologic response at the cellular level to try to stimulate production of angiogenic growth factors, including vascular endothelial growth factor, endothelial nitric oxide synthase, and proliferating cell nuclear antigen. This is asserted to lead to growth of newly formed vessels and increased cellular proliferation and tissue regeneration needed to heal a wound. Sanuwave, Inc., Alpharetta, GA Phase III trial completed; Dec 2011, FDA issued a major deficiency letter in response to the premarket approval application for dermaPACE; Sanuwave plans additional clinical trials.	Acellular wound matrices Cellular wound matrices Hyperbaric oxygen therapy Negative pressure wound therapy	Increased percentage of ulcers healed Shortened time to complete healing Reduced ulcer size Reduced incidence of gangrene Reduced incidence of amputation
Pyridoxamine (Pyridorin, BST-4001, K-163) for treatment of diabetic nephropathy	Patients with type 2 diabetes mellitus who have been given a diagnosis of diabetic nephropathy	Although a variety of treatments exist to manage symptoms of diabetic neuropathy, none of these address the underlying cause, and few can slow disease progression. Pyridorin™ is an oral pharmaceutical that targets pathogenic oxidative chemistries, including advanced glycation end-products, toxic carbonyls, and reactive oxygen species, which develop in patients with diabetes and are considered a principal causative factor in the development of diabetic microvascular disease. NephroGenex, Inc., Research Triangle Park, NC Phase II trials completed; company is seeking a partner for phase III development; Nov 2011, NephroGenex and FDA have agreed on design for Phase III trial; awarded fast track status by FDA	Dialysis (end-stage renal failure) Kidney transplantation (end-stage renal failure) Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors)	Reduced disease progression (as measured by serum creatinine and biomarkers) Improved renal function Reduced complications of diabetic nephropathy Increased survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ranibizumab (Lucentis) for treatment of diabetic macular edema	Patients in whom clinically significant diabetic macular edema has been diagnosed	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. Ranibizumab is being studied for diabetic macular edema (a new indication). Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Novartis International AG, Basel, Switzerland Positive results reported from 2 phase III trials; biologics license application submission was expected within 2011, but no action had been taken as of Jan 2012; in Nov 2011, UK National Health Service rejected coverage of the drug for this indication saying it did not meet its requirement for being cost-effective	Intravitreal triamcinolone acetonide with or without laser photocoagulation Laser photocoagulation Pharmacotherapy (e.g., vascular endothelial growth factor antagonists)	Improved vision Stabilized vision Reduced side effects of existing treatment Improved quality of life
Sodium-glucose cotransporter (LX4211) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	T2DM accounts for about 90% of diabetes cases globally, with incidence and prevalence rising. Many current treatments for T2DM help control glucose levels, but these treatments often come with significant side effects, which include gastrointestinal effects (e.g., nausea, diarrhea), weight gain, hypoglycemia, and edema. Additionally, many patients have difficulty achieving control of blood glucose with current treatments. LX4211 is an oral dual sodium-glucose cotransporter-2 (SGLT2), sodium-glucose cotransporter1 (SGLT1) inhibitor. Inhibition of SGLT2 might reduce glucose reabsorption and increase glucose excretion through urine, potentially reducing blood glucose without affecting insulin uptake and risking hypoglycemia. SGLT2 inhibitors are intended to be used with other oral agents and insulin and are without significant adverse effects. They also are believed to have potential to promote weight loss in overweight and obese patients. Lexicon Pharmaceuticals, Inc., The Woodlands, TX Phase II trial completed; achieved proof of concept	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Rapid improvement in glycemic control Improved blood pressure Improved triglyceride levels Weight loss

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Sodium-glucose cotransporter-2 inhibitor (ASP1941) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	T2DM accounts for about 90% of diabetes cases globally, with incidence and prevalence rising. Many current treatments for T2DM help control glucose levels, but these treatments often come with significant side effects, which include gastrointestinal effects (e.g., nausea, diarrhea), weight gain, hypoglycemia, and edema. Additionally, many patients have difficulty achieving control of blood glucose with current treatments. ASP1941 is a sodium-glucose cotransporter-2 (SGLT2) inhibitor that blocks the reabsorption of glucose in the kidney and increases its excretion in the urine. Inhibition of SGLT2 might reduce glucose reabsorption and increase glucose excretion through urine, potentially reducing blood glucose without affecting insulin uptake and risking hypoglycemia. SGLT2 inhibitors are intended to be used with other oral agents and insulin and are without significant adverse effects. They also are believed to have potential to promote weight loss in overweight and obese patients. Astellas Pharma, Inc., Tokyo, Japan Phase III trials ongoing in Japan	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Reduced blood glucose levels Weight loss
Sodium-glucose cotransporter-2 inhibitor (BI 10773) for treatment of type 2 diabetes	Patients with type 2 diabetes mellitus (T2DM) who have not achieved adequate blood glucose control	T2DM accounts for about 90% of diabetes cases globally, with incidence and prevalence rising. Many current treatments for T2DM help control glucose levels, but these treatments often come with significant side effects, which include gastrointestinal effects (e.g., nausea, diarrhea), weight gain, hypoglycemia, and edema. Additionally, many patients have difficulty achieving control of blood glucose with current treatments. BI 10773 is a sodium-glucose cotransporter-2 (SGLT2) inhibitor; because of their unique mechanism of action, SGLT2 inhibitors have a different safety profile from other agents traditionally used to treat T2DM. Inhibition of SGLT2 might reduce glucose reabsorption and increase glucose excretion through urine, potentially reducing blood glucose without affecting insulin uptake and risking hypoglycemia. SGLT2 inhibitors are intended to be used with other oral agents and insulin and are without significant adverse effects. They also are believed to have potential to promote weight loss in overweight and obese patients. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trial completed; phase III trials ongoing	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Improved glycosylated hemoglobin (HbA_{1c}) levels Delayed progression of complications

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Sodium-glucose cotransporter-2 inhibitor (canagliflozin) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	T2DM accounts for about 90% of diabetes cases globally, with incidence and prevalence rising. Many current treatments help control glucose levels, but these treatments often come with significant side effects, which include gastrointestinal effects (e.g., nausea, diarrhea), weight gain, hypoglycemia, and edema. Additionally, many patients have difficulty achieving control of blood glucose with current treatments. Canagliflozin is an inhibitor of sodium-glucose cotransporter-2 (SGLT2), a solute carrier predominantly found in the proximal convoluted tubule of the kidney cortex. Inhibition of SGLT2 might reduce glucose reabsorption and increase glucose excretion through urine, potentially reducing blood glucose without affecting insulin uptake and risking hypoglycemia. SGLT2 inhibitors are intended to be used with other oral agents and insulin and are without significant adverse effects. They also are believed to have potential to promote weight loss in overweight and obese patients. Johnson & Johnson, New Brunswick, NJ Phase III trials ongoing	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Near-normal glycosylated hemoglobin (HbA_{1c}) levels Weight loss Fewer hypoglycemic events Halted or delayed acute and secondary complications
Sodium-glucose cotransporter-2 inhibitor (dapagliflozin) for treatment of type 2 diabetes	Patients with type 2 diabetes mellitus (T2DM) who have not achieved adequate blood glucose control with metformin	T2DM accounts for about 90% of diabetes cases globally, with incidence and prevalence rising. Many current treatments help control glucose levels, but often come with significant side effects, which include gastrointestinal effects (e.g., nausea, diarrhea), weight gain, hypoglycemia, and edema. Additionally, many patients have difficulty achieving control of blood glucose with current treatments. Dapagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor. Inhibition of SGLT2 might reduce glucose reabsorption and increase glucose excretion through urine, potentially reducing blood glucose without affecting insulin uptake and risking hypoglycemia. SGLT2 inhibitors are intended to be used with other oral agents and insulin and are without significant adverse effects. They also are believed to have potential to promote weight loss in overweight and obese patients. Drug is taken orally, once a day. Bristol-Myers Squibb, New York, NY AstraZeneca, London, UK In Jan 2012 FDA rejected dapagliflozin for this indication and issued a complete response letter to the company.	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Achieved target glycosylated hemoglobin (HbA_{1c}) levels Weight loss Decreased hypoglycemic events Halted or delayed secondary complications of diabetes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Sodium-glucose cotransporter-2 inhibitor (tofogliflozin) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	T2DM accounts for about 90% of diabetes cases globally, with incidence and prevalence rising. Many current treatments for T2DM help control glucose levels, but these treatments often come with significant side effects, which include gastrointestinal effects (e.g., nausea, diarrhea), weight gain, hypoglycemia, and edema. Additionally, many patients have difficulty achieving control of blood glucose with current treatments. Tofogliflozin inhibits sodium-glucose cotransporter-2 (SGLT2), a solute carrier predominantly found in the proximal convoluted tubule of the kidney cortex. Inhibition of SGLT2 might reduce glucose reabsorption and increase glucose excretion through urine, potentially reducing blood glucose without affecting insulin uptake and risking hypoglycemia. SGLT2 inhibitors are intended to be used with other oral agents and insulin and are without significant adverse effects. They also are believed to have potential to promote weight loss in overweight and obese patients. Chugai Pharmaceuticals Co., Ltd., Tokyo, Japan Phase III trial ongoing	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Near-normal glycosylated hemoglobin (HbA_{1c}) levels Weight loss Decreased hypoglycemic events Halted or delayed acute and secondary complications
Sodium-glucose cotransporter-2 inhibitor (TS-071) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	T2DM accounts for about 90% of diabetes cases globally, with incidence and prevalence rising. Many current treatments for T2DM help control glucose levels, but these treatments often come with significant side effects, which include gastrointestinal effects (e.g., nausea, diarrhea), weight gain, hypoglycemia, and edema. Additionally, many patients have difficulty achieving control of blood glucose with current treatments. TS-071 is an inhibitor of sodium-glucose cotransporter-2 (SGLT2), a solute carrier predominantly found in the proximal convoluted tubule of the kidney cortex. Inhibition of SGLT2 is purported to reduce glucose reabsorption and increase glucose excretion through urine, potentially reducing blood glucose without affecting insulin uptake and risking hypoglycemia. SGLT2 inhibitors are intended for use with other oral agents and insulin and are without significant adverse effects. They also are believed to have potential to promote weight loss in overweight and obese patients. Taisho Pharmaceutical Co., Ltd., Tokyo, Japan Phase III trial ongoing, although trial is not registered in National Clinical Trials database	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Near-normal glycosylated hemoglobin (HbA_{1c}) levels Weight loss Fewer hypoglycemic events Halted or delayed acute and secondary complications

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Subconjunctival insert (EyeSense) for blood glucose monitoring	Patients with diabetes who require regular glucose monitoring	Options to improve patients' self blood-glucose monitoring are needed to improve adherence with treatment regimen and management of diabetes. The EyeSense system has 2 components; ophthalmologists implant a small sensor below the conjunctiva of the patient's eye in a short office-based procedure; the implantable sensor calculates blood glucose in the subconjunctival interstitial fluid; to take readings, patients place a small handheld device near the implantable sensor to read transmitted fluorescent light signals. EyeSense GmbH, Grosssostheim, Germany Phase II trial ongoing (in Germany); unknown when/if U.S. trials will be undertaken	Standard blood-based glucose monitors	Improved adherence with glucose testing Better management of blood glucose levels
Transmembrane protein antagonist (Nexagon) for treatment of type 2 diabetes–associated leg ulcers	Patients with venous leg wounds and foot ulcers associated with type 2 diabetes mellitus (T2DM)	Current treatments for leg wounds have been largely ineffective and may not improve patient quality of life. Nexagon™ is a gel acting as an antagonist to connexin-43, a gap junction protein that may be overproduced and may cause chronic delay of wound healing. If proven effective, this connexin-43 antagonist could potentially serve as 1st-line therapy for treating chronic wounds for patients with T2DM. Nexagon is administered topically (1 or 3 mg/mL used with compression dressings). CoDa Therapeutics, Inc., San Diego, CA Phase II trial completed; phase II trials ongoing	Pharmacotherapy (e.g. corticosteroids) Surgery intervention (e.g., vascular surgery)	Reduction of wound size Complete healing of venous leg wounds and foot ulcers Improved mobility Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Triolex anti-inflammatory (HE3286) for treatment of obesity-induced type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	Research has implicated inflammation in the development of insulin resistance associated with T2DM; however, no anti-inflammatory treatments for obesity-induced T2DM are available. Triolex® is an oral, steroid anti-inflammatory whose mechanism of action may involve inhibition of the MAPK and NFκB pathways, specifically when the TLR4 and TNFα receptors stimulate these pathways. These pathways are a main component of the type-2 diabetes syndrome characterized by the presence of a chronic inflammatory state. The company states that Triolex is believed to be the 1st in a new class of insulin sensitizers to target obesity-mediated dysregulated metabolism. Harbor BioSciences, Inc., San Diego, CA Phase IIa trial completed and did not reach primary endpoints, but a reanalysis of data under FDA's guidance examined body mass index (BMI) impact on response to the treatment and showed that the drug showed signs of activity in treatment-naïve chronically inflamed, obese diabetes patients as both a single agent and when taken in combination with metformin. Company stated having limited financial resources as of Dec 31, 2011, and is looking to merge with or license its compounds to other companies.	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Improved blood glucose levels Reduced glycemic excursions
Ultra-long-acting insulin (Degludec) for treatment of type 2 diabetes	Patients with type 2 diabetes mellitus who require oral medication, insulin, or both	Degludec releases over several days; flexible dosing regimen allows 8–40 hours between dosing, which could lead to thrice-weekly dosing, or dosing once in the evening; may also be combined with insulin aspart (NovoMix 30) to form DegludecPlus. Novo Nordisk a/s, Bagsvaerd, Denmark Phase IIIa trials completed for Degludec and DegludecPlus; phase III trial initiated May 2011; Sept 2011, Novo Nordisk filed new drug applications with the FDA for Degludec and DegludecPlus	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Achieved target glycosylated hemoglobin (HbA_{1c}) levels Reduced progression of complications Improved quality of life

Table 8. AHRQ Priority Condition: 08 Functional Limitations and Disability: 171 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
1-deoxyno-jirimycin (AT2220) co-administered with enzyme replacement therapy for Pompe disease	Patients in whom late-onset Pompe disease has been diagnosed	Pompe disease is a rare genetic disorder that results in a deficiency in alpha-glucosidase activity, leading to progressive muscle weakness and respiratory insufficiency. Current enzyme replacement therapies have multiple shortcomings, including minimal efficacy in skeletal muscle, short half-life, poor cellular uptake, and induction of allergic reactions. AT2220 acts to promote the proper folding of alpha-glucosidase, potentially increasing the effectiveness of enzyme replacement therapy and/or increasing the activity of endogenous mutant protein. Amicus Therapeutics, Inc., Cranbury, NJ Phase II trial ongoing	Standard alpha-glucosidase enzyme replacement therapy (Myozyme, Lumizyme) without AT2220	Decreased muscle atrophy, increased strength and function Improved pulmonary function and/or ventilation conditions Reduced cardiomyopathy Reduced fatigue Improved quality of life
3-Dimensional printed titanium jaw implant for lower jaw replacement	Patients needing reconstructive jaw surgery because of a severe health condition (i.e., osteomyelitis, facial trauma, tumor)	3-Dimensional (3-D) printing technology has existed for decades, but recently has been investigated for medical uses, particularly surgical use. Particularly in cases where reconstructive surgery could lead to poor patient outcomes, 3-D printed implants might offer a viable option. The 1st titanium jaw was created using 3-D printing technology and implanted in an 83-year-old woman with osteomyelitis. This procedure was a 4-hour surgery using a patient-specific jaw implant, replacing the entire lower jaw. The implant has articulated joints and cavities to promote muscle attachment and grooves to direct nerve and vein regrowth. A 3-D printed lower jaw is made with titanium powder, melting and fusing thin titanium powder layers with a high-powered laser and coating the implant with bioceramics for implant compatibility with host body tissue to prevent graft rejection. Once transplantation is complete, a set of dentures can be screwed into preset holes on the implant. BIOMED Research Institute at Hasselt University, Diepenbeek, Belgium, in collaboration with LayerWise NV, Leuven, Belgium First-in-human trial (1 woman)	Reconstructive jaw surgery	Reduced morbidity Shorter recovery times Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Adenosine 2A antagonist (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. SYN115 is an oral, adenosine 2A (A2A) receptor antagonist intended to increase “on” time for patients taking levodopa; the striatopallidal output pathway synthesizes gamma aminobutyric acid (GABA) and enkephalin as neurotransmitters and expresses the A2A subtype of adenosine receptors. Pharmacologic inhibition of A2A adenosine receptors may inhibit the overactive striatal GABAergic blocking of neurons associated with PD. Biotie Therapies Corp., Turku, Finland Phase II/III trial ongoing	Adenosine A2A receptor antagonist in development Dopamine agonists Glutamate receptor 5 modulators in development Levodopa/carbidopa Monoamine oxidase-B inhibitors Nicotinic receptor agonist in development	Improved motor skills Improved symptoms Reduced disease progression Reduced incidence/severity of levodopa-induced dyskinesia Improved quality of life
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 claimed to last for more than 1 year; once-yearly treatment regimen (once a day for 5 days) via intravenous administration. The drug is FDA approved for treating refractory chronic lymphocytic leukemia. Genzyme Corp., Cambridge, MA Phase III trial ongoing; submitted new drug application to FDA in Jun 2012; FDA issued refusal to file Aug 27, 2012, stating a need for data reorganization	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Reduced frequency of relapse Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Allogeneic liver cell infusion as bridge to liver transplant for treatment of urea cycle disorders	Patients in whom a genetic-based urea cycle disorder has been diagnosed	Urea cycle disorders are a family of genetic disorders in which patients lack 1 of the enzymes required for conversion of ammonia to urea; ammonia builds up, causing significant morbidity and possible mortality. Patients with urea cycle disorders have a 10-year survival rate of less than 50% using current pharmaceutical and dietary treatments. Patients receiving successful liver transplants have a survival rate of more than 90%; however, liver transplantation in patients 5 years of age or younger is technically difficult. Effective treatments are needed that could allow control of disease symptoms in young patients until transplantation is possible. This treatment is intended for patients between birth and 5 years of age as a bridge to a definitive liver transplantation, which in many cases resolves the disorder. Allogeneic liver cell infusion is intended to temporarily populate the liver with cells that can provide a sufficient level of enzymatic activity to reduce ammonia levels to manageable levels. Cells are isolated from livers from the transplant pool that were determined to be unsuitable for whole liver transplant, and then infused over the course of 6 days. Cytonet GmbH & Co., KG, Weinheim, Germany Phase II trials ongoing in U.S. and Europe	Ammonia scavengers (sodium phenylbutyrate, sodium benzoate) Dietary therapy Urea cycle enzyme catalysts (L-citrulline, L-arginine)	Changes in 13C urea formation Reduced frequency and severity of metabolic crises
ALN-TTR01/RNAi for treatment of *TTR*-mediated amyloidosis	Patients in whom ATTR amyloidosis has been diagnosed	ATTR (familial) amyloidosis affects the heart, nerve system, and other organs. Currently, the only treatment for amyloidosis is liver transplantation, which is not an option for many patients with ATTR amyloidosis. An effective pharmacologic treatment could reduce or possibly postpone the need for transplantation. ALN-TTR is an infused RNAi therapeutic that targets the transthyretin (*TTR*) gene to treat ATTR. ALN-TTR01 prevents pathogenic TTR deposits in peripheral tissues, including dorsal root ganglia, sciatic nerve, stomach, and intestines, by silencing the *TTR* gene and serum levels of TTR. Alnylam Pharmaceuticals, Cambridge, MA Phase I trial completed	Liver transplantation	Reduced TTR deposits Improved function of cardiac and nervous tissues Reduced symptoms of amyloidosis (variable) Reduced need for liver transplant Improved survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Alpha-tocopherol quinone (EPI-A0001) for treatment of Friedreich's ataxia	Patients in whom Friedreich's ataxia (FA) has been diagnosed	FA is an autosomal nDNA inherited mitochondrial disease that globally affects about 50,000 individuals; it is a progressively debilitating disease and patients typically present with energy failure symptoms including heart failure, ataxia, diabetes, and visual and hearing deficiencies. FDA has not approved any drugs for treating FA. EPI-A0001 is a coenzyme Q10 analog that was shown to improve mitochondrial energy production and reduce oxidative stress in yeast cells by buffering free radical formation that is induced by excess mitochondrial iron. EPI-A0001 is administered orally, 1.0 or 1.5 g total daily dose, twice daily. Edison Pharmaceuticals, Inc., Mountain View, CA Phase IIa trial completed; FDA granted orphan drug and fast track status	Behavioral and physical therapy	Improved neurologic function (assessed by Friedreich's Ataxia Rating Scale) Improved quality of life
Amino-benzothiazole (dexpramipexole) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	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. Dexpramipexole likely represents a new mechanism of action for this disease state. Dexpramipexole is a synthetic amino-benzothiazole; (R)-(+) enantiomer of pramipexole (high-affinity dopamine agonist, already approved for Parkinson's disease and restless leg syndrome, but would be dosed at very high levels for ALS); its mechanism of action is unknown, but may be related to its ability to increase the efficiency of mitochondria, which undergo significant stress in patients with ALS. Dosed orally, daily. Biogen Idec International GmbH, Zug, Switzerland Knopp Bioscience, Pittsburgh, PA Phase III trial ongoing; FDA granted fast track and orphan drug status	Riluzole Supportive care	Increased survival Delayed disease progression Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ampakine (CX-1739) for treatment of obstructive sleep apnea	Patients in whom obstructive sleep apnea (OSA) has been diagnosed	No pharmacotherapies are FDA approved for treating OSA; standard therapy (continuous positive airway pressure [CPAP]) has a low adherence rate; a pharmaceutical intervention has the potential to increase adherence with therapy. CX-1739 is a "low impact" ampakine that has specificity for the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (subtype of glutamate receptor) and lowers the amount of neurotransmitter required to generate a response, thereby increasing the amplitude of the response to glutamate. It may have utility in disorders characterized by reduced functioning of the glutamatergic pathways, and research has shown a relationship between glutamate levels and OSA. Cortex Pharmaceuticals, Inc., Irvine, CA Phase IIa trial ongoing	Standard therapy (e.g., CPAP) Oral appliances (e.g., mouth guards) Surgical therapy	Increased glutamate activity Improved respiratory parameters Improved cognition Improved sleep quality Improved quality of life
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 following 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 dietary, lifestyle, stress management, and self-awareness treatments. Stress tools and techniques are performed for a minimum of 30 minutes a day in 1 sitting (meditation, "soften and flow," alternate nostril breathing), along with some neurolinguistic-programming, 30-2nd 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. Ashok Gupta, holistic medicine practitioner, London, UK Ann Vincent, M.D., Mayo Clinic, Rochester, MN Trial completed (unphased); sold as a proprietary program; currently clinically implementable	Behavioral and lifestyle modifications Psychotherapy Pharmacotherapy (e.g., antidepressants, sleeping aids)	Improved ability to perform daily activities Reduced symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 following 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 1 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. Ashok Gupta, holistic medicine practitioner, London, UK Ann Vincent, M.D., Mayo Clinic, Rochester, MN Trial completed (unphased); sold as a proprietary program; currently clinically implementable	Pharmacotherapy (e.g., duloxetine, fluoxetine, gabapentin, lorazepam, milnacipran, pregabalin, tricyclic antidepressants Behavioral and lifestyle modification	Improved ability to perform daily activities Reduced symptoms Improved quality of life
Antisense molecule (ISIS-SMNRx) for treatment of spinal muscular atrophy	Children in whom spinal muscular atrophy (SMA) has been diagnosed	SMA is an inherited neuromuscular disease in which muscles atrophy and weaken, and it often results in death of infants born with the most severe form of the disorder. SMA occurs in an estimated 1 in 10,000 live births worldwide. Affected infants typically appear normal at birth, and symptoms develop within several months after birth. Current SMA treatments address disease symptoms only; treatments are needed that address the underlying cause of disease. ISIS-SMNRx is an antisense molecule that is purported to boost levels of survival motor neuron 1 protein by addressing an RNA splicing irregularity. Low levels of survival motor neuron 1 protein are purported to lead to the development of SMA. An ongoing trial is enrolling children aged 2–14 years who are medically stable; the drug is administered during a single injection of 1 of 4 dosage levels into the spinal cord fluid. ISIS Pharmaceuticals, Inc., a unit of Johnson & Johnson, Inc., New Brunswick, NJ Biogen Idec International GmbH, Zug, Switzerland Phase I trial ongoing; FDA granted fast track and orphan drug status	Supportive care	Reduced symptoms Improved motor function Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous bone marrow progenitor cells for treatment of traumatic brain injury in children	Children aged 5–14 years in whom severe traumatic brain injury (TBI) (Glasgow coma score between 5 and 8) has been diagnosed	Children who survive severe TBI typically experience significant physical and cognitive disability; no effective treatments protect or promote repair of the brain in children who have experienced TBI. This procedure involves harvesting bone marrow from the hip very soon after hospital admission for acute TBI; collected bone marrow is taken to a specialized center to isolate the mononuclear fraction and process it; the bone marrow–derived mononuclear cells are then reinfused intravenously within 48 hours of the TBI injury, The intention is to have these cells migrate to the site of brain injury and differentiate into neurons and cell-supporting elements to try to improve functional outcomes. University of Texas Health Science Center at Houston Medical School Phase I trial completed with 10 patients; procedure performed under an investigational new drug process because of the manipulation of the cells	No effective treatments are available to protect or promote repair of the brain in TBI-injured children	Reduced adverse neurologic events (seizures, change in Glasgow coma scale, cerebral vascular accident) Reduced disability Reduced infectious morbidity and secondary organ injury Improved cognitive function
Autologous cell preparation and spraying system (ReCell) for treatment of burn wounds	Patients in need of therapy for skin burns	About 2.4 million burn injuries are reported each year in the U.S., with 75,000 patients being hospitalized for their burns. About 1 million will sustain substantial or permanent disabilities resulting from their burn injuries. Current therapies have varying degrees of efficacy, warranting development of novel treatments. The ReCell® Spray-On Skin™ is a rapid, autologous, cell-harvesting, processing, and delivery technology that uses epithelial cells from the patient in a regenerative process, spraying a sheet of these cultured cells directly on the wound site, which purportedly accelerates healing, minimizes scar formation, eliminates tissue rejection, and rehabilitates skin pigmentation. Avita Medical, Ltd., Cambridge, UK Phase II trial ongoing	Cultured epithelial autograft Donor stem cell transplantation and skin printing Wound débridement	Improved would healing Decreased postsurgical blister and skin damage Improved quality of life
Autologous knee bone and cartilage transfer for surgical treatment of wrist injuries	Patients with wrist fractures, chronic wrist pain, and ligament tears that require surgical intervention	About 1/6 of fractures evaluated in U.S. emergency rooms are wrist fractures. Some wrist injuries are unstable, with ligament tears and dissociation of the wrist bones. Conventional ligament reconstruction surgery often does not alleviate pain, warranting the need for better surgical procedures. Knee bone and cartilage transfer represent an innovative surgical procedure that involves resecting, shaping, and transferring the patient's own cartilage-bearing bone from the knee to the wrist, with the intent of eliminating the previously existing gap caused by the torn ligament(s). Union Memorial Hospital's Curtis National Hand Center, Baltimore, MD First reported procedure completed Aug 2011	Conventional ligament reconstruction surgery	Decreased wrist pain Decreased risk of wrist arthritis Improved wrist function Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous mesenchymal stem cell therapy (NurOwn) for amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis has been diagnosed	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™ differentiated autologous adult stem cell therapy form bone marrow–derived mesenchymal stems cells. Using the technology, clinicians collect adult human mesenchymal stem cells from the patient's autologous bone marrow and process the cells in vitro. In the proprietary process, the cells are intended to differentiate into astrocyte-like cells capable of releasing neurotrophic factors, including glial-derived neurotrophic factor. The cells are reinfused through either a single intrathecal injection into the cerebrospinal fluid or multiple intramuscular injections into the biceps or triceps. BrainStorm Cell Therapeutics, Inc., New York, NY Phase II trial ongoing; FDA granted orphan drug status in Feb 2011; company stated intention to pursue FDA regulatory approval	Riluzole Supportive care	Slowed disease progression Maintained independence and activities of daily living Improved quality of life
Autologous stem cell transplantation for facial reconstruction after osteoradionecrosis and other advanced craniofacial diseases	Patients in whom late stage osteoradionecrosis (ORN) has been diagnosed	ORN is defined as a condition of nonvital bone at a site of injury from radiotherapy; ORN can be spontaneous, but most often results from tissue injury; existing treatment options are palliative or limited in restorative capacity. In this therapy, bone marrow is harvested from the patient, cultured and incubated in a fibrin- and platelet-rich medium for 12 days. The mix of cultured bone marrow cells (stem and progenitor) is transplanted into the patient in an effort to regenerate damaged nerve, bone, skin, and vessels from maxillary and mandibular ORN (hard and soft tissue). POLUSA Hospital, Lugo, Spain Pilot trial completed	Other forms of craniofacial reconstruction Allografts Mechanical devices Vascularized and nonvascularized tissue transfers	Restored form and function (masticatory) Resolved fistulas, trismus, xerostomia Resolved chronic pain

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Balloon angioplasty and/or stenting of azygos and internal jugular vein for treatment of multiple sclerosis	Patients with multiple sclerosis (MS) who exhibit evidence of chronic cerebrospinal venous insufficiency (CCSVI)	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 vein, is hypothesized to play a role in the etiology, disease progression, and/or pathogenesis of MS. Image-guided interventional endovascular management is a procedure in which an interventional radiologist performs percutaneous transluminal angioplasty using either an angioplasty balloon and/or stent to improve circulation/reduce hypoperfusion of brain parenchyma to relieve MS symptoms. Procedure uses existing technologies and is in early diffusion in Europe and U.S.; 1st reported by University of Ferrara, Italy Clinical trials under way to further assess validity	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Improved cognitive and motor function Reduced relapse Reduced lesions on imaging Improved quality of life
Beta-3 adrenoceptor agonist (Mirabegron) for treatment of overactive bladder	Patients in whom overactive bladder leading to urinary incontinence has been diagnosed	Current therapeutic approaches for overactive bladder have a poor side-effect profile and are generally not very effective. Mirabegron is a selective beta-3 adrenoceptor agonist that is purported to relax bladder smooth muscles, potentially allowing bladder filling and urine storage. Drug is administered orally. Astellas Pharma, Inc., Tokyo, Japan FDA approved Jun 2012 extended-release tablets for treating overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency	Pharmacotherapy (e.g., darifenacin, oxybutynin, oxybutynin skin patches, solifenacin, tolterodine, trospium) Onabotulinum toxin A Sacral nerve stimulation Surgical therapy Behavioral and lifestyle modifications	Decreased urge to urinate Decreased urination episodes per week Improved International Consultation on Incontinence Questionnaire-Overactive Bladder score Improved quality of life
Bioabsorbable bupivacaine implant (XaraColl) for postsurgical pain relief	Patients who undergo hysterectomy	Current therapeutic approaches for postsurgical pain relief include local analgesics; however, a need exists for more effective treatments. Implant (XaraColl®) intended to deliver localized pain relief after surgery; implant is biodegradable and bioabsorbable matrix of purified fibrillar collagen filled with local anesthetic bupivacaine. Innocoll, Inc., Ashburn, VA Phase II trials ongoing; several phase II trials completed; phase III trial planned	Pharmacotherapy (e.g., opioids, nonsteroidal anti-inflammatory drugs)	Improved localized pain relief Fewer side effects (e.g., nausea, constipation, dependence) compared to systemic postsurgical pain relief modalities

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bioartificial liver system (Excorp Medical) for fulminant hepatic failure	Patients with fulminant hepatic failure (acute liver failure) awaiting a liver transplant	Extracorporeal bioartificial liver support systems are intended to replace lost liver function, such as the synthesis of metabolic enzymes and key proteins (e.g., blood clotting factors), while a transplant candidate awaits a donor liver. Cell-based liver support systems add a "bioreactor" filter cartridge to standard liver dialysis systems that temporarily remove blood from the body to remove circulating toxins. For its bioreactor component, this bioartificial liver system uses porcine hepatocytes harvested from a controlled animal herd. Excorp Medical, Inc., St. Paul, MN Phase I/II trial ongoing; granted orphan product status by FDA	Pharmacotherapy (e.g., antibiotics and lactulose) Liver transplantation	Improved survival
Bioartificial liver system (Extracorporeal Liver Assist Device) as bridge to 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 remove 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. ELAD is regulated as a combination biologic by FDA's Division of Cellular, Tissue and Gene Therapy in the Center for Biologics Evaluation and Research. Vital Therapies, Inc., San Diego, CA Phase II/III trial completed; phase III pivotal trial being planned	Pharmacotherapy (e.g., antibiotics and lactulose) Liver transplantation	Improved rate of 30-day transplant-free survival
Bioartificial liver system (Extracorporeal Liver Assist Device) for management of fulminant hepatic failure	Patients in whom fulminant hepatic failure (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 remove 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. Vital Therapies, Inc., San Diego, CA Phase II trials completed; 1 phase II trial recently withdrawn to focus on another indication	Pharmacotherapy (e.g., antibiotics and lactulose) Liver transplantation	Improved survival for liver transplant patients awaiting a donor liver

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	Buprenorphine is an opioid that is used in current formulations for treating opioid addiction 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 check for buccal delivery. The technology was FDA approved for use with fentanyl and is under development for delivery of buprenorphine. BioDelivery Sciences International, Raleigh, NC Phase III trial completed; 2nd phase III trial planned; company anticipated filing new drug application in 1st half of 2012	Pharmacotherapy (e.g., COX-2 inhibitors, Buprenex, nonsteroidal anti-inflammatory drugs, opioids)	Reduced pain Reduced risk of addiction
BreathID test to monitor liver function	Patients at risk of or in liver failure	Breath test (BreathID®) is intended to monitor liver function; theory is that breath test could give additional liver function assessment not available with blood tests. The test requires a patient to breathe into a device and is administered in the physician's office. The company purports to provide a novel diagnostic option in patients with impaired liver function. Exalenz Bioscience, Inc., Modi'in, Israel Phase III trials ongoing in Israel; approved to detect *Helicobacter pylori* infection	Liver function blood tests	Improved patient comfort Increased adherence with liver function testing Earlier detection of liver function problems
Bupivacaine extended-release liposome injection (Exparel) for treatment of postsurgical pain	Patients who have undergone soft-tissue or orthopedic procedures and require local anesthesia postsurgery	Local analgesics such as bupivacaine have been successfully used for many years in the management of postsurgical pain; however, their activity is of limited duration (about 7 hours); a need exists for a long-acting nonopioid postsurgical analgesic. Exparel® is a formulation of bupivacaine that is an extended-release liposome injection that uses Pacira's DepoFoam® technology; it is intended to provide up to 72 hours of post-surgical analgesia. Pacira Pharmaceuticals, Inc., Parsippany, NJ Oct 2011, the manufacturer announced the FDA's approval of this therapy for treating postsurgical pain	Pharmacotherapy (e.g., opioids, nonsteroidal anti-inflammatory drugs)	Reduced pain on visual analog pain scale Reduced need for other pain medication

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Caspase-1 inhibitor (VX-765) for treatment of partial-onset epilepsy	Patients in whom treatment-resistant partial-onset epilepsy has been diagnosed	Some patients with partial-onset epilepsy are not responsive to current therapy; use of anti-inflammatory medication is a novel approach to treat this condition. VX-765 is intended to inhibit caspase-1, which is an enzyme involved in the production of interleukin-1-beta (IL-1-beta); both induction of caspase-1 and activation of IL-1-beta occur in human epilepsy. In clinical trials, is being dosed orally at 900 mg, 3 times per day, while patients continue to receive standard therapy. Vertex Pharmaceuticals, Inc., Cambridge, MA Phase II trial completed; phase IIb trial ongoing	Pharmacotherapy (e.g., lamotrigine, levetiracetam, tiagabine, tricyclics, valproate)	Reduced frequency of partial-onset seizures Improved quality of life
CF101 for treatment of moderate to severe dry-eye syndrome	Patients in whom moderate to severe dry-eye syndrome has been diagnosed	Immunomodulatory effect of adenosine receptor agonist (CF101) inhibits inflammatory cytokine production and auto-regulatory T-cell proliferation; CF-101 is intended to relieve symptoms and reduce intraocular pressure. Tablets were taken orally for 12 weeks as monotherapy in phase II trial. Can-Fite BioPharma, Ltd., Petah-Tikva, Israel Phase III trial ongoing	Pharmacotherapy (e.g., antibiotics, corticosteroids, Restasis, Lacrisert)	Improved corneal fluorescein staining (a measure of ocular surface inflammation) Increased tear production Improved dry-eye symptom score
Clip-on smart phone device (Catra) for detection of cataracts	Patients at risk of developing cataracts	Cataracts are the leading cause of blindness, accounting for about 48% of cases of blindness. Late detection has resulted in cataract progression to the point of blindness, particularly in rural and more disadvantaged areas in the U.S. and globally. Current diagnostic tools are expensive and may not accurately detect cataracts, particularly in earlier stages of disease. The smart phone device (Catra) is a clip-on device intended for use by a clinician; it emits beams of light that sweep across the eye to detect cloudy patches formed in the eye as a result of cataracts. The beams of the device are focused to the same point on the fovea, also known as the maximum resolution area of the retina. Catra depends on light passing through the lens, as indicated by the patient, who notifies the doctor if the point of light remains steady, dims, or disappears. The device may also map the size, position, shape, and density of the cataract. It may also detect cataracts at earlier stages, particularly because it detects changes in the lens caused by cataracts that haven't yet become opaque. Massachusetts Institute of Technology, Cambridge, MA Pilot trial completed	Catatrac (handheld device) Ocular tonometry Slit lamp exam Visual acuity exam	Reduced incidence of blindness from cataracts Improved daily activity functioning Reduced need for services required to support people with blindness Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
CM2489 calcium release-activated calcium channel inhibitor for treatment of psoriasis	Patients in whom moderate to severe plaque psoriasis has been diagnosed	Current treatments for psoriasis include pharmacotherapy and phototherapy; however, the disease does not respond adequately to the therapy for all affected patients. More effective treatment options are needed. CM2489 is a 1st-in-class inhibitor of calcium release-activated calcium (CRAC) channels. CRAC channels are central mediators of immune cell response through calcineurin/NFAT, which leads to cytokine production and lymphocyte proliferation. Downregulation of these proinflammatory signals is proposed as a treatment for psoriasis. CalciMedica, La Jolla, CA Phase I trial completed	Topical ointments such as: Anthralin Calcineurin inhibitors Coal tar Corticosteroids Phototherapy Systemic medications: Cyclosporin Hydroxyurea Immunomodulators Methotrexate Retinoids Thioguanine	Improved psoriasis severity index scale scores Improved quality of life
CNV2197944 for treatment of chronic neuropathic pain	Patients in whom chronic neuropathic pain has been diagnosed	Current pain medications are not effective in all patients and are associated with significant side effects such as the potential for addiction and gastrointestinal complications. CNV2197944 is a novel, small-molecule, calcium-channel blocker specific for the cav2.2 ion channel, which has been implicated in the pathogenesis of pain. Convergence Pharmaceuticals, Ltd., Cambridge, UK Phase I trial ongoing	Pharmacotherapy (e.g., opioids, nonsteroidal anti-inflammatory drugs)	Reduced pain Improved quality of life
Collagenase clostridium histolyticum (Xiaflex) for treatment of Peyronie's disease	Men in whom Peyronie's disease has been diagnosed	Peyronie's disease is the development of a collagen plaque that causes the penis to curve while erect; treatments for Peyronie's disease are experimental or require surgical correction. Collagenase clostridium histolyticum (Xiaflex®) is a locally injected protein mixture that is intended to disrupt the collagen plaques. Xiaflex has been approved for treating the hand disorder Dupuytren's contracture. Auxilium Pharmaceuticals, Inc., Malvern, PA Phase III trial completed	Surgical therapy Interferon local injections Verapamil local injections	Change in penile curvature from baseline Improved Peyronie's Disease Questionnaire (PDQ) score

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Combination bioreactor, cell spraying, and wound support system for treatment of burn wounds	Patients in need of therapy for skin burns	About 2.4 million burn injuries are reported each year in the U.S., with 75,000 patients being hospitalized for their burns. About 1 million will sustain substantial or permanent disabilities resulting from their burn injuries. Current therapies have varying degrees of efficacy, warranting development of novel treatments. A 3-phase approach to regenerative skin therapy is proposed for burn treatment: in phase I, clinicians prepare a skin cell mix, including a patient's skin stem cells, that is intraoperatively isolated and directly applied (using a bioreactor to breed the cells); in phase II, clinicians use a specialized spray gun to apply a sheet of single cultured stem cells directly onto the wound; in phase III, the wound is dressed with a bioreactor bandage that distributes glucose, amino acids, antibiotics, and electrolytes to the wound area. The system purportedly improves cell regeneration significantly in a faster time than current therapies while mitigating skin damage. McGowan Institute for Regenerative Medicine (in collaboration with the University of Pittsburgh Department of Surgery), Pittsburgh, PA One patient received treatment (Berlin Burn Center, Germany)	Cultured epithelial autograft Donor stem cell transplantation and skin printing Wound débridement	Improved wound healing Decreased post-surgical blister and skin damage Improved quality of life
Concussion Management System to assess concussion and prevent 2nd impact syndrome	Patients in whom a concussion has been diagnosed	Athletes or participants in recreational activities who return too soon to action after concussion and before accurate and proper assessment are at increased risk of 2nd impact syndrome, a condition involving 2nd trauma to the head before the concussion has resolved and the brain is fully healed. The Concussion Management System involves the use of a dual-function mouth guard, which acts as a dosimeter to record each hit to an athlete's head and serves as a monitoring device, recording energy activity during head hits and reporting the data via Bluetooth technology. This might enable more accurate assessment of cognitive and motor function for athletes, compared with existing concussion assessment tools and software. Cleveland Clinic, Cleveland, OH Pilot trial ongoing	Axon Sports' CCAT Biodex Balance System SD CNS Vital Signs™ CSMi's ImPACT™ Sport Concussion Assessment Tool 2 SportsWare™ Concussion HeadMinder™ Standardized Assessment of Concussion tool	Decreased recurrence of concussions Improved management of concussions Prevention of 2nd impact syndrome Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Corneal collagen cross-linking for treatment of progressive keratoconus	Patients in whom progressive keratoconus has been diagnosed	Keratoconus is a degenerative disease of the eye and is the leading cause of corneal transplants in the U.S. Progressive keratoconus requires invasive interventions, such as corneal transplants and insertion of corneal rings. 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 a procedure performed by removing the corneal epithelium and applying riboflavin drops to the eye; the eye is then exposed to ultraviolet light, interacting 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. Avedro, Inc., Waltham, MA Phase III trial completed; Conformité Européene (CE) marked	Corneal ring segment inserts Surgical Therapy	Improved corneal structure Improved vision Improved quality of life
Cyclic pyranopterin monophosphate enzyme replacement therapy for molybdenum cofactor deficiency type A	Patients in whom molybdenum cofactor deficiency (MoCD) type A has been diagnosed	No current treatments are available for MoCD type A, which results from a deficiency in cyclic pyranopterin monophosphate activity leading to accumulation of sulfite and death within weeks or months of birth. Cyclic pyranopterin monophosphate enzyme replacement therapy is intended to restore the enzymatic activity missing in patients with MoCD type A. Alexion Pharmaceuticals, Inc., Cheshire, CT Early phase trials ongoing	No treatments currently available	Improved urine sulfite levels Improved neurological symptoms Reduced mortality
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 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 protective myelin sheath. Administered 150 mg, injected subcutaneously, once every 4 weeks Biogen Idec International GmbH, Zug, Switzerland Abbott Laboratories, Abbott Park, IL Phase III trials ongoing; data expected in late 2012; FDA granted fast track status	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Delayed disease progression Decreased demyelination Fewer relapses Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 is a 1st-in-class agent intended to target tau tangles and 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 (programmed cell death) by repairing the microtubular network and potentially restoring both axonal transport within nerve cells and chemical transmission between them; also intended to promote neurite growth and restore transmission between nerve cells; is derived from naturally occurring activity-dependent neuroprotective protein; also known as AL-108. Administered intranasally, 30 mg twice a day. Allon Therapeutics, Inc., Vancouver, British Columbia, Canada Phase II/III rial ongoing; FDA granted orphan drug status in Jan 2010	Pharmacotherapy (e.g., anticholinergic medications, antidepressants) Botulinum toxin type A (Botox®) injection	Improved symptom control Delayed or halted disease progression Improved quality of life
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 iron 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. CorMedix, Inc., Bridgewater, NJ Phase II trial completed Jun 2011; phase III trial registered but not yet open for participant recruitment.	Pharmacotherapy (e.g., deferoxamine) Hydration	Reduced occurrence and complications of CI-AKI Reduced incidence of CI-AKI in high risk patients with CKD

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Dimethyl fumarate (BG-12, Panaclar) for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis has been diagnosed	Available treatments provide unsatisfactory efficacy for many patients. Dimethyl fumarate (BG-12, Panaclar®) is a fumaric acid ester (FAE) which is purported to reduce peripheral CD4+ and CD8+ T lymphocytes (because FAE can induce apoptosis [programmed cell death]). Dimethyl fumarate is purported to represent a novel mechanism of action through modulating the Nrf-2 pathway, mediating neuroprotective and anti-inflammatory effects, Safety profile may allow combination dosing. Administered orally, 240 mg, twice daily. Biogen Idec International GmbH, Zug, Switzerland Phase III trial completed; FDA granted fast track status in 2008; in May 2012, FDA accepted new drug application for review	Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Reduced frequency of relapse Reduced symptom severity Slowed disease progression Improved quality of life
DNA chip for detecting lipoprotein lipase gene mutations that cause lipoprotein lipase deficiency	Patients at risk of lipoprotein lipase (LL) deficiency and resulting acute pancreatitis	Current diagnostics for detecting lipoprotein lipase deficiency include blood and genetic tests; however, more effective diagnostic tools are needed. DNA chip (microarray) diagnostic tool to detect mutations in the LL gene from a blood sample to identify patients at risk of acute pancreatitis. Progenika Biopharma S.A., Vizcaya, Spain Amsterdam Molecular Therapeutics Holding N.V., Amsterdam, The Netherlands U.S. trial status unclear; Conformité Européene (CE) marked Sept 2010	Standard lipid profile laboratory test Other laboratory exams	Increased definitive diagnosis of LL deficiency Identification of patients at risk of acute pancreatitis
Dopamine stabilizer pridopidine (ACR16, 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 (ACR16, Huntexil®) is a small-molecule, dopamine stabilizer that is purported to increase or decrease dopamine to healthy levels in patients with HD. Pridopidine is purported to contrast with neuroleptics that reduce dopamine activity regardless of baseline level. Administered orally, 45 and 67.5 mg, twice daily. NeuroSearch a/s, Ballerup, Denmark Phase III trials completed	Pharmacotherapy (e.g., tetrabenazine, antidepressants, antipsychotics)	Improved clinical global impression of change, cognitive function, behavior, and symptoms of depression and anxiety Improved voluntary motor function

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Doxepin nasal solution (Dolorac) for migraine prophylaxis	Patients in whom chronic migraine headaches (more than 180 headache days per year) have been diagnosed	Current treatments for chronic migraine headaches include pharmacotherapy such as NSAIDs, triptans, and opiates; however, many patients do not achieve adequate relief with available therapies and more effective treatment options are needed. A nasal solution (Dolorac) formulation of the tricyclic antidepressant doxepin; tricyclic antidepressants have been used off label for some time for migraine prophylaxis. Winston Pharmaceuticals, Inc., Vernon Hills, IL Phase II trials completed Nov 2010; company announced plans to initiate 2 phase III pivotal trials for chronic migraine in the 2nd quarter of 2011, but no updates as of Jul 2012	Off-label Pharmacotherapy (e.g., beta blockers, tricyclic antidepressants, antiepileptics), botulinum toxin type A (Botox®) injection	Migraines prevented Reduced side effects
Droxidopa (Northera) for treatment of symptomatic neurogenic orthostatic hypotension	Patients who have received diagnosis of 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; 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. Chelsea Therapeutics, Inc., Charlotte, NC Phase III trials completed; FDA granted orphan drug and fast track status; in Feb 2012, FDA Cardiovascular and Renal Drugs Advisory Committee voted 7-4 with 1 abstention and 1 non-vote recommending approval; Mar 2012 FDA issued complete response letter requesting additional efficacy data. In Jul 2012, FDA issued a complete response letter calling for an additional trial to demonstrate a significant and persistent effect of Northera.	Pharmacotherapy (e.g., midodrine hydrochloride) Dietary and lifestyle modifications	Decreased orthostatic hypotension Decreased risk of falling Decreased confusion from reduced cerebral circulation

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Drug-releasing implant (Propel system) to prevent occlusion of sinuses after surgery for chronic sinusitis	Patients in whom chronic sinusitis has been diagnosed	Chronic sinusitis affects about 1 in 7 adults in the U.S. and can lead to complications such as headaches, breathing difficulties, facial pain, and reduced olfactory and gustatory senses. Current treatment for chronic sinusitis are medical treatments that may lack efficacy for some patients or surgical interventions that may be too invasive and are associated with high rates of recurrence of symptoms. The Propel™ system is a springlike implant that is surgically implanted during endoscopic sinus surgery to maintain open sinuses after surgery and to prevent complications by delivering advanced corticosteroids directly to the sinus. It is intended to prevent obstruction of the ethmoid sinus. Intersect ENT, Inc., Palo Alto, CA Aug 2011, FDA approved under premarket approval process	Pharmacotherapy (e.g., antibiotics, decongestants, nasal corticosteroids, nonsteroidal anti-inflammatory drugs) Saline nasal spray Immunotherapy Surgical therapy	Reduced sinus inflammation Improved breathing Decreased headaches and facial pain Improved gustatory and olfactory senses Improved quality of life
Dual orexin receptor antagonists (MK-6096 and MK-4305) for treatment of primary insomnia	Patients in whom primary insomnia has been diagnosed	Insomnia is a common sleep problem that may stem from factors including stress, poor sleeping habits, depression, and chronic pain. Primary insomnia is known as the inability to sleep that is not attributed to any medical, psychological, or environmental factor. Current pharmacotherapies for this indication may come with unwanted adverse events and have limited efficacy. Dual orexin receptor antagonists act by inhibiting the binding of neuropeptide orexin to its receptor, known to regulate the sleep-wake cycle through control of downstream pathways that involve histaminergic, dopaminergic, and cholinergic activity. MK-6096 is administered orally, 2.5, 5, 10, or 20 mg per dose before bedtime; MK-4305 is administered orally, 15, 20, 30, or 40 mg per dose. Merck & Co., Inc., Whitehouse Station, NJ MK-6096: phase II trial completed MK-4305: phase III trials completed	Pharmacotherapy (e.g., Ambien®) Lifestyle and behavior modifications	Improved sleep cycle Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ear implant for treatment of Meniere's disease	Patients with persistent, severe vertigo in whom Meniere's disease has been diagnosed	No cure currently exists for Meniere's disease. Current treatment options include anti-vertigo and anti-nausea medications, but provide suboptimal treatment for many patients and also can impair performance of daily activities. This intervention is an inner ear implant modeled after cochlear implant and designed to quell vertigo attacks experienced by people with Meniere's disease. An electrode is inserted into each of 3 semicircular canals; external processor is worn behind the ear and communicates wirelessly with internal components; patient activates when vertigo episode begins; less invasive, permanent alternative to surgery, alternative to medications that address only symptoms and have many side effects. University of Washington, Seattle Phase III trial ongoing	Pharmacotherapy (e.g., motion sickness medications, anti-nausea medications) Surgical therapy	Cessation of vertigo
Electrical Nerve Block system for treatment of chronic amputation pain	Patients who have had an amputation who experience chronic amputation pain	No treatment is currently approved for chronic amputation pain, and many patients do not experience pain relief with the current treatment options. The Electrical Nerve Block system uses high frequency stimulation of peripheral nerves to prevent transmission of pain signals to the central nervous system. The Electrical Nerve Block system consists of a pacemaker-like implanted device that transmits electrical pulses through an electrode attached to a peripheral nerve. Neuros Medical, Inc., Willoughby, OH Pilot trials ongoing	Pharmacotherapy (e.g., analgesics, tricyclic antidepressants, anticonvulsants, intrathecal catheter-delivered drugs) Acupuncture Transcutaneous electrical nerve stimulation Surgical therapy	Reduced pain Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Electromagnetic field therapy (Resonator) 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. Electromagnetic field (EMF) therapy with the Resonator™ system is purported to generate an EMF, weaker than that of an MRI machine, that is applied to the entire body to restore atomic interactions associated with a healthy state that are disrupted in the pathologic state of fibromyalgia. The device includes a computer that controls a magnetic therapy driver, which includes a signal generator and attenuation circuit. The system produces a signal of predetermined amplitude and frequency to purportedly generate the desired EMF. The EMF is produced by Helmholtz coils that are connected to the magnetic therapy driver; the patient sits in a chair and is surrounded by the coils. Pico-Tesla Magnetic Therapies, Clearwater, FL Phase II trial completed	Pharmacotherapy (e.g., duloxetine, fluoxetine, gabapentin, lorazepam, milnacipran, pregabalin, tricyclic antidepressants Behavioral and lifestyle modification	Improved ability to perform daily activities Reduced symptoms Improved quality of life
Enzyme replacement therapy (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, osteomalacia, or both. Incidence has been estimated at 1 per 100,000 births. ENB-0040 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 effect and at a half-life 30% longer in bone, compared with serum. Alexion Pharmaceuticals, Inc., Cheshire, CT Phase II trials ongoing; phase II/III trial ongoing; 1 phase II study withdrawn "pending further review of clinical design"; FDA granted fast track and orphan drug status	Pharmacotherapy (e.g., cortisone) Vitamin supplementation (e.g., magnesium, vitamin B_6, zinc)	Restoration of bone mineralization Decreased risk of rickets and osteomalacia Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Enzyme replacement therapy (SBC-102) for treatment of lysosomal acid lipase deficiency	Patients in whom lysosomal acid lipase deficiency has been diagnosed	Lysosomal acid lipase deficiency is a rare genetic syndrome for which no treatment is FDA approved. SBC-102 is a recombinant protein intended to be used as an enzyme replacement therapy for this disease. Synageva BioPharma, Lexington, MA Phase II and II/III trial ongoing; FDA granted orphan drug status	Palliative treatments	Improved cholesteryl ester and triglyceride levels Improved quality of life
Eprodisate disodium (Kiacta) for treatment of amyloid A amyloidosis	Patients at risk of amyloid A amyloidosis, especially those in whom rheumatoid arthritis or chronic infection is present	No curative treatment for AA amyloidosis is currently available. Eprodisate disodium (Kiacta™) is designed to interfere with the formation of amyloid A fibrils that can accumulate in organs and tissues. Orally administered capsules. Bellus Health, Inc. (formerly Neurochem), Laval, Quebec, Canada Celtic Therapeutics Management LLP, St. Thomas, U.S. Virgin Islands Phase III trial ongoing; new drug application submitted to FDA in 2006, but FDA requested more data before approval; company initiated phase III confirmatory trial in 2010 to address this concern	Supportive care Immunosuppressants(e.g., chlorambucil, cyclophosphamide, melphalan methotrexate) Biologics (e.g., tumor necrosis factor-alpha inhibitors and interleukin-1-receptor antagonists Surgical excision of infected tissue and antibiotics for chronic infection Kidney transplantation (for kidney failure) Colchicine for familial Mediterranean fever	Reduced risk of organ failure (especially kidneys, liver, spleen) Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Erythropoiesis-stimulating agent (peginesatide, Omontys) for treatment of anemia from chronic renal failure	Patients with chronic kidney disease (CKD) who are on dialysis and in whom anemia has been diagnosed	Anemia is a common consequence of chronic renal failure, affecting more than 90% of patients with chronic renal failure stage 5. Erythropoiesis stimulating agents (ESAs) have been established as a treatment for anemia in chronic renal failure subjects and have improved the management of anemia over alternatives such as transfusion. Peginesatide (Omontys®) is a long-acting, parenteral formulation being developed for treating anemia in patients on dialysis (i.e., with CKD). It binds to and activates the human erythropoietin receptor (on bone marrow cells) and stimulates erythropoiesis in human red cell precursors in a manner similar to other known ESAs. Peginesatide is administered once monthly, by subcutaneous or intravenous injection, 0.04–0.16 mg/kg of body weight per dose. It is not intended for use in patients with CKD who are not on dialysis or for use in patients with anemia from other conditions, such as cancer. Affymax, Inc., Palo Alto, CA, in collaboration with Takeda Pharmaceutical Co., Ltd., Osaka, Japan FDA approved Mar 2012 with a Risk Evaluation and Mitigation Strategy for treating anemia in adults on dialysis; it is the 1st agent approved for this condition since 2001. The labeling includes a boxed warning that states**: "**ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence."	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride) Renal transplantation	Reduced frequency of drug administration Resolution of anemia Improved quality of life
Etanercept (Enbrel) for treatment of dermatomyositis	Patients in whom dermatomyositis has been diagnosed	Dermatomyositis is a chronic inflammatory disease of skin and muscle that is associated with patches of slightly raised reddish or scaly rash accompanying, or more often, preceding muscle weakness, which can result in difficulty performing physical activities. If untreated in adults, death may occur from severe and prolonged muscle weakness, malnutrition, pneumonia, or lung failure. The major causes of death from the disorder are cancer and lung disease; in some patients trouble with swallowing may occur, as well as fatigue and discomfort. Some patients do not respond to current anti-inflammatory therapy that may not be proven effective for dermatomyositis. Etanercept (Enbrel®) is a dimeric soluble 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 dermatomyositis. Etanercept may be administered 50 mg, once weekly, by subcutaneous injection. Amgen, Inc., Thousand Oaks, CA Phase I trials completed; FDA approved in 1998 for moderate to severe rheumatoid arthritis and other inflammatory conditions	Pharmacotherapy (e.g., azathioprine intravenous immunoglobulin, methotrexate, prednisone)	Symptom resolution as measured by International Myositis Assessment Clinical Study score Halted or slowed disease progression

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Exon-skipping agent (Eteplirsen, AVI-4658) for treatment of Duchenne muscular dystrophy	Patients in whom Duchenne muscular dystrophy (DMD) has been diagnosed	Current treatments for DMD address symptoms only; additionally, patients who receive available treatment still have a reduced lifespan and require additional support from devices. Eteplirsen is intended for patients in whom DMD has been diagnosed 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 administered once weekly in intravenous infusion. AVI BioPharma, Inc., Bothell, WA, now Sarepta Therapeutics, Inc., Cambridge, MA Phase IIb trial completed; phase III trial planned; FDA granted orphan drug status in 2007	Symptom control using corticosteroids and beta-2 agonists Physical therapy Orthopedics Respiratory support (respirator/ ventilators)	Delayed or halted muscle degeneration Reduced symptoms Increased survival Improved quality of life
Extended-release cysteamine bitartrate (RP103) for treatment of nephropathic cystinosis	Patients in whom nephropathic cystinosis has been diagnosed	Nephropathic cystinosis is a disease 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. RP103 is an enteric-coated, delayed-release, microbead, oral formulation of cysteamine bitartrate that is intended to reduce gastrointestinal adverse events associated with immediate-release cysteamine bitartrate and requires half the number of daily doses as existing medical treatment. Cysteamine bitartrate converts cystine to cysteine and cysteamine-mixed disulfide, preventing resultant organ damage. RP103 is administered orally, 75 mg, twice daily. Raptor Pharmaceutical Corp., Novato, CA Phase III trial completed; extension phase III trial ongoing; Mar 2012, company submitted new drug application to FDA; FDA granted orphan drug status	Pharmacotherapy (e.g., Cystagon®, indomethacin) Urinary loss supplementation Growth hormone therapy Renal transplantation	Improved glomerular function Reduced morbidity and mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ezogabine (Potiga) for treatment of partial onset seizures in epilepsy	Patients in whom epilepsy has been diagnosed	Treatment options for partial onset seizures, the most common form of seizure in epilepsy, include pharmacotherapy; but were limited in efficacy for some patients. Ezogabine (Potiga™) is a drug with a new mechanism of action intended for treating partial epileptic seizures. As a potassium channel opener, it stabilizes neuronal potassium channels in the open position with the intention of modifying ion channels so they modify neuronal hyperexcitability, and thus reduce seizures. The drug is available in tablet form in 50 mg, 200 mg, 300 mg, and 400 mg sizes. Valeant Pharmaceuticals International, Inc., Mississauga, Ontario, Canada GlaxoSmithKline, Middlesex, UK FDA approved Jun 2011	Pharmacotherapy (e.g., lamotrigine, levetiracetam, tiagabine, tricyclics, valproate)	Reduced frequency of partial seizures Improved quality of life
Fentanyl iontophoretic transdermal system (Ionsys™) for patient-controlled delivery of pain medication	Patients who would receive opioid treatment for pain (e.g., postsurgery patients)	The iontophoretic transdermal system delivers fentanyl (Ionsys™) for pain relief through a device about the size of a credit card that is affixed to the patient's upper arm or upper chest. The patient pushes a button on the patch, activating a battery and allowing iontophoretic (electrotransport) delivery of fentanyl HCl (40 mcg) over 10 minutes through intact skin. The device can be activated up to 6 times an hour and automatically shuts off after 24 hours. ALZA Corp. and Janssen Pharmaceuticals, Inc., both subsidiaries of Johnson & Johnson, New Brunswick, NJ Incline Therapeutics, Inc., Redwood City, CA Received FDA new drug application approval May 2006, but product was not launched; in Jun 2010, Ionsys was acquired by Incline Therapeutics, which must reapply for FDA approval following introduction of new safety features; approved in Europe but the marketing authorization was suspended by the European Medicines Agency in Nov 2008 after a recall because some devices had self-activated	Non-patient–controlled fentanyl patches Patient-controlled analgesic pumps	Adequate postsurgery pain management Fewer side effects because of delivery mode

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 about 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 used the ExAblate device, which consists of a helmet-like apparatus containing phased array focused ultrasound transducers. Computed tomography images can be used to reconstruct the skull and configure the ultrasound beams to focus on the targeted area. Magnetic resonance (MR) imaging or MR thermography can be used to track the delivery of ultrasound beams. Purported benefits of focused ultrasound therapy include the following: noninvasive transcranial treatment; no ionizing radiation, allowing for repeated treatment without long-term toxicity; immediate biophysical tissue response from thermal ablation; and precise tissue targeting with 1-mm accuracy. University of Virginia (UVa) Focused Ultrasound Center, Charlottesville (partnership of UVa; Commonwealth of Virginia; Focused Ultrasound Surgery Foundation, Charlottesville, VA; and InSightec, Ltd., Tirat Carmel, Israel) Phase I trial ongoing	Pharmacotherapy (e.g., antiepileptics, beta blockers) Deep brain stimulation Surgical therapy	Improvement in contralateral tremor as assessed on the Clinical Rating Scale for Tremor (CRST) Improved functional activities score as assessed on disabilities section of CRST Improved quality of life
Gel polymer (LeGoo) for prevention of blood loss in vascular surgery	Patients undergoing vascular surgical procedure	Vascular surgery often requires the anastomosis, or joining, of 2 or more blood vessels for the creation of a bypass. A primary adverse event for this surgical procedure is blood loss, which may also obstruct a surgical team's field of view. Elastic loops and surgical clamps are devices used to temporarily block blood flow, but the damaging and weakening of blood vessels has been a complication. LeGoo is a thermosensitive gel polymer that works paradoxically by solidifying at high temperature and liquefying at room temperature or below. The gel polymer is injected into the preferred suture site of the blood vessel, where a plug is formed in the shape of the blood vessel, blocking blood flow for 15 minutes. After 15 minutes, the gel polymer dissolves and passes through the microcirculation before being passed in urine. If a surgeon is finished in less than 15 minutes, a cold pack of ice or cold saline can be used to dissolve the gel polymer. This device is specifically indicated for blood vessels below the neck, 4 mm or less in diameter. This device is also specifically contraindicated for vessels supplying blood to the brain. Pluromed, Inc., Woburn, MA FDA approved Oct 2011 under premarket approval process	Elastic vessel loops Surgical clamps	Effective temporary blood vessel block Minimized blood loss Decreased damage to blood vessels

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gene therapy (CD34+ cells) for childhood severe combined immunodeficiency	Children in whom severe combined immunodeficiency has been diagnosed (also known as "bubble boy disease")	One form of severe combined immunodeficiency is caused by an enzyme deficiency, adenosine deaminase, known to compromise the immune system function; disease is often fatal and is typically treated with multiple weekly injections of enzyme replacement therapy. This intervention uses autologous (i.e., the cells came from the patients) adenosine deaminase vector-transduced CD34+ cells to reconstitute the immune system in an effort to cure the underlying immunodeficiency. The multi-center study was conducted by the San Raffaele Telethon Institute for Gene Therapy, Milan, Italy Phase I/II trials ongoing at multiple institutions; cells have received orphan drug designation from the European Medicines Agency	Bone marrow transplantation from unrelated donors or parents	Improved survival Fewer infections Freedom from weekly enzyme injections Improved quality of life
Glucocerebrosidase (taliglucerase alfa) for treatment of Gaucher's disease	Patients with Gaucher's disease who have not yet begun treatment or who are currently being treated with enzyme replacement therapy via imiglucerase (Cerezyme)	Gaucher's disease is caused by a hereditary deficiency of glucocerebrosidase, which leads to enlarged and malfunctioning organs, skeletal disorders, and painful neurologic complications. Taliglucerase alfa is a plant-cell expressed form of glucocerebrosidase; intended as a lower-cost enzyme replacement therapy; compound also known as recombinant active form of lysosomal enzyme, glucocerebrosidase. Administered via an infusion. Pfizer, Inc., New York NY Protalix BioTherapeutics, Inc., Carmiel, Israel Phase III trial completed; new drug application submitted to FDA; complete response letter from FDA issued in Feb 2011; timeline for resubmission unclear pending meeting with FDA; granted orphan drug status; available under "expanded access" protocol; marketing authorization application submitted to European Medicines Agency Nov 2010; granted orphan designation in Europe	Blood transfusions Bone marrow transplant Enzyme replacement therapy (e.g., imiglucerase) Joint replacement surgery Splenectomy	Decreased spleen volume as confirmed by MRI Secondary endpoints including the following: Reduced liver volume Improved hemoglobin measurements Increased platelet counts Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Perampanel (Fycompa) for treatment of partial-onset epilepsy	Patients age 12 and older in whom partial-onset epilepsy has been diagnosed	Some patients with partial-onset epilepsy do not respond to current therapy. Perampanel (Fycompa®) represents a new mechanism of action/class of drugs for this disease state. A highly selective, noncompetitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptor antagonist, AMPA receptors (located in excitatory neurons) transmit signals stimulated by glutamate and are believed to play a role in diseases characterized by excess neuroexcitatory signaling, such as epilepsy. The drug is taken as an oral tablet once daily in 8 or 12 mg doses. Eisai Co., Ltd., Tokyo, Japan Phase III trials completed; FDA approved Oct 2012 as adjunctive treatment of partial-onset seizures with or without secondarily generalised partial onset seizures in patients with epilepsy ages 12 years and older. FDA stated the approval includes a boxed warning “to alert prescribers and patients about the risk of serious neuropsychiatric events, including irritability, aggression, anger, anxiety, paranoia, euphoric mood, agitation, and mental status changes.” FDA recommended that the drug be classified by the U.S. Drug Enforcement Administration (DEA) as a scheduled drug; DEA will review the recommendation and determine the final scheduling designation. The drug was also approved by the European Medicines Agency in Jul 2012.	Pharmacotherapy (e.g., lamotrigine, levetiracetam, tiagabine, tricyclics, valproate)	Reduced frequency of partial seizures Improved quality of life
Glycogen synthase kinase-3 enzyme inhibitor (tideglusib; Zentylor) for treatment of progressive supranuclear palsy	Patients in whom progressive supranuclear palsy (PSP) has been diagnosed	Currently, no treatments exist for PSP. Tideglusib (Zentylor™) represents a novel drug class for this indication as a glycogen synthase kinase 3 (GSK-3) inhibitor for treating PSP. In patients with PSP, hyperphosphorylation of the tau protein occurs and contributes to microtubule destabilization and axonal transport dysfunction; GSK-3 is believed to be the major enzyme responsible for the abnormal hyperphosphorylation of tau; it may also be involved in the formation of the beta-amyloid peptide. It is a disease-modifying drug. Noscira, S.A., Madrid, Spain Phase II trial completed; FDA granted orphan drug and fast track status; has orphan drug status in EU	Anticholinergic medications	Improved symptom control Delayed or halted disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gracilis muscle transplant for treatment of facial paralysis in pediatric population	Pediatric patients in whom facial paralysis has been diagnosed	Current surgical measures may have higher failure rates and less optimal outcomes in the event of successful muscle transfer. Gracilis muscle implantation involves transferring a segment of the gracilis muscle into the cheek, allowing for blood vessel and nerve regeneration and consequent facial reanimation. Massachusetts Eye and Ear Infirmary, Boston, MA Pilot study completed Jul 2011	Facial slings (masseter, temporalis, or anterior belly of digastric muscle) Surgical therapy	Improved surgery success rate Improved facial reanimation Improved quality of life
GSK-2402968 (PRO-051) for treatment of Duchenne muscular dystrophy	Ambulatory patients 5 years and older who have been given a diagnosis of Duchenne muscular dystrophy (DMD) who have a dystrophin gene mutation including deletions of exon 50, exon 52, exons 45–50, exons 48–50, and exons 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 devices. GSK2402968 is an antisense oligonucleotide which 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. GlaxoSmithKline, Middlesex, UK, in partnership with Prosensa, Leiden, The Netherlands Phase III trial ongoing; FDA granted orphan drug status	Pharmacotherapy (e.g., corticosteroids, beta-2 agonists) Physical therapy Orthopedics Respiratory support (respirator/ ventilators)	Decreased muscle degeneration Improved symptoms Decreased need for supportive devices Improved quality of life Increased survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Handheld intracranial scanner (Infrascanner, Model 1000) 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 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. 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™ Model 1000 is a handheld near-infrared spectroscopy device that directs near-infrared light into the skull, where the light 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. InfraScan Inc., Philadelphia, PA, in collaboration with the Office of Naval Research, Arlington, VA FDA approved Dec 2011	Automated Neuropsychological Assessment Metrics (computerized cognitive test) Computed tomography scans MRI studies Onsite neurophysical exam	Reduced morbidity Reduced mortality Improved quality of life
Helminthic therapy (pig whipworm) for treatment of multiple sclerosis	Patients in whom multiple sclerosis (MS) has been diagnosed	Current treatments for MS may slow disease progression, but the disease has no cure. Effective treatments are needed. Autoimmune diseases such as MS are less common in parts of the world where helminthic exposure and infestations are common. Exposure to helminths purportedly promotes production of regulatory T cells and immunomodulatory cytokines that dampen autoimmune responses. Patients are treated orally with 2,500 *Trichuris suis* ova (TSO; pig whipworm eggs), every 2 weeks. Changes in the patient's cytokine balance in response to the infestation are intended to lead to reduced MS symptoms. Coronado Biosciences, Inc., Burlington, MA Copenhagen University, Copenhagen, Denmark Phase II trial planned	Dimethyl fumarate Fingolimod Glatiramer Interferon beta-1a Natalizumab Oral immunomodulators in development	Reduced brain tissue loss/atrophy Reduced frequency of relapse Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
High-intensity focused ultrasound for treatment of primary hyper-parathyroidism	Patients with primary hyperparathyroidism who either decline or are not candidates for parathyroidectomy	The most common treatment for primary hyper-parathyroidism is invasive surgery. High-intensity focused ultrasound using TH-One under sonographic guidance is intended to provide a minimally invasive option to ablate the gland while the patient is under conscious sedation. Theraclion, Paris, France Pilot trial completed in Bulgaria; phase I trial ongoing in France	Surgical therapy Pharmacotherapy (e.g., calcimetrics, bisphosphonates) Hormone replacement therapy	Decreased serum parathyroid hormone levels Decreased serum calcium levels Reduced size of benign parathyroid tumors Reduced blurred vision, back pain, depression, fatigue Improved quality of life Adverse events
Hormone stimulation drug (FG-2216) for treatment of anemia from dialysis	Patients needing dialysis who are at risk of anemia	First oral drug (FG-2216) intended to stimulate production of the hormone erythropoietin in dialysis patients who are at risk of anemia; erythropoietin stimulates production of oxygen-carrying red blood cells. Astellas Pharma, Inc., Tokyo, Japan Fibrogen Inc., San Francisco, CA Phase II trial completed	Erythropoietin replacement therapy with erythropoiesis-stimulating agents	Resolution of anemia Improved quality of life
Human spinal cord–derived neural stem cells (NSI-566RSC) for treatment of amyotrophic lateral sclerosis	Patients who have received a diagnosis of amyotrophic lateral sclerosis (ALS)	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. Stem cell therapy may potentially repair neurologic damage. NSI-566RSC was developed from human spinal cord–derived neural stem cells; this neural stem cell product is injected into the lumbar spinal cord. Neuralstem, Inc., Rockville, MD Phase I trial ongoing on 12 patients; FDA granted orphan drug designation for ALS treatment; May 2012, FDA granted approval to advance the trial enabling administration of a 2nd dose to 3 patients in the cervical spine.	Riluzole Supportive care	Slowing or halting progression of ALS Reduced symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
IGF-2 peptide conjugated alpha-glucosidase (BMN-701) enzyme replacement therapy for Pompe disease	Patients in whom late-onset Pompe disease has been diagnosed	Pompe disease, which is a genetic disease that results in a deficiency in alpha-glucosidase activity; current enzyme replacement therapies for the disease do not adequately address disease impact on skeletal muscle. Insulin-like growth factor 2 (IGF-2) peptide conjugated alpha-glucosidase (BMN-701) is an enzyme replacement therapy. Current enzyme replacement therapies have poor uptake in skeletal muscle, potentially due to low level skeletal muscle expression of the key transporter required for cellular entry of the enzyme. BMN-701 purports to circumvent this problem through the addition of the IGF-2 peptide, which is recognized by the transporter. BioMarin Pharmaceuticals, Inc., Novato, CA Phase I/II and phase II trial ongoing	Standard alpha-glucosidase enzyme replacement therapy (Myozyme, Lumizyme) without AT2220	Improved muscle strength, functional status, pulmonary function and/or ventilation Improved quality of life
Inhaled apomorphine (VR040) for fluctuating, idiopathic Parkinson's disease	Patients in whom fluctuating, idiopathic Parkinson's disease has been diagnosed	VR040 is a proprietary formulation of apomorphine using proprietary delivery technology delivered to the bloodstream by inhalation through the lungs using proprietary dry powder inhalation technology. Vectura Group, plc, Chippenham, UK Phase II trials completed; European Medicines Agency granted orphan drug designation 2006; Vectura is seeking to license	Levodopa/carbidopa MOA-B inhibitors	Improved ability to control movement Slowed disease progression
Integrin agonist (SAR 1118) for treatment of dry-eye disease	Patients in whom dry-eye disease has been diagnosed	About 20 million people in the U.S. are affected by dry-eye disease. Numerous causal factors lead to dry eye, with most diseases secondary to dry-eye disease causing T-cell inflammation and proliferation and cytokine production. This may result in ocular surface damage and degradation of tear film. Several behavioral and pharmacologic therapies are available for treating dry eye but can work with limited efficacy or may be too invasive with resultant complications. SAR 1118 is a lymphocyte-associated antigen-1 (LFA-1) antagonist that binds to intercellular adhesion molecule-1, the LFA-1 cognate ligand, purportedly inhibiting cell adhesion, cytokine production, and cell proliferation. SARcode Bioscience, Inc., Brisbane, CA Phase III trial completed	Artificial tears Hot compresses Lubricating ointments Proper eyelid cleaning and sanitary behavior modification Tetracycline and doxycycline Topical azithromycin Topical corticosteroids	Reduced occurrence and recurrence of dry eye Decreased incidence of blindness from chronic dry eye Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interferon-alfa kinoid (IFN-K) for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	No cure exists for SLE; treatments provide only partial symptomatic relief and can cause immunosuppression and other adverse events. Treatments with improved efficacy and safety are needed. Interferon-alfa-kinoid (IFN-K) is a novel immunotherapy platform that uses inactivated cytokines conjugated to a carrier protein and delivered with an adjuvant or immune stimulant. IFN-K purportedly elicits a polyclonal antibody response against IFN-alfa, which is thought to be overexpressed in patients with SLE, resulting in pathogenesis. It is administered in 3–4 injections over 3 months. Neovacs S.A., Paris, France Phase II trial ongoing	Antimalarial drugs Belimumab Corticosteroids Cyclophosphamide and mycophenolate Methotrexate and azathioprine Intravenous immunoglobulin	Disease remission Improved symptoms Slowed disease progression
Intranasal gel (Compleo TRT) for treatment of hypogonadism	Patients in whom hypogonadism has been diagnosed	About 13 million American men are affected by low testosterone levels, and as many as 90% go untreated. Treatment guidelines focus on restoring physiologic testosterone levels through exogenous testosterone preparations. Compleo TRT™ is a bioadhesive intranasal gel formulation of testosterone applied to the interior lateral wall of the nasal cavity, where absorption into the nasal mucosa occurs in 10–15 minutes. It is purported this targeted delivery area to the nasal mucosa will avoid skin-to-skin transference to others, an issue seen with existing topical testosterone gel preparations. Additionally, the drug-delivery system could mitigate adverse events from 1st-pass metabolism on the liver. Trimel Pharmaceuticals Corp., Mississauga, Ontario, Canada Phase III trial ongoing	Various formulations of testosterone	Increased testosterone levels Reduced adverse events
Keratin gel for nerve regeneration of traumatically injured peripheral nerves	Patients who have experienced traumatic injury to peripheral nerves	Treatments for nerve gaps (severed nerves) include grafts or conduits, but neither is highly effective with nerve gaps greater than 5 mm. Keratin gel applied inside a nerve guidance conduit during nerve-repair surgery is proposed as a treatment to promote nerve regeneration that bridges that gap. Wake Forest University, Winston-Salem, NC Phase I/II trials planned pending FDA authorization to proceed; Keretec Ltd., Canterbury, New Zealand, received marketing clearance in 2009 for a keratin-based wound dressing (Keretec Keragel); Wake Forest received $2.4 million grant from U.S. military to study university-developed keratin gel for peripheral nerve repair	Autologous grafts of healthy nerve tissue Implantation of nerve guidance conduits (tubes) between severed nerve endings	Improved efficacy of nerve repair with nerve grafts or guidance conduits Absence of reduced nerve function in healthy nerves, which may happen with graft harvesting

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Kidney growth factor peptide (NX-001) for prevention of delayed graft function in renal transplantation	Patients who have received a kidney transplant	NX001 is a kidney growth factor peptide; growth factors are proteins that bind to receptors on the cell surface and activate cellular proliferation and/or differentiation. Several kidney-specific growth factors are known and could stimulate dormant cells to initiate DNA synthesis to promote repair and regeneration of kidney cells to try to speed and improve function of transplanted kidneys. NephRx Corp., Kalamazoo, MI Phase I trial ongoing; phase II trial planned for late 2011, but not registered trial on National Clinical Trials database as of Oct 2012; FDA granted orphan drug status in 2010	No other treatment for delayed graft function	Faster graft function Improved graft function Improved graft survival Improved patient survival
KIT tyrosine kinase inhibitor (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 purported to target 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. Masitinib is administered orally, 6 mg/kg of body weight, daily, in clinical trials. AB Science S.A., Paris, France Phase IIb/III trial ongoing	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Delayed disease progression Reduced symptoms Improved quality of life
Laquinimod for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	Results seen with current RRMS therapies are unsatisfactory. Laquinimod represents a new mechanism of action for this disease state. Laquinimod is a synthetic immunomodulator with anti-inflammatory properties; exact mechanism of action has not yet been elucidated, but may exert its effect by modulating the immune system from a proinflammatory to an anti-inflammatory response and by preventing damaging immune system cells from entering the central nervous system. Dosed once daily, orally. Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel Active Biotech, Lund, Sweden Two phase III trials completed; others ongoing; Teva decided to not file a new drug application and after discussions with FDA in Aug 2012 agreed on a 3rd clinical trial (CONCERTO) to evaluate 2 doses (0.6mg and 1.2mg) in about 1,800 patients for up to 24 months	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Reduced brain tissue loss/atrophy Reduced frequency of relapse Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Laser surgery 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 recurrence may commonly occur. Surgical procedures such as craniotomy may be performed, but may leave the brain susceptible to unintended injury and resultant neurological complications. If accepted, laser therapy would provide a minimally invasive, potentially curative therapy for patients receiving a diagnosis of epilepsy. Laser 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. Texas Children's Hospital, Houston, TX Pilot trial completed	Pharmacotherapy (e.g., lamotrigine, levetiracetam, tiagabine, tricyclics, valproate)	Reduction or elimination of seizures
Lasmiditan (COL-144) for treatment of migraine headaches	Patients in whom migraine headaches have been diagnosed	Lasmiditan is a small-molecule, serotonin receptor agonist that binds to the 5-HT^1F receptor and is intended to have a reduced vasoconstrictive effect compared with other drugs. Oral and intravenous formulations are under study. CoLucid Pharmaceuticals, Inc., Research Triangle Park, NC Phase IIb trial completed (outside U.S.); FDA accepted investigational new drug application in Aug 2011; phase III trial planned for 2012	Pharmacotherapy (e.g., pain relievers, triptans, ergot, anti-nauseates, opiates, dexamethasone)	Quicker reduction in pain and light/noise sensitivity Reduced recurrence of symptoms Reduced side effects
Levadex (MAP-0004) orally inhaled for treatment of migraine headaches	Patients in whom migraine headaches have been diagnosed	A derivative (Levadex™ [MAP-0004]) of the currently available dihydroergotamine; intended to alleviate migraine headache symptoms quickly through oral inhalation using the company's Tempo inhaler. MAP Pharmaceuticals, Inc., Mountain View, CA Positive phase III results reported; in Jan 2011, company partnered with Allergan for Levadex commercialization; new drug application accepted by FDA in Aug 2011; Mar 2012, FDA issued a complete response letter citing chemistry, manufacturing, and control issues, but did not request additional efficacy or safety information	Pharmacotherapy (e.g., pain relievers, triptans, ergot, anti-nauseates, opiates, dexamethasone)	Quicker reduction in pain and light/noise sensitivity Reduced recurrence of symptoms Reduced side effects

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Levetiracetam (Keppra) for treatment of chronic poststroke aphasia	Patients who have experienced stroke in whom chronic aphasia (speech difficulty) has been diagnosed	The main treatment for aphasia is conventional speech and language therapy. However, it does not achieve adequate effectiveness for many stroke patients with speech and language deficits poststroke. Of all the drugs used in an attempt to improve aphasia, only piracetam, donepezil, and amphetamine have shown some limited efficacy in some patients. Levetiracetam (Keppra®) is an S-enantiomer derived from piracetam, and both levetiracetam and piracetam derive from gamma aminobutyric acid. Levetiracetam was initially studied in animal models of cognitive impairment to try to find a drug more effective than piracetam. In trials of stroke patients with poststroke aphasia, levetiracetam is administered 250 mg orally twice daily for 7 days; it is being tested also at 500, 750, and 1,000 mg dosages. Kessler Foundation, West Orange, NJ Phase I trial ongoing	Pharmacotherapy (e.g., amphetamine, donepezil, piracetam) Speech-language therapy	Improved comprehension Improved memory Improved speech capability Improved capacity to read and write
Macrophage regulator (NP001) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	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. 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; intended to restore normal functioning of macrophages in central nervous system, reducing inflammation and normalizing the cellular environment. Administered intravenously. Neuraltus Pharmaceuticals, Inc., Palo Alto, CA Phase II trial ongoing; FDA granted fast track and orphan drug status Aug 2011	Riluzole Supportive care	Improved biomarker levels Restoration of macrophages to their neuroprotective state Improved activities of daily living Delayed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Magnetic tongue-piercing aid for directing mobile wheel chair	Patients with spinal cord paralysis, particularly from the neck down	The magnetic pierced-tongue aid is a magnetic device in the mode of a ball-shaped tongue ring that is intended to mobilize a wheelchair by sending signals to a headset containing sensors. Sensors in the user's headset respond to the tongue ring's magnetic signals based on the direction in which the user moves the tongue (e.g., tongue moves to the mouth's upper left corner, prompting wheelchair to move forward). The tongue was targeted for device implant because it does not tire easily and is generally unaffected by spinal cord injuries. Current technologies, including the "sip and puff" wheelchair, may be less flexible, more difficult to use, and less aesthetically pleasing. The magnetic pierced-tongue aid for wheelchair users may provide more flexibility, better accuracy, and greater quality of life for patients who have severe muscle weakness (e.g., paraplegia, quadriplegia, multiple sclerosis, stroke, muscular dystrophy). Georgia Institute of Technology, Atlanta Pilot trial and unphased trials completed	Comparators depend on severity of spinal cord paralysis Chin control wheelchair Head control wheelchair "Sip and puff" wheelchair Speech control wheelchair Tongue keyboard controller wheelchair	Improved wheelchair function and control Improved aesthetics of device Improved mobility Improved quality of life
Mapracorat ophthalmic suspension for treatment of postcataract-surgery inflammation	Patients who have undergone cataract surgery	Selective glucocorticoid receptor agonist (Mapracorat; BOL-303242-X) exhibits glucocorticoid-like anti-inflammatory activities; intended for use to reduce inflammation and adverse effects of classic steroids used to treat ophthalmic inflammation. Bausch & Lomb, Inc., Rochester, NY Phase III trials ongoing; 1 phase III trial terminated	Pharmacotherapy (e.g., antibiotics, corticosteroids, nonsteroidal anti-inflammatory drugs)	Reduced inflammation-related complications Reduced side effects
Mecobalamin (E-0302) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	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. Mecobalamin (E-0302) is a methylated form of vitamin B_{12} proposed for parenteral therapy for ALS. Eisai Co., Ltd., Tokyo, Japan Phase II/III trials ongoing in Japan	Pharmacotherapy (e.g., riluzole) Supportive care	Increased survival rate Improved functional rating scale Increased safety Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Menerba (MF-101) for treatment of hot flashes in postmenopausal women	Postmenopausal women experiencing hot flashes	The experience of hot flashes is a highly common symptom of menopause, affecting about 80% of women at some point at the end of reproductive lives. Hormone replacement therapy has been used to treat postmenopausal women suffering from hot flashes, but has associated risks, including breast cancer, endometrial cancer, stroke, and heart disease. MF-101 is a selective estrogen receptor beta (Erb) agonist that stimulates estrogen activity while not stimulating the estrogen alpha receptors known to be in association with the development of breast and endometrial cancer; MF-101 contains liquiritigenin, purported to be a highly active estrogen (specifically Erb) compound derived from the root of *Glycyrrhizae uralensis* Fisch. MF-101 is administered orally, 5, 10, or 15 g, daily. Bionovo, Inc., Emeryville, CA Phase III trial ongoing	Antidepressants Estrogen therapy (pill or cream form) Hormone therapy Ibuprofen Neurontin® Phytoestrogens Progesterone/pro-gestin-estrogen Raloxifene Tamoxifen Vitamin B complex Vitamin E	Decreased incidence of hot flashes Improved quality of life
Mesenchymal stem cells for treatment of multiple sclerosis	Patients in whom multiple sclerosis (MS) has been diagnosed	Current MS therapies are intended to minimize immune-system damage to the central nervous system (CNS) and slow disease progression; however, no therapies are designed to prevent and reverse damage to the CNS by the immune system. Mesenchymal stem cells injected into the blood are purported to have a wide range of effects that decrease the reactivity of immune cells and encourage tissue repair, which may be beneficial to patients with MS. The cells are purported to migrate into areas of inflammation or injury in the CNS and mediate protective effects. Cleveland Clinic, Cleveland, OH University Hospitals Seidman Cancer Center, Cleveland, OH Case Western Reserve University, Cleveland, OH Phase I/II trial completed; phase II trials ongoing as well at other institutions	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Improved motor/cognitive function Reduced brain tissue loss/atrophy Reduced frequency of relapse Slowed rate of disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mesenchymal stem cells (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. Osiris Therapeutics, Inc., Columbia, MD Phase III trials complete; FDA granted orphan drug and fast track status; available under expanded access program since 2008; Health Canada gave approval in 2012	Anti-thymocyte globulin Corticosteroids Methotrexate and cyclosporine Mycophenolate mofetil Other immunosuppressants Photopheresis	Increased overall survival Improved quality of life
Metabotropic glutamate receptor 5 antagonist dipraglurant (ADX48621) for treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	Current PD therapies are associated with poor tolerability including development of levodopa-induced dyskinesia (PD-LID), which occurs in about half of patients receiving treatment. Although dystonia is a significant problem for PD patients, no products are specifically licensed for treating dystonias. New therapies with better efficacy and tolerability are needed. Dipraglurant is a negative allosteric modulator of metabotropic glutamate receptor 5 (mGluR5), which is purported to be found in regions of the brain that serve as key control points in the neuronal motor circuits responsible for abnormal glutamate signaling. Perturbations in glutamate signaling (along with disruptions in dopaminergic signaling) are believed to be an underlying cause of PD. By inhibiting mGluR5, dipraglurant is intended to restore normal movement via a nondopaminergic mechanism, thereby offering a dopamine sparing therapy. Additionally, preclinical findings suggest that mGluR5 inhibitors may be neuroprotective and may hold potential to treat PD progression. Dipraglurant is purported to reduce both of the major PD-LID symptoms, chorea (rapid uncontrolled movements) and dystonia (writhing and cramping movements). Administered orally, 50 mg, once daily, up to 100 mg, 3 times daily. Addex Pharmaceuticals, Geneva, Switzerland Phase IIa trial completed	Levodopa/carbidopa MOA-B inhibitors.	Improved motor skill functions Reduced disease progression Sustained effect of treatment over time Reduced incidence/severity of levodopa-induced dyskinesia Reduced symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Metabotropic glutamate receptor 5 antagonist mavoglurant (AFQ056) for treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	Current therapies for PD are associated with poor tolerability including the development of levodopa-induced dyskinesia (PD-LID), which occurs in about half of all PD patients. New therapies with better efficacy and tolerability are needed. Mavoglurant is an antagonist of metabotropic glutamate receptor (5mGluR5), which is purported to be found in regions of the brain that serve as key control points in the neuronal motor circuits responsible for abnormal glutamate signaling. Perturbations in glutamate signaling (along with disruptions in dopaminergic signaling) are believed to be an underlying cause of PD. By inhibiting mGluR5, mavoglurant is intended to restore normal movement via a nondopaminergic mechanism, thereby offering a dopamine sparing therapy. Additionally, preclinical findings suggest that mGluR5 inhibitors may be neuroprotective and may hold potential to slow PD progression. Mavoglurant is purported to reduce both of the major PD-LID symptoms, chorea (rapid uncontrolled movements) and dystonia (writhing and cramping movements). Drug is administered 100 mg, daily. Novartis International AG, Basel, Switzerland Phase IIb and phase II/III trials ongoing	Levodopa/carbidopa MOA-B inhibitors	Improved motor skill functions Slowed disease progression Sustained effect of treatment over time Reduced incidence/severity of levodopa-induced dyskinesia Reduced symptoms Improved quality of life
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 due to uncontrolled elevated reduce intraocular pressure (IOP)	iStent Trabecular Micro-Bypass Stent System is intended for implantation during cataract surgery in patients with or at risk of 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. Use of the procedure avoids having to move the iris, conjunctiva, or sclera and preserves other surgical and medical options for treating glaucoma. Glaukos Corp., Laguna Hills, CA FDA approved Jul 2012 approved "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 currently being treated with medication to reduce intraocular pressure." Conformité Européene (CE) marked in select countries in Europe; approved in Canada	Trabectome (device) Pharmacotherapy (e.g., eye drops) Surgical therapy	Preserved vision Reduced elevated or uncontrolled IOP

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Migalastat hydrochloride (AT1001) for treatment of Fabry disease	Patients with Fabry disease who have either migalastat-responsive mutations in alpha-galactosidase A or who are receiving enzyme replacement therapy	Current enzyme replacement therapies for Fabry disease are expensive to produce and have been subject to recent shortages. AT1001 is a small-molecule drug that acts as a molecular chaperone that enhances the activity of alpha-galactosidase A, the enzyme that is deficient in Fabry disease; 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, testing as monotherapy and in combination with enzyme replacement therapy. Amicus Therapeutics, Inc., Cranbury, NJ Phase III trial ongoing	Enzyme replacement therapy Palliative treatment	Increased GL-3 levels (urine, kidney biopsy) Improved renal function (e.g., glomerular filtration rate) Improved quality of life
Mu-opioid agonist (NKTR-181) for treatment of chronic pain	Patients experiencing chronic pain	Current opioid analgesics have the potential for addiction and dangerous suppression of central nervous system (CNS) activity leading to respiratory distress. NKTR-181 is a novel mu-opioid agonist formulation that modifies the opioid by pegylation, which is intended to reduce the rate at which the drug crosses the blood-brain barrier, thereby limiting high CNS concentrations that could lead to respiratory distress or feelings of euphoria. Nektar Therapeutics, San Francisco, CA Phase Ia trial complete; phase II trial ongoing	Pharmacotherapy (e.g.,COX-2 inhibitors, Buprenex, nonsteroidal anti-inflammatory drugs, opioids)	Improved pain relief Reduced adverse effects Reduced risk of addiction 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	Few effective treatment options are available for patients with MS. Sativex® is a whole plant medicinal cannabis extract that contains Tetranabinex® and Nabidiolex® (cannabidiol) as its main component; delta-9-tetrahydrocannabinol (THC) in the extract acts as a partial agonist at both cannabinoid receptors, CB1 and CB2, mimicking the effects of the endocannabinoids, which may modulate the effects of neurotransmitters (e.g., reduce effects of excitatory neurotransmitters such as glutamate) to improve symptoms. Sativex is sprayed under the tongue, 100 mcL/dose, which contains 2.5 mg cannabidiol and 2.7 mg THC. Sativex is intended to be an add-on treatment to current MS therapies. GW Pharmaceuticals, plc, Salisbury, UK Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan Phase III trial completed; approved in New Zealand and Canada for treating spasticity due to MS; approved in Canada for relief of MS-related neuropathic pain	Pharmacotherapy (e.g., opioids, nonsteroidal anti-inflammatory drugs)	Reduced pain Reduced spasticity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
N-acetylgalactos-amine 6-sulfatase (GALNS) for treatment of Morquio 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; no treatments are available to address the underlying cause of the disease; only palliative treatments are available. N-acetylgalactosamine 6-sulfatase (BMN-110) is an enzyme replacement therapy intended to treat the underlying disorder. BioMarin Pharmaceutical, Inc., Novato, CA Phase III trial ongoing	No current treatments are available to resolve the underlying disease.	Disease regression Improved bone growth as measured by radiograph Improved activities of daily living Increased physical endurance (6-minute walk test) Improved respiratory function Reduced urine keratan sulfate levels
Neural stem cell therapy (ReN001) for stroke recovery	Patients in whom a stroke has been diagnosed	Stem cell therapy with ReN001, a clonal human neural stem cell line generated in the laboratory; stem cells are injected into the brain under local anesthetic and intended to assist in recovery from stroke. ReNeuron Group, Inc., Guildford, UK Phase I trial ongoing in UK; investigational new drug application on hold with FDA in U.S.	Current rehabilitative treatment for disabled stroke survivors	Resolution of functional deficits
Neuron transplantation (MotorGraft) for patients with spinal muscular atrophy type 1	Patients in whom spinal muscular atrophy (SMA) type I has been diagnosed	A stem cell–derived motor neuron transplantation therapy, MotorGraft™ is intended for treating SMA type I; cells are delivered surgically into the spinal cord of these patients. California Stem Cell, Inc., Irvine, CA Phase I trial placed on clinical hold (delayed) per FDA official response to company's investigational new drug application	Supportive therapy	Improved function in muscles that control crawling, walking, swallowing, and breathing

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nicotinic receptor agonist NP002 for treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	Current PD therapies are associated with poor tolerability, including the development of levodopa-induced dyskinesia (PD-LID), which occurs in about half of all PD patients receiving treatment. New therapies with better efficacy and tolerability are needed. Patients with PD have been found to have fewer nicotinic receptors in their brains, and smoking has been shown to have a neuroprotective effect against PD; NP002 is a small-molecule, orally available nicotinic receptor agonist which is purported reduce PD-LID without negatively affecting PD symptoms. Administered 1–6 mg, 4 times daily. Neuraltus Pharmaceuticals, Inc., Palo Alto, CA Phase I/II trial completed	Levodopa/carbidopa MOA-B inhibitors	Improved motor skill functions Reduced disease progression Sustained effect of treatment over time Reduced incidence/severity of levodopa-induced dyskinesia Reduced symptoms Improved quality of life
Nitroglycerin for prevention of osteoporosis	Postmenopausal women who have normal bone density or osteopenia	Currently available treatments for osteoporosis either prevent bone resorption or promote bone formation, but no compound performs both functions, which nitroglycerin is purported to do. Nitroglycerin leads to the production of nitric oxide, which has been demonstrated in vitro to cause decreased bone resorption, increased osteoblast cell proliferation, increased osteocalcin synthesis, and increased osteoblastic cell mineralization; these processes could all prevent bone loss. National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD Phase III trial completed.	Anti-bone–resorptive drugs (bisphosphonates, selective estrogen receptor modulators, estrogen, calcitonin, denosumab) Bone formation stimulators (teriparatide)	Increased lumbar vertebrae and hip bone mineral density Improved serum osteocalcin levels Improved bone-specific alkaline phosphatase levels Reduced hip and spine fractures
Nonsurgical, removable dental hearing device (SoundBite) for treatment of single-sided deafness	Patients in whom single-sided deafness has been diagnosed	Hearing loss affects more than 28 million people in the U.S., prompting use of hearing devices. Available hearing aids may not provide optimal quality for patients, and surgical interventions or bone anchored implants may be too invasive and expensive. The nonsurgical, removable dental hearing device (SoundBite™) consists of a behind-the-ear (BTE) microphone unit which houses the receiver, a wireless transmitter, an attached microphone, and a discreet, removable in-the-mouth (ITM) hearing device. The BTE unit transmits sound to the ITM device, which then is intended to produce imperceptible sound vibrations via the teeth through bones and to both cochleae. The ITM device is custom molded to the teeth without surgery or alterations to tooth structure. Sonitus Medical, Inc., San Mateo, CA FDA 510(k) clearance granted 2011	Bone anchored implants Hearing aid devices (BTE, in-the-ear devices, canal aids)	Improved hearing Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
NuQu injectable cell-therapy for spinal disc regeneration	Patients in whom degenerative disc disease (DDD) of the lower back has been diagnosed	Conservative treatment (physical therapy, pain medication) is not effective in a small proportion of patients with chronic low back pain from degenerative disc disease. Invasive surgical options such as spinal fusion have significant risks and can adversely affect adjacent discs; less invasive, effective options are needed. NuQu® treatment involves the injection of culture-expanded juvenile knee cartilage cells into the intervertebral disc, where they are intended to restore nucleus structure and disc height and prevent further degeneration. The procedure is performed under fluoroscopic guidance in an outpatient setting. ISTO Technologies, Inc., St. Louis, MO Phase I trial ongoing	Artificial disc replacement Discectomy Spinal fusion	Reduced back pain Increased function Improved quality of life
NX-1207 for treatment of benign prostatic hyperplasia	Patients in whom benign prostatic hyperplasia (BPH) has been diagnosed	Current therapies for BPH address only secondary symptoms (muscle relaxation by alpha blockers) and can have adverse effects (impotence, decreased libido by 5-alpha reductase inhibitors). NX-1207 is a small-molecule drug administered by ultrasound-guided transrectal intraprostatic injection that is intended to shrink the size of an enlarged prostate. Although its exact mechanism of action is unknown, it is thought that NX-1207 has pro-apoptotic properties. Nymox Pharmaceutical Corp., Hasbrouck Heights, NJ Phase III trials ongoing	Pharmacotherapy (e.g., 5-alpha reductase inhibitors, alpha blockers) Surgical therapy	Improved International Prostate Symptom Score or improved American Urological Association Symptom Index Increased urine flow rate Improved quality of life
Obeticholic acid (INT-747) for treatment of nonalcoholic steatohepatitis	Patients in whom nonalcoholic steatohepatitis (NASH) has been diagnosed	Obeticholic acid (INT-747) is a farnesoid X receptor agonist derived from human bile intended for administration to decrease liver tissue scarring and fibrosis. Intercept Pharmaceuticals, Inc., New York, NY Phase II trial completed in type II diabetes patients with nonalcoholic fatty liver disease; study of 280 patients with NASH to be initiated in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD	Currently, no other treatment exists	Reduced tissue scarring Slowed progression of fibrosis Improved liver function Improved quality of life Reduced need for liver transplantation

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ocrelizumab for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	Current therapy for RRMS provides unsatisfactory results for many patients. Ocrelizumab represents a novel mechanism of action for this disease state; 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. F. Hoffman-La Roche, Ltd., Basel, Switzerland Biogen Idec International GmbH, Zug, Switzerland Phase III trials ongoing	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Decreased frequency of relapse Slowed disease progression Improved quality of life
Off-label beta blockers for treatment of serious infantile hemangiomas	Infants in whom a hemangioma has been diagnosed	Superficial hemangiomas often are not treated and resolve on their own to leave normal-appearing skin. Sometimes, laser ablation is used to remove small vessels. Significant hemangiomas, however, can impair vital or sensory functions or cause disfigurement. They are treated with lasers and/or steroid injections. Oral pharmacologic options are desired. Propranolol is a nonselective beta blocker that works via vasoconstriction and could decrease expression of vascular endothelial growth factor 1 and basic fibroblast growth factor by downregulating the RAF-mitogen-activated-protein kinase pathway; this is believed to trigger apoptosis in endothelial capillary cells, thereby reducing size of hemangiomas. Hackensack University Medical Center, Hackensack, NJ, and various centers conducting trials Unphased trials completed; phase II and III trials ongoing	Pharmacotherapy (e.g., corticosteroids) Laser treatment	Reduced hemangiomas Improved functional ability Prevention of future complications Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label bevacizumab for treatment of retinopathy of prematurity	Infants weighing 1,500 grams 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 who are 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 in premature infants 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; off-label use of bevacizumab is injected into the infant's vitreous to reduce incidence of blindness by suppressing VEGF. Manufacturer is not pursuing a labeled indication. BEAT-ROP cooperative (trial sponsor) Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland (manufacturer) Postmarket trial of off-label use completed	Peripheral retinal ablation with lasers (e.g., xenon, argon, diode)	Prevented recurrence of neovascularization arising from the retinal vessels 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 patients whose disease is refractory to treatment. Etanercept (Enbrel®) is a dimeric soluble 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 of body weight per dose, 2 times weekly. Amgen, Inc., Thousand Oaks, CA Phase II trial ongoing; FDA approved in 1998 for moderate to severe rheumatoid arthritis and other inflammatory conditions	Corticosteroids High-dose aspirin IVIG	Improved survival Prevented increase in coronary artery diameter Prevented new coronary artery dilation/cardiac dysfunction Reduced fever

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label fingolimod (Gilenya) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	Only 1 agent (riluzole) is approved for treating ALS (Lou Gehrig's disease), 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 purported to be an agonist to sphingosine 1-phosphate receptors on the surface of thymocytes and lymphocytes. This mechanism of action purportedly reduces the number of circulating lymphocytes available to cause autoimmune reactions and destroy nerve tissue. Reduced inflammatory reactions against peripheral nerves could reduce ALS symptoms. Administered orally, 0.5 mg daily. ALS Therapy Development Institute, Cambridge, MA Phase II trial planned; FDA approved for treating relapsing-remitting multiple sclerosis	Physical and speech therapy Medications for symptom management (muscle cramps, constipation, fatigue, excessive salivation, excessive phlegm, pain, depression) Riluzole (Rilutek®)	Increased survival Reduced symptoms Slowed or halted disease progression Improved quality of life
Off-label rifampicin for treatment of multiple system atrophy	Patients in whom multiple system atrophy (MSA) has been diagnosed	MSA is a progressive neurodegenerative disorder characterized by cytoplasmic inclusions containing abnormally aggregated alpha-synuclein proteins, which are purported to be associated with the neurodegeneration observed in MSA. Current MSA treatments are aimed at controlling symptoms rather than treating the underlying cause of neurodegeneration. The antibiotic rifampicin is purported to reduce the aggregation of alpha-synuclein and the associated neurodegeneration in a preclinical models, as well as disaggregate preformed alpha-synuclein fibrils. Mayo Clinic, Minneapolis, MN Phase III trial ongoing	Pharmacotherapy (e.g., anticholinergics, beta blockers, MAO inhibitors, vasoconstrictors)	Improved symptoms based on Unified Multiple System Atrophy Rating Scale Reduced neurodegeneration Improved quality of life
Off-label teriparatide (Forteo) for hard-to-heal fractures	Patients in whom unhealed bone fractures of the pelvis have been diagnosed	Teriparatide (Forteo®) subcutaneous injection intended to promote fracture healing in Jones, pelvic, and shoulder fractures. Eli Lilly and Co., Indianapolis, IN Unphased trial ongoing; already approved as treatment for osteoporosis	Electrical stimulation Fracture healing without teriparatide Growth factors	Faster and more complete healing time Improved function Improved mobility Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Olesoxime (TRO19622) for treatment of spinal muscular atrophy	Patients who have been given a diagnosis of spinal muscular atrophy (SMA)	No drugs are currently approved to treat SMA. Olesoxime potentially promotes neuroaxonal repair and remyelination and the function and survival of neurons and other cell types under disease-relevant stress conditions through interactions with the mitochondrial permeability transition pore. This oral compound potentially promotes remyelination and provides neuroprotection. Trophos SA, Marseille, France Phase II trial ongoing	Supportive therapy	Increased survival Increased progression-free survival Improved quality of life
Oral calcitonin (Ostora) for prevention and treatment of postmenopausal osteoporosis	Women at risk of or in whom postmenopausal osteoporosis has been diagnosed	No oral formulation of (salmon) calcitonin is available; oral formulation has the potential to increase adherence and prescription habits compared with injection and nasal formulations. Salmon calcitonin (Ostora™) is a naturally occurring hormone involved in calcium regulation; binds to osteoclasts to slow the rate of bone breakdown and resulting bone loss; approved and widely used in other forms. Tarsa Therapeutics, Philadelphia, PA Phase III treatment trial completed; phase II prevention trial ongoing; company planned to file new drug application in 2nd half of 2012	Injectable calcitonin Intranasal calcitonin	Slowed rate of bone breakdown Decreased bone loss Decreased numbers of hip and spine fractures Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oral growth hormone secretagogue (AEZS-130) for diagnosis of adult growth hormone deficiency	Patients in whom adult growth hormone deficiency (AGHD) has been diagnosed	AGHD affects about 35,000 adults in the U.S., leading to complications such as reduced muscle mass and bone mass, reduced energy levels, increased body fat, cardiac dysfunction, and increased insulin resistance. Current diagnostic measures for growth hormone (GH) deficiency are blood screenings without provocation by an agent, intravenous application of pharmacologic agents to stimulate GH production, or MRI detection of pituitary dysfunction. These diagnostic tests have been deemed invasive, inconclusive, or have unwanted adverse effects. AEZS-130 is an orally active molecule, ghrelin agonist that purportedly stimulates the secretion of GH. Stimulation of GH secretion, which normally occurs in the body during sleep, is believed to allow a clinician to observe the body's response to AEZS-130. If GH levels remain low after administration of AEZS-130, this might confirm a diagnosis of AGHD. Growth hormone secretagogues are potent regulators of lipid, sugar, and protein metabolism that directly stimulate GH secretion from the pituitary gland without the involvement of growth-hormone-releasing hormone or somatostatin. AEZS-130 is administered once, orally, for the stimulation of GH secretion. Æterna Zentaris, Inc., Quebec, Quebec, Canada Phase III trial completed; FDA granted orphan drug status; company filed for fast track designation in Jul 2012	Blood GH testing Insulin-like growth factor level testing Insulin tolerance testing MRI of pituitary to detect dysfunction	Increased sensitivity and specificity Improved diagnostic accuracy Increased patient adherence with recommended diagnostic strategy Reduced risk of adverse events from invasive tests
Oral opioid antagonist (ALKS-37) for treatment of opioid-induced bowel dysfunction	Patients in whom opioid-induced bowel dysfunction has been diagnosed	No oral pharmaceuticals are available to treat the bowel dysfunction often induced by opioid treatment. ALKS 37 is an orally active, peripherally restricted opioid antagonist intended to improve gastrointestinal (GI) motility and the frequency of bowel movements while preserving the analgesic effects of the opioid for pain management; ALKS 37 is intended to be a metabolically stable molecule that targets the GI tract with limited systemic exposure; also known as RDC-1036. Alkermes, Inc., Waltham, MA Phase III trials completed	Injectable opioid antagonists (methylnaltrexone) Laxatives	Reduced bowel dysfunction Increased frequency of bowel movements Improved adherence with opioid treatment

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oral opioid antagonist (NKTR-118) for treatment of opioid-induced bowel dysfunction	Patients in whom opioid-induced constipation or other manifestations of opioid-induced bowel dysfunction have been diagnosed	No oral pharmaceuticals are available to treat the bowel dysfunction often induced by opioid treatment, and bowel dysfunction is a common reason for not using opioids for pain management. NKTR-118 combines AstraZeneca's polymer conjugate technology platform with naloxol, a derivative of naloxone (opioid antagonist) to make an orally active, peripherally restricted opioid antagonist intended to improve gastrointestinal motility and the frequency of bowel movements while preserving the analgesic effects of the opioid for pain management; targets peripheral opioid receptors to alleviate constipation while limiting the penetration across the blood-brain barrier which would reduce analgesic effects. AstraZeneca, London, UK Nektar Therapeutics, San Francisco, CA Phase III trials ongoing completed. FDA filing expected 2nd half of 2013	Injectable opioid antagonists (methylnaltrexone) Laxatives	Reduced bowel dysfunction while on opioid therapy Increased frequency of bowel movements Improved adherence with opioid therapy
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 management of complications of SCD (i.e., pain crises), the only drug currently 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 of body weight, once a day (on dosing days). HemaQuest Pharmaceuticals, Inc., San Diego, CA Phase I/II trial completed; phase II trial ongoing; FDA granted orphan drug status	Allogeneic hematopoietic stem cell transplantation Antioxidant therapy Azacitidine Decitabine butyrate Gardos channel inhibition Gene therapy Hydroxyurea Lenalidomide Nitrous oxide and vasodilators Statins	Reduced severity and duration of vaso-occlusive crises Reduced health disparities (African Americans) Improved quality of life
Osseointegrated implants for lower-limb prostheses	Patients who have had amputation of a lower limb	Prosthetic legs typically attach over a stump of the remaining limb. Osseointegrated implants feature a body-prosthesis interface that is fused into bone of the residual limb to potentially improve mobility and comfort of prostheses; the prosthetic limb connects to the fused metal implant that protrudes through the skin. Specific device manufacturer(s) unclear In early use in Europe; FDA has not yet approved any trials	Conventional prosthetic legs that attach over stump of residual lower limb	Improved gait, mobility, and comfort Reduced pain Improved fit

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oxybutynin intravaginally (FP 1097) for treatment of urinary urge incontinence	Women in whom urinary urge incontinence has been diagnosed	FP 1097 is an intravaginal delivery method for the anticholinergic drug oxybutynin and is of interest because of its potential to avoid systemic side effects of oral drugs (e.g., dry mouth, constipation, blurry vision, confusion) used to treat the condition. FemmePharma Global Healthcare, Inc., Wayne, PA Phase II trial completed Jan 2011; phase III trial planned, but currently not registered on National Clinical Trials database; FDA agreed to grant 505(b)(1) filing status (lower evidence requirement)	Behavior therapy Pharmacotherapy (e.g., darifenacin, fesoterodine fumarate, oxybutynin, solifenacin, tolterodine) Surgical therapy	Reduced micturition and incontinence episodes Reduced systemic side effects (dry mouth, constipation, blurry vision, confusion)
Pasireotide (SOM230) for treatment of gastrointestinal (GI) injuries from acute radiation exposure	Patients with 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, gastrointestinal (GI), respiratory, and skin complications. Although few treatments exist for irradiated bone marrow, none exist for irradiated GI organs. Additionally, no treatments are FDA approved for use as medical radiation countermeasures for preventing or treating ARS. In Sept 2011, the 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 the University of Arkansas to develop ARS treatments. 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. The drug is being provided by Novartis to the University for this 2-year study. Novartis International AG, Basel, Switzerland (manufacturer) University of Arkansas for Medical Sciences, Little Rock (investigator) Clinical trial phase not reported; data generated from the study are intended to form the basis for a new drug application that Novartis will submit to FDA.	Pharmacotherapy (e.g., antibiotics, hematopoiesis-stimulating agents) Stem cell therapy	Prevented or reduced GI flora Decreased mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pegylated recombinant phenylalanine ammonia lyase (PEG-PAL) enzyme replacement therapy for treatment of phenylketonuria	Individuals in whom phenylketonuria has been diagnosed	Pegylated recombinant phenylalanine ammonia lyase (PEG-PAL); phenylketonuria is an inherited disorder in which an enzyme that is needed to break down essential amino acid phenylalanine is missing; drug is intended to reduce levels of phenylalanine in patients unresponsive to Kuvan®. Administered by injection, 1–3 times a week. BioMarin Pharma, Inc., Novato, CA Phase II trials ongoing; FDA granted orphan drug status	Kuvan (tetrahydrobiopterin or BH4)	Decreased phenylalanine levels Fewer diet restrictions Improved quality of life Injection site inflammation is most common adverse event (43%)
Personalized T-cell immunotherapy (Tcelna) for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	No cure exists for MS. Current treatments do not sustain long-term remission, and some have severe secondary effects. Tcelna™ (formerly Tovaxin®) is a personalized cellular immunotherapy derived from T cells isolated from peripheral blood, expanded ex vivo, and reintroduced into the patients via subcutaneous injections; process triggers a potentially potent immune response against specific subsets of autoreactive T cells known to attack myelin and reduces the risk of relapse over time. Opexa Therapeutics, Inc., The Woodlands, TX Phase IIb trial completed	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Decreased annualized relapse rate Improvement in disability score Improved safety Improved long-term management of disease
PET/MRI integrated imaging system (Biograph mMR) for diagnosis of neurologic conditions	Patients who require morphologic, functional, and metabolic imaging exams for neurologic indications	Imaging exams (Biograph mMR™) that combine positron emission tomography (PET) with MRI; intended to provide simultaneous acquisition of morphologic, functional, and metabolic imaging data; exam intended to take 30 minutes compared with 1 hour or more for sequential PET and MRI exams. Siemens Healthcare, Malvern, PA FDA 510(k) clearance granted Jun 2011	Stand-alone PET and MRI exams	More efficient imaging for patient Improved diagnosis from combined morphologic, functional, and metabolic imaging Improved treatment planning

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Phrenic nerve stimulation (Remedē system) for central sleep apnea associated with heart failure	Patients in whom central sleep apnea associated with heart failure (HF) has been diagnosed	Remedē™ system is a device that is implanted in chest (similar to pacemaker). It is attached to 2 insulated wires inserted into veins; stimulation wire placed in vein near 1 of patient's phrenic nerves sends communication between diaphragm and the brain, which stimulates phrenic nerve and returns patient to normal breathing. Respicardia, Inc., Minneapolis, MN Phase II trial ongoing	Adaptive servo ventilator Oxygen therapy	Slowed progression of HF Improved quality of life
PN1/Nav1.7 sodium channel blocker for treatment of pain	Patients with any form of pain (e.g., pain associated with cancer, arthritis, migraine headaches; muscle pain; pain from burns)	This agent is intended to block PN1/Nav1.7, a sodium channel expressed on peripheral neurons that research has demonstrated is essential for transmitting pain signals to the central nervous system (CNS). Unlike CNS-acting opioids, PN1/Nav1.7 blockers would terminate pain signals peripherally, potentially avoiding CNS-based side effects such drowsiness and respiratory distress. Icagen, Inc., Durham, NC, in collaboration with Pfizer, Inc., New York, NY Phase I trial ongoing	Pharmacotherapy (e.g.,COX-2 inhibitors, Buprenex, nonsteroidal anti-inflammatory drugs, opioids)	Reduced pain Maintained alertness Improved quality of life
PPAR-gamma agonist (ATx08-001) for treatment of postherpetic neuralgia	Patients who have ongoing neuropathic pain after an outbreak of shingles (postherpetic neuralgia [PHN])	Postherpetic neuralgia can be very painful and debilitating; current treatments have variable efficacy for different patients and often require trial and error to determine optimal treatment; even then treatment can be suboptimal and the syndrome can persist long-term. ATx08-001 is a novel oral peroxisome proliferator-activated receptor (PPAR)-gamma agonist that is purported to have a safety and toxicology profile distinct from current PPAR-gamma agonists; preclinical studies and preliminary human trials have demonstrated that modulation of PPAR-gamma activity is able to modify pain sensation. Aestus Therapeutics, Inc., North Brunswick, NJ Phase II trial completed	Lidocaine skin patches Pharmacotherapy: (e.g., tricyclic antidepressants, anticonvulsants, opioids)	Reduced pain on visual analog scale Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Preladenant for treatment of moderate to severe Parkinson's disease	Patients in whom moderate to severe Parkinson's disease (PD) has been diagnosed	Current treatments for PD address symptoms rather than underlying cause, and the patient eventually plateaus or ceases to respond to them; new interventions are needed. Preladenant acts as a potent and selective antagonist at the adenosine A2A receptor; unlike L-dopa, effects do not appear to decrease over time and it appears to have fewer side effects. Merck & Co., Inc. (Schering-Plough), Whitehouse Station, NJ Phase III trials ongoing	Levodopa/carbidopa MOA-B inhibitors	Improved symptoms (motor function) Slowed disease progression Preserved independence Delayed need for assisted care
Prosthetic arm to restore natural function	Patients with trauma-induced amputations of the upper limbs	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). U.S. Defense Advanced Research Projects Agency, Arlington, VA. (commissioned and funded research) U.S. Department of Defense, Washington, DC, and U.S. Department of Veterans Affairs, Washington, DC (conducting clinical testing); several U.S. and international research partners participating Early phase trials ongoing; FDA is piloting a new regulatory pathway for this technology, the Innovative Device pathway, which is intended to get innovative devices to market within 4 years	Conventional prosthetic arms	Significant restoration of limb function compared with current prosthetic devices
PYM50028 (Cogane) for treatment of Parkinson's disease	Patients in whom early-stage Parkinson's disease has been diagnosed	Current treatments for PD address symptoms rather than underlying cause, and the patient eventually plateaus or ceases to respond to them. PYM50028 (Cogane™) is a small-molecule, neurotrophic factor inducer that readily crosses the blood-brain barrier. In preclinical studies, Cogane stimulated release of neurotrophic factors and increased neurite outgrowth; importantly, also reversed the decrease of neurotrophic factors and reversed dopaminergic neuronal degeneration in vitro; intended to significantly reduce parkinsonian symptoms. Phytopharm, plc, Huntingdon, UK Phase II trial ongoing	Levodopa/carbidopa MOA-B inhibitors	Improved motor skill function and reduction in symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Real-time functional magnetic resonance imaging with cognitive training to treat chronic pain	Patients in whom chronic pain has been diagnosed	Chronic pain is often unresponsive to conventional treatment over time. Well-defined regions of the brain (i.e., rostral anterior cingulate cortex) are believed to be responsible for pain perception; real-time functional MRI (fMRI) is under study to determine whether patients in pain who are able to view their brain activity during an MRI can use that information to learn how to control pain; until recently, fMRI data had to be analyzed off-line, but now software developed at Stanford University (Stanford, CA) is enabling researchers to analyze imaging data in near real time to show patients their brain activity moment by moment; fMRI is being used over a 6-month period consisting of 12 visits that include 6 sessions in an MRI scanner and cognitive training to try to control the brain activity triggering the pain signals. Omneuron, Inc., Menlo Park, CA National Institute of Neurological Disorders and Stroke, Bethesda, MD Phase II trial ongoing	Pharmacotherapy (e.g.,COX-2 inhibitors, Buprenex, nonsteroidal anti-inflammatory drugs, opioids)	Ability to perform activities of daily living Decreased pain Return to work Improved quality of life
Reciprocating gait orthoses (ReWalk and Ekso exoskeleton systems) for independent mobility after spinal cord injury	Patients with spinal cord injury resulting in paraplegia and need for wheelchair use	Currently, 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 assist users in walking or climbing stairs. Two reciprocating gait orthosis systems in development, the ReWalk-I™ system 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 retain the ability 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 is purported to transfer 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 5'2" and 6'2" tall, and with partial upper body strength. The system has 3 walk modes. The patient provides the balance and proper body positioning. Argo Medical Technologies, Ltd., Yokneam Illit, Israel (ReWalk system) distributed in the U.S. by Bionics Research, Inc., Mt. Laurel, NJ Ekso Bionics, Richmond, CA (Ekso system) The ReWalk-I (institutional use) system is currently 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 was available through 16 U.S. rehabilitation centers as of Aug 2012.	Wheelchairs	Improved mobility Improved independence Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Recombinant human interleukin-12 (HemaMax) for treatment of acute radiation syndrome	Patients in whom acute radiation syndrome (ARS) has been diagnosed	ARS is a disease caused by harmful exposure to high doses of ionizing radiation, resulting in bone marrow, cardiovascular, gastrointestinal, respiratory, and skin complications. No therapies are approved to specifically treat ARS, and current management of the disease has been variable, with suboptimal outcomes. Recombinant human interleukin-12 (HemaMax™) is intended to provide regenerative function to the hematopoietic system by reducing degradation of bone marrow caused by acute radiation and stimulating hematopoiesis after harmful radiation exposure. Neumedicines, Inc., Pasadena, CA Phase I trial completed	Pharmacotherapy (e.g., antibiotics, hematopoiesis-stimulating agents) Stem cell therapy	Decreased secondary complications (i.e., hematopoietic syndrome) Decreased mortality
Recombinant human microplasmin injection (Ocriplasmin) 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 (fibrinolysis) that adhere the vitreous gel to the macula; intravitreal injection of microplasmin (Ocriplasmin) is thus a potential nonsurgical treatment for VMA. ThromboGenics NV, Heverlee, Belgium Phase III trials completed; company filed biologics license application Dec 2011	Pharmacotherapy (e.g., Macugen®) Surgical therapy	Preserved vision Reduced complications associated with surgical treatment Improved quality of life
Recombinant human parathyroid hormone (PTH 1-84; Natpara) for treatment of hypo-parathyroidism	Patients in whom hypoparathyroidism has been diagnosed	Hypoparathyroidism is a rare disorder in which parathyroid hormone is markedly decreased or absent from the circulation: the hormone regulates and maintains a balance of calcium and phosphorus; low levels of parathyroid hormone may lead to low calcium levels in blood and bones and an increased amount of phosphorus. Therapy to replace missing hormone has been unavailable up to this point; treatment has consisted of daily supplementation of calcium; recombinant human (rh)PTH 1-84 (Natpara™) is hormone replacement therapy intended to provide long-term control of serum calcium and urinary calcium excretion. Administered by injection. Columbia University, New York, NY Phase III trial completed; Biologics License Application to FDA expected to be filed mid-2013	High-dose calcium High-dose vitamin D	Controlled serum and urinary calcium Improved safety Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 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. Inspiration Biopharmaceuticals, Inc., Laguna Niguel, CA Phase II/III and phase III trial ongoing	Human factor VIIa	Adequate control of bleeding episodes
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 where creating and maintaining high urine output is essential. The single-use urine collection set is connected to a Foley catheter and an infusion set is connected to a standard intravenous catheter. The console is managed by monitoring software that measures urine volume in the collection set and matches patient urine output with an equal volume of hydration fluid. PLC Systems, Inc., Milford, MA Pivotal trial completed	Pharmacotherapy (e.g. deferoxamine) Hydration	Reduced occurrence and complications of CIN Reduced incidence of CIN in high risk patients with CKD Improved quality of life
Retargeted endopeptidase (AGN-214868) for treatment of overactive bladder and urinary incontinence	Patients in whom overactive bladder leading to urinary incontinence has been diagnosed	Current therapeutic approaches for overactive bladder have a poor side-effect profile and are generally not very effective. AGN-214868 is a recombinant protein that is based on the botulinum toxin; in AGN-214868, the neuron binding domain of the botulinum neurotoxin has been replaced with a peptide that targets the endopeptidase activity of the toxin to peripheral neurons involved in the overactivity of bladder muscles leading to urinary incontinence. Syntaxin Ltd., Oxford, UK, in collaboration with Allergan, Inc., Irvine, CA Phase II trial ongoing	Behavioral and lifestyle modifications Pharmacotherapy (e.g., darifenacin, oxybutynin, oxybutynin skin patches, solifenacin, tolterodine, trospium) Onabotulinum toxin A Sacral nerve stimulation Surgical therapy	Decrease in urge to urinate Decrease in urination episodes per week Improved International Consultation on Incontinence Questionnaire-Overactive Bladder score Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Retargeted endopeptidase (AGN-214868) for treatment of postherpetic neuralgia	Patients in whom postherpetic neuralgia has been diagnosed	Postherpetic neuralgia can be very painful and debilitating; current treatments have variable efficacy for different patients and often require trial and error to determine optimal treatment; even then treatment can be suboptimal and the syndrome can persist long-term. AGN-214868 is a recombinant protein that is based on botulinum toxin; in AGN-214868, the neuron-binding domain of the botulinum neurotoxin has been replaced with a peptide that targets the endopeptidase activity of the toxin to peripheral neurons involved in transmission of postherpetic neuralgia pain. Syntaxin Ltd., Oxford, UK, in collaboration with Allergan, Inc., Irvine, CA Phase II trial completed	Lidocaine skin patches Tricyclic antidepressants: Amitriptyline Nortriptyline Anticonvulsants: Gabapentin Pregabalin Opioids: Morphine Oxycodone Tramadol	Reduced pain score on visual analog pain scale Improved quality of life
Retinal prosthesis system (Argus II) for treatment of retinitis pigmentosa	Patients with retinitis pigmentosa (RP) and a functioning optic nerve	Currently 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. Second Sight, Inc., Sylmar, CA Phase II trial ongoing under FDA investigational device exemption status, Conformité Européene (CE) marked in 2011	Currently, no treatment exists	Improved visual acuity Improved quality of life and independence
Rituximab (Rituxan) for treatment of Wegener's granulomatosis and microscopic polyangiitis	Patients in whom Wegener's granulomatosis has been diagnosed	Wegener's granulomatosis and microscopic polyangiitis can cause vasculitis, which can be fatal within months. Immunosuppressive therapies for the disease have many side effects, and better treatments are needed. Rituximab (Rituxan®), a genetically engineered anti-CD20 antibody approved for treating B-cell lymphoma, is purported to reduce the antibody production that leads to the inflammation associated with Wegener's granulomatosis and microscopic polyangiitis. The treatment is intended to be used with glucocorticoids. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland FDA approved Apr 2011 for this indication	Pharmacotherapy (e.g., Imuran®, Cytoxan®, methotrexate, prednisone)	Disease remission

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Robotic navigation aid (Guide Vest) to assist visually impaired persons	Patients with visual impairment	Current assistive devices and measures, such as long canes and guide dogs, have limitations that subject patients to injuries that affect quality of life. The guide vest robotic navigation aid is a head-mounted camera/vest combination that allows the head camera to capture images wirelessly through the simultaneous localization and mapping software to build maps of the patient's environment. This allows the technology to accurately identify a safety path devoid of obstacles. The safety route is communicated to the patient through vibratory micro motors in the shoulder and waist that vibrate in the event that the route is obstructed. Vibrations to the shoulders are intended to indicate a higher object (i.e. left shoulder vibration for higher left obstacle) and vibrations to the waist indicate a lower object. If adopted, the guide vest may serve as a 1st-line assistive technology device for individuals in whom visual impairment has been identified. University of Southern California Keck School of Medicine's Doheny Eye Institute, Los Angeles Pilot study completed at Braille Institute	Long canes Remote Infrared Audible Signage (RIAS) "Sighted" wheelchair	Decreased risk of falls and injury Improved mobility Increased independence
Sclerostin neutralizing monoclonal antibody (AMG 785) for treatment of postmenopausal osteoporosis	Patients in whom postmenopausal osteoporosis (PMO) has been diagnosed	Sclerostin antibodies represent a new class of anabolic therapy for PMO. AMG 785/CDP7851 is a humanized monoclonal antibody that binds to and inhibits sclerostin, a protein secreted by osteocytes that inhibits bone formation by reducing osteoblastogenesis; AMG 785 is intended to allow the body to add more bone to the skeleton through osteoblastogenesis. Delivered via subcutaneous injection in 4 doses. Amgen, Inc., Thousand Oaks, CA Phase II and phase III trials ongoing	Bisphosphonates Calcitonin Denosumab Estrogen therapy Glucagon-like peptide 2 Osteoprotegerin Parathyroid hormone Selective estrogen receptor modulators Strontium ranelate	Higher bone density Reduced fracture rate Improved quality of life Increased survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Selective phosphodiesterase 4 inhibitor (AN2728) for treatment of psoriasis	Patients in whom mild to moderate plaque psoriasis has been diagnosed	Current immunomodulatory treatments for psoriasis have significant shortcomings; topical corticosteroids can cause thinning of the skin and systemic immune modulators can have immunosuppressive effects. Like corticosteroids, AN2728 is applied topically and inhibits NF-kappa B thereby reducing inflammation; however, AN2728 has a novel target for psoriasis treatment (phosphodiesterase type 4); this novel anti-inflammatory mechanism of action may allow longer topical treatment and/or combination treatment with existing therapies. Anacor Pharmaceuticals, Inc., Palo Alto, CA Phase II trials completed	Topical ointments such as: Anthralin Calcineurin inhibitors Coal tar Corticosteroids Phototherapy Systemic medications: Cyclosporin Hydroxyurea Immunomodulators Methotrexate Retinoids Thioguanine	Improved psoriasis area severity index scale Improved quality of life
SMT C1100 for treatment of Duchenne muscular dystrophy	Patients in whom Duchenne muscular dystrophy (DMD) has been diagnosed	Current treatments for DMD may reduce symptoms, but do not address the underlying cause of disease. SMT C1100 is a small molecule purported to upregulate utrophin, a naturally occurring protein that has a similar function to dystrophin. Utrophin is purported to be produced only during fetal development. The manufacturer postulates that if utrophin production can be maintained, it could act as a substitute for dystrophin to maintain muscle function. SMT C1100 is intended to complement other therapeutic approaches in development. Summit, plc, Oxfordshire, UK Phase I trial ongoing; FDA granted orphan drug status	Symptom control using corticosteroids and beta-2 agonists Physical therapy Orthopedics Respiratory support (respirator/ventilators)	Decreased muscle degeneration Decreased need for supportive devices Improved symptoms Reduced mortality 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 is 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; differentiated from other surgical glaucoma options, because it is purported to reduce IOP without creating a bleb, which is a source of serious complications. SOLX, Inc., Waltham, MA Phase III trials ongoing; approved in Canada and parts of Europe	Pharmacotherapy (e.g., eye drops) Surgical therapy Trabectome (device)	Reduced IOP Preserved vision

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Somatostatin analog (pasireotide) for treatment of Cushing's disease	Patients in whom Cushing's disease caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary tumor has been diagnosed	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; too much ACTH results in too much cortisol, which controls the body's use of carbohydrates, fats, and proteins and helps reduce inflammatory responses. No medical treatments directly targeting ACTH-secreting pituitary tumors are available and not all patients respond to surgical or radiotherapy treatment. Pasireotide is a subcutaneously administered, somatostatin analog that activates a wide range of somatostatin receptors and has demonstrated the ability to inhibit ACTH secretion. Novartis International AG, Basel, Switzerland Phase III trial ongoing	Pharmacotherapy (e.g., ketoconazole, metyrapone, mitotane) Radiation therapy Surgical therapy	Reduced ACTH levels Reduced morbidity from excess cortisol Improved quality of life
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 ulcer formation before it becomes visible. This device can transmit data wirelessly to a storage system for analysis. Bruin Biometrics, LLC, Los Angeles, CA Pilot trial completed	Visual assessment	Prevention or early treatment of decubitus ulcers Reduced morbidity and mortality from complications
Subretinal micro-electrode for treatment of blindness	Patients with hereditary retinal degeneration who are going blind	Device (chip) with 1,500 individual light-sensitive elements is surgically implanted into the eye under the retina; light-sensitive elements are designed to pass electrical impulses to the nerve cells in the eye. Retina Implant AG, Reutlingen, Germany Pilot trial completed; early unphased clinical trial ongoing	Epiretinal implants with external camera and processor unit	Vision restoration Improved activities of daily living Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Subretinal transplantation of retinal pigment epithelial cells to treat Stargardt macular dystrophy	Children and young adults in whom Stargardt macular dystrophy has been diagnosed	Study to determine the safety and tolerability of subretinal transplantation of retinal pigment epithelial cells derived from human embryonic stem cells. Advanced Cell Technology, Inc., Santa Monica, CA Phase I/II trials ongoing; FDA and EU granted orphan drug status	Currently, no treatment exists	Significantly improved visual performance Reversed loss of central vision Improved functional status
Sumatriptan iontophoretic patch (Zelrix) for treatment of acute migraine	Patients who are having an acute migraine episode	The Zelrix patch is new formulation of sumatriptan; a single-use transdermal patch that delivers low, controlled levels of migraine drug sumatriptan; patch is based on SmartRelief patch technology. NuPathe, Inc., Conshohocken, PA Phase III trials completed; new drug application (NDA) submitted to and accepted by FDA Jan 2011; company received complete response letter from FDA in Aug 2011; resubmitted the NDA in Jul 2012	Pharmacotherapy (e.g., pain relievers, triptans, ergot, anti-nauseates, opiates, dexamethasone)	Fast pain relief Reduced side effects compared with high level oral dose
Teriflunomide (Aubagio) for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS)has been diagnosed	No cure is available for RRMS, and more effective treatments with fewer serious side effects are needed. Teriflunomide (Aubagio®) is purported to be an immunomodulator with anti-inflammatory properties, but its exact mechanism of action is not fully known. Researchers believe it may involve reducing the number of activated lymphocytes in the central nervous system, and it is intended to block new synthesis of pyrimidines and reduce T- and B-cell proliferation. The medication is administered as a once daily oral pill in a 7 mg or 14 mg dose. Genzyme Corp., A Sanofi Company, Cambridge, MA FDA approved Sept 2012, for treating RRMS with boxed warning citing risk of hepatotoxicity and teratogenicity	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Longer remission time Reduced relapse rate Improved quality of life
Terlipressin 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 a poor prognosis 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 currently available. Given intravenously in combination with albumin. Ikaria Holdings, Inc., Clinton, NJ Phase III and II/III trials ongoing	Liver transplantation Pharmacotherapy (e.g., dopamine, misoprostol, vasoconstrictors)	Confirmed HRS reversal Increased survival to time of transplantation Transplant-free survival up to 90 days

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Therapeutic vaccine PD01A (Affitope) for Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	Current treatments for PD address symptoms, not the underlying cause, and the disease eventually plateaus or ceases to respond to drug therapies. Treatments that target the underlying cause are needed. PD purportedly is the result of pathological deposits of the protein alpha-synuclein in the brain. These deposits cause cell death, particularly in the substantia nigra, resulting in decreased production of dopamine in the brain, which, in turn, impairs motor function and other activities. PD01A (Affitope®) is a vaccine intended to induce antibodies against alpha-synuclein, which would prevent the accumulation of pathological deposits in the brain and reduce PD symptoms or halt its progression. AFFiRiS AG, Vienna, Austria Phase I trial ongoing	Adenosine A2A receptor antagonist in development Dopamine agonists Glutamate receptor 5 modulators in development Levodopa/carbidopa Monoamino oxidase-B inhibitors, etc. Nicotinic receptor agonist in development	Improved motor skills Improved movement control Slowed disease progression Improved quality of life
Thermal pulsation system (LipiFlow) for treatment of meibomian gland dysfunction	Patients in whom meibomian gland dysfunction (MGD) has been diagnosed	MGD occurs when the oil produced by the meibomian glands in eyelids becomes slightly thicker than normal, which can block the narrow duct that through which the oil travels from the gland to the tear film. Oil production continues and fills and swells the glands, causing dry eye because of the blockage; severe blockage can create enlarged glands (a cyst) or even infection. MGD may be the leading cause of dry eye and is often misdiagnosed for classic dry eye. LipiFlow® is a single-use eyepiece that applies directed energy (48º Celsius) to warm and massage the eyelids and heat the obstructive material to enable it to pass through the duct without damaging glands or other delicate structures of the eye; 25 ducts are present on each eyelid. A 12-minute per eye procedure is performed in a doctor's office. TearScience, Inc., Morrisville, NC Received FDA 510(k) clearance Jul 2011	Eyelid heat treatment (warm compresses) Fluoroquinolones Macrolide antibiotics (topical azithromycin) Omega 3 supplementation Tetracyclines	Decreased symptoms and complications

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
THR-184 for treatment of acute kidney injury postsurgery	Patients in whom acute kidney injury (AKI) postsurgery has been diagnosed	AKI is characterized by a rapid, temporary loss of kidney function resulting in a failure to maintain fluid, electrolyte, and acid-base homeostasis. AKI is diagnosed in about 1 million patients each year in the U.S., all of whom experience some permanent loss of kidney function. Causal factors for AKI include cardiac and/or vascular surgery, sepsis, inflammatory disease, trauma, or the administration of contrast dye for imaging. AKI is common in hospitalized patients and has a poor prognosis with mortality ranging from 10% to 80%. Treatment options for AKI are limited, with no pharmacological therapy approved for treatment. THR-184 is a peptide that selectively activates the bone morphogenetic protein type II receptor and type I activin-like kinase receptors, responsible for regulation of growth, differentiation, chemotaxis, and apoptosis of various cell types such as epithelial, mesenchymal, hematopoietic, and neuronal cells. Through activation of these receptors, this therapy might serve as a preventive and therapeutic option for patients with AKI. Thrasos, Inc., Montreal, Quebec, Canada Phase I trial completed	Pharmacotherapy (e.g., deferoxamine) Hydration	Reduced incidence and complications Improved quality of life
Tissue bulking agent (Nasha/Dx; Solesta) for treatment of fecal incontinence	Patients in whom fecal incontinence has been diagnosed	Current pharmaceutical, diet, and nerve-stimulation therapies for fecal incontinence may not lead to effective improvement, and surgical treatments may be too invasive, costly, and result in unfavorable outcomes. Solesta is a biocompatible tissue bulking agent, comprised of dextranomer microspheres and stabilized sodium hyaluronate; this gel may allow for narrowing of the anal canal and increased sphincter control. Treatment may serve as a 1st-line therapy that provides optimal outcomes in a less invasive and less costly manner for this indication. NASH/Dx (Solesta®) is administered via injection (dextranomer microspheres, 50 mg/mL, and stabilized sodium hyaluronate, 15 mg/mL, in a phosphate buffered 0.9 % sodium chloride solution) in the deep submucosal layer in the proximal anal canal. Oceana Therapeutics, Inc., Edison, NJ FDA approved Apr 2011	Pharmacotherapy (e.g., antidiarrheal drugs, laxatives, stool softeners) Bowel training mechanisms Dietary and lifestyle changes Enemas/laxatives Sacral nerve stimulation Surgical therapy	Improved sphincter control Decreased fecal incontinence Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Topical JAK/SYK inhibitor (R333) for treatment of discoid lupus erythematosus	Patients in whom discoid lupus erythematosus (DLE) has been diagnosed	DLE is an autoimmune disorder that causes inflamed, disc-shaped lesions on the face, chest, and scalp, which may result in scarring, swelling, and hair loss. DLE has an acute phase that research has connected to SYK tyrosine kinase signaling, which is involved in B-cell activation and proliferation. DLE also exhibits a chronic phase, attributed to the abundance of JAK signaling, which is also involved in inflammatory signalling cascades. Few treatment options are available, and they are associated with toxicities that further limit their use. R333 is a topical treatment purported to be a JAK/SYK tyrosine kinase inhibitor. Rigel Pharmaceuticals, Inc., South San Francisco, CA Phase I trial initiated	Antimalarial medications Dapsone and immune suppression medications Local cortisone injections	Resolved skin lesions
Topical XEN402 for treatment of postherpetic neuralgia	Patients in whom postherpetic neuralgia has been diagnosed	Postherpetic neuralgia can be very painful and debilitating; current treatments have variable efficacy among patients and often require trial and error to determine optimal treatment. Even then treatment can be suboptimal and the syndrome can persist long-term. XEN402 blocks sodium channel sub-type Nav1.7 (sodium channels regulate electrical conductivity in the neurons) and is intended to alleviate pain from postherpetic neuralgia, which develops after shingles in a large proportion of elderly patients. Applied topically. Xenon Pharmaceuticals, Inc., Burnaby, British Columbia, Canada Phase IIa trial completed, Phase IIb trial completed	Lidocaine skin patches Tricyclic antidepressants: Amitriptyline Nortriptyline Anticonvulsants: Gabapentin Pregabalin Opioids: Morphine Oxycodone Tramadol	Reduced or eliminated pain Reduced time to pain reduction Shorter recovery time

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
TrkA kinase inhibitor (CT327) for treatment of psoriasis	Patients in whom mild to moderate psoriasis vulgaris has been diagnosed	Current psoriasis treatments address symptoms or the inflammatory pathway in psoriasis. Keratinocyte homeostasis may underlie the pathophysiology of psoriasis; therefore, therapies targeting keratinocyte proliferation may represent novel therapeutic options. CT327 is a TrkA kinase inhibitor that is administered in a topical ointment; drug is modified with the manufacturer's “low systemic exposure” technology intended to allow local levels of the drug without systemic spread; the TrkA receptor is activated by nerve growth factor, which has been implicated in keratinocyte homeostasis and the pathophysiology of psoriasis. Creabilis SA, Luxembourg City, Luxembourg Phase II trial completed; phase II trial ongoing	Topical ointments such as: Anthralin Calcineurin inhibitors Coal tar Corticosteroids Phototherapy Systemic medications: Cyclosporin Hydroxyurea Immunomodulators Methotrexate Retinoids Thioguanine	Improved psoriasis area severity index scale Improved quality of life
Troponin activator (CK-2017357) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	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. CK-2017357 is purported to be a fast skeletal muscle troponin activator. It 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. Cytokinetics, Inc., South San Francisco, CA Phase II trials completed; FDA granted orphan drug status	Riluzole Supportive care	Improved patient/investigator global assessment of symptoms Improved pulmonary function Reduced muscle fatigue
Troponin activator (CK-2017357) for treatment of myasthenia gravis	Patients in whom generalized myasthenia gravis (MG) has been diagnosed	The drugs used to control MG either diminish in effectiveness over time (cholinesterase inhibitors) or cause severe side effects of their own (immunosuppressants). Most patients need treatment for the remainder of their lives, and more effective options are needed. Oral CK-2017357 is a fast skeletal muscle troponin activator; selectively activates the fast skeletal muscle troponin complex and increases its sensitivity to calcium, which increases skeletal muscle force in response to neuronal input and delays onset and reduces degree of muscle fatigue. Cytokinetics, Inc., South San Francisco, CA Phase II trial ongoing; FDA granted orphan drug status	Emergency plasmapheresis or intravenous immunoglobulin Pharmacotherapy (e.g., cholinesterase inhibitors, corticosteroids, immunosuppressants) Surgical therapy	Improved muscle function Delayed onset and reduced magnitude of muscle fatigue Reduced need for therapeutic thymectomy (nonthymoma) Fewer side effects

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
UroLift system for treatment of benign prostatic hyperplasia	Patients in whom benign prostatic hyperplasia (BPH) is causing lower urinary tract symptoms (e.g., difficulty urinating, recurrent bladder infections, frequent urge to urinate)	BPH is currently treated either with drugs that address only secondary symptoms or have significant side effects or with minimally invasive or invasive surgery, which involves significant recovery time. The UroLift® system is a set of minimally invasive devices intended to expand the urethral lumen through the use of sutures to retract the expanded lobes of the prostate; the treatment is performed under local anesthesia and recovery time may be as short as 2 weeks. NeoTract, Inc., Pleasanton, CA Phase III and IV trials ongoing	Pharmacotherapy (e.g., 5-alpha reductase inhibitors, alpha blockers:) Surgical therapy	Improved International Prostate Symptom Score (IPSS) Increased urine flow rate Improved quality of life
Vagus nerve stimulation for treatment of fibromyalgia	Patients in whom treatment refractory fibromyalgia has been diagnosed	Fibromyalgia remains poorly understood and there remains a lack of effective treatment options for many patients. The vagus nerve stimulation (VNS) stimulator device is implanted in patients with fibromyalgia and is adjusted to the highest current that can be comfortably tolerated. The device is intended to alter nerve centers in the brain, which may inappropriately mediate pain responses in patients; VNS is intended to be used as an adjunctive therapy. Under study at the University of Medicine and Dentistry of the New Jersey Medical School, Newark, and Pain and Fatigue Study Center, Beth Israel Medical Center, New York, NY Various manufacturers make VNS systems Phase I/II trial completed	Pharmacotherapy (e.g., duloxetine, fluoxetine, gabapentin, lorazepam, milnacipran, pregabalin, tricyclic antidepressants Behavioral and lifestyle modification	Minimal clinically important difference (pain, overall wellness, and physical function)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vascular endothelial growth factor (Eylea, aflibercept) for treatment of wet age-related macular degeneration	Patients in whom the neovascular form of age-related macular degeneration (ARMD; "wet") has been diagnosed	Vascular endothelial growth factor (VEGF) Trap-Eye (Eylea™, aflibercept) is a recombinant fusion protein consisting of human VEGF receptors 1 and 2 extracellular domains that are fused to the Fc portion of human immunoglobulin G1. The drug is formulated as a solution for intravitreal injection. It is intended to inhibit the binding and activation of VEGF receptors. Aflibercept is "indicated for the treatment of patients with neovascular ARMD (wet AMD)." It is "contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients" in the drug. The recommended dose is 2 mg by injection once a month for the 1st 3 months, followed by 2 mg every 2 months. Regeneron Pharmaceuticals, Inc., Tarrytown, NY Phase III trials completed; FDA approved Nov 2011	Pharmacotherapy(e.g., Lucentis®) Laser therapy Photodynamic therapy	Improved visual acuity Improved treatment adherence because of reduced number of eye injections
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	Only 1 treatment is approved for this condition, and the development of the disease is not yet well understood. More and better treatment is 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. Neurocrine Biosciences, Inc., San Diego, CA Phase II trials completed; FDA granted fast track status Jan 2012	Pharmacotherapy (e.g., benzodiazepines, Cogentin®, omega-3 fatty acids, Mirapex®, Tarvil®, tetrabenazine)	Reduced abnormal involuntary movements
Video game therapy for stroke rehabilitation	Patients who are recovering from mild to moderate ischemic or hemorrhagic strokes	Wii is a video gaming system. A motion-detection system allows patients to see their actions on a television screen with real-time sensory feedback; Wii tennis and Wii Cooking Mama, which uses movements that simulate cutting a potato, peeling an onion, and shredding cheese, are being used in stroke rehabilitation intended to improve motor skills and speed. Heart and Stroke Foundation, Ottawa, Ontario, Canada Ontario Stroke System, Toronto, Ontario, Canada Phase I trial completed	Standard physical therapy Standard occupational therapy Robot-assisted rehabilitative therapy	Improved motor function Improved strength Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Viral delivery of nerve growth factor (CERE-120; AAV2-neurturin) for treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	Current treatments for PD address symptoms rather than underlying cause, and the patient eventually plateaus or ceases to respond to them. CERE-120 is an adeno-associated virus vector carrying the gene for neurturin, a naturally occurring protein that repairs damaged and dying dopamine-secreting neurons, keeping them alive and restoring normal function. Degeneration of these neurons is responsible for the major motor impairments of PD. CERE-120 has been delivered by stereotactic injection into the brain. Ceregene, Inc., San Diego, CA Phase I/II trial ongoing; phase II trial completed	Levodopa/carbidopa MOA-B inhibitors	Reduced symptoms Increased motor skill functions Slowed disease progression Continued effect of treatment over time Improved quality of life
Wearable artificial kidney (WAKs) 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. AWAK Technologies, Inc., Burbank, CA FDA selected this technology in Apr 2012 as 1 of 3 technologies to be piloted for its "Innovation Pathway." Phase I study completed by developers Royal Free London NHS Foundation Trust (formerly Royal Free Hampstead NHS Trust) and Xcorporeal, Inc. (purchased by Fresenius Medical Care Holdings AG & Co. KGaA), in the United Kingdom; 5 randomized controlled trials planned, but none registered on National Clinical Trials database as of Jul 2012	Conventional home dialysis systems Kidney transplantation	Adequate filtration of toxins from kidneys Improved mobility Improved quality of life
Zotarolimus-eluting stent (Endeavor) implantation in pelvic arteries for treatment of erectile dysfunction	Men receiving a diagnosis of erectile dysfunction despite phosphodiesterase type 5 (PDE-5) inhibitor treatment	An estimated 18 million men in the U.S. experience erectile dysfunction. Although most men are adequately treated with prescription medications (e.g., sildenafil citrate) some require more invasive interventions. The zotarolimus-eluting peripheral stent (Endeavor®) involves stenting of the pelvic arteries (i.e., the pudendal arteries) that pass under the pelvic bone and terminate in the common penile artery. Patients also undergo 6 months of dual antiplatelet therapy. Medtronic, Inc., Minneapolis, MN ZEN (Zotarolimus-Eluting Peripheral Stent System for the Treatment of Erectile Dysfunction in Males with Sub-Optimal Response to PDE5 Inhibitors) trial completed Nov 2011; ongoing IMPASSE trial on erectile dysfunction due to arterial insufficiency	Intraurethral suppository of alprostadil PDE-5 inhibitors Pharmacotherapy (e.g., sildenafil citrate) Surgical therapy Vacuum pump	Improved erectile function Improved quality of life

Table 9. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 113 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
ALN-RSV01/RNAi for treatment of respiratory syncytial virus	Patients (children and adults) who have been given a diagnosis of respiratory syncytial virus (RSV) infection, including lung transplant recipients	Currently, no pharmacologic interventions are available for RSV infection; the only treatment is supportive care. ALN-RSV01 is an inhaled (nebulized) RNAi therapeutic that targets the nucleocapsid *N* gene of the RSV genome, a gene required for replication of RSV; ALN-RSV01 is intended to silence the *N* gene, thereby reducing the virus' ability to reproduce. Alnylam Pharmaceuticals, Cambridge, MA Phase II trial completed	Hypertonic saline Salbutamol Supportive care (e.g., oxygen support, hydration, suctioning of mucus from the airways etc.)	Reduced infection rate Improved lung function Reduced progression of bronchiolitis obliterans syndrome Shorter hospital stay for treating RSV infection
Amikacin Inhale for treatment of gram-negative pneumonia	Critically ill patients who are on ventilators in intensive care units (ICUs)	Amikacin Inhale (NKTR-061, BAY41-6551) is a drug-device combination that combines a special liquid formulation of the aminoglycoside antibiotic amikacin with proprietary liquid pulmonary technology; intended to deliver amikacin deep into the infected lungs of patients in the ICU with gram-negative pneumonia. Nektar Therapeutics, San Francisco, CA Bayer AG, Leverkusen, Germany Phase III trial planned	Intravenous antibacterial therapy	Resolution of infection Reduced treatment failures Increased survival
Anthrax antitoxin monoclonal antibody raxibacumab (ABthrax) for treatment of inhalation anthrax	Patients suspected to have inhaled anthrax spores	Patients can be unaware that they 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. Human Genome Sciences, Rockville, MD Phase III trial completed; biologics license application (BLA) filed in 2009; resubmitted BLA Jul 2012	Anthrax vaccine Antibiotics	Protection against inhalation anthrax Rapid resolution of symptoms

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anthrax antitoxin monoclonal antibody (Valortim) for treatment of inhalation anthrax	Patients suspected of having inhaled anthrax spores	Patients can be unaware that they inhaled anthrax spores, leading to late intervention that may render antibiotics ineffective. Treatments for later stage inhalation anthrax are needed. Valortim® is a fully human antitoxin, monoclonal antibody intended to treat inhalation anthrax by inhibiting the activity of the protective antigen of anthrax toxin, inhibiting the protein's pathogenesis. PharmAthene, Inc., Annapolis, MD Phase I trial ongoing	Antibiotics Anthrax vaccine Raxibacumab (ABthrax™; investigational)	Rapid resolution of symptoms Increased survival
Attachment inhibitor BMS-663068 for treatment of HIV	Patients in whom HIV infection has been diagnosed	HIV infection remains a chronic illness resulting in high morbidity and mortality. HIV drug resistance, poor tolerance of existing treatments, and high lifelong costs of therapy indicate a need for improved therapeutic options. BMS-663068 is an oral HIV-1 attachment inhibitor purported to bind the HIV envelope glycoprotein gp120 and interfere with attachment of the virus to the cellular CD4 receptor expressed on helper T cells and macrophages. Administered 400 mg, twice daily, in combination with a patient's existing treatment regimen. Bristol-Myers Squibb, New York, NY Phase II trial ongoing	Antiretroviral therapy Enfuvirtide Maraviroc Therapeutic vaccines (investigational)	Decreased viral load Slower development of resistance Reduced morbidity Reduced mortality
Autologous dendritic cell vaccine (AGS-004) for treatment of HIV infection	Patients in whom HIV infection has been diagnosed	HIV remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments; HIV drug resistance, poor tolerance to existing treatments, and high lifelong cost of therapy present opportunities for the development of novel and effective HIV therapies. AGS-004 is a personalized dendritic cell vaccine loaded with HIV RNA derived specifically from the patient; intended to generate a relevant immune response to the HIV strain actively infecting the patient, thus controlling viral load after cessation of therapy. Administered in a series of 4 injections. Argos Therapeutics, Inc., Durham, NC Phase II trial ongoing	Antiretroviral therapy Therapeutic vaccines (investigational)	Improved CD4+ T-cell counts Improved CD8+ T-cell responses Sustained control of viral load after cessation of therapy Time to viral load reduction Reduced morbidity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous dendritic cell vaccine for treatment of HIV infection	Patients in whom chronic HIV infection has been diagnosed	HIV remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments. HIV drug resistance, poor tolerance to existing treatments, and high lifelong cost of therapy present opportunities for the development of novel and effective HIV therapies. Autologous dendritic cells (DC) are the most efficient antigen presenting cells in the immune system; priming DC with antigen can lead to the generation of adaptive immune responses (B cell and T cell); the vaccine consists of DC generated with granulocyte-macrophage colony-stimulating factor and interferon; the cells are also pulsed with lipopeptides encoding HIV-1 antigens; these cells are then readministered into the patient in 4 injections over 6 months; the vaccine is intended to induce CD8+ T-cell responses against HIV-1 infected cells, capable of controlling the infection and reducing the need for medication. Baylor College of Medicine, Houston, TX Phase I/II trial ongoing	Antiretroviral therapy Therapeutic vaccines (investigational)	Reduced morbidity Reduced time to viral load reduction Reduced use of ART Sustained control of viral load after cessation of therapy Improved quality of life
Autologous encapsulated fecal matter to rehabilitate gastrointestinal flora after *Clostridium difficile* infection	Patients at risk of *Clostridium difficile* infection (CDI)	Recurrent CDI is responsible for significant morbidity, mortality, and costs, and is resistant to treatment. Up to 60% of patients previously treated for recurrent CDI with antibiotics develop further recurrence after therapy is stopped. This suggests that other therapeutic options are needed. Autologous rehabilitation of gastrointestinal flora is purported to consist of freeze-dried fecal material taken from a patient prior to hospitalization and placed into capsules. Should recurrent CDI occur while the patient is hospitalized, the patient can take the capsules in an attempt to restore the natural flora of the patient and resolve the CDI. Intended to be 1st-line therapy. Medilink North West, Manchester, UK No trials identified	Allogeneic fecal microbiota transplant Fidaxomicin Metronidazole Vancomycin	Faster time to resolution of CDI-related diarrhea Reduced CDI recurrence and morbidity Shorter hospitalization time

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AVI-6002 for treatment of Ebola virus exposure	Patients who have been exposed to Ebola virus	Ebola infection has an 80% mortality rate with no effective treatments. AVI-6002 is a drug that uses phosphorodiamidate morpholino oligomer (PMO) antisense technology; PMOs are synthetic structures modeled after RNA, but with modifications purported to improve pharmacologic properties. PMOs have the same nucleic acid bases found in RNA or DNA, but they are bound to morpholine rings instead of ribose rings and are linked through phosphorodiamidate rather than phosphodiester or phosphorothioate groups, which are purported to eliminate ionization in physiologic pH, making PMOs uncharged. AVI-6002 utilizes the manufacturer's PMOplus™ technology to add position-specific, molecular charges to the PMO backbone, which is purported to improve targeted cell penetration to improve efficacy in the presence of viral mutations. PMOs could be created in a very short (i.e., days or weeks) timeframe. AVI BioPharma, Inc., Bothell, WA, now Sarepta Therapeutics, Inc., Cambridge, MA Phase I trial completed; manufacturer to file for approval through the animal efficacy rule after completing studies in healthy human subjects	Supportive care	Increased symptom resolution Reduced mortality
AVI-6003 for treatment of Marburg virus	Patients who have been exposed to Marburg virus	Marburg infection has an 80% mortality rate with no effective treatments. AVI-6003 uses phosphorodiamidate morpholino oligomer (PMO) antisense technology; PMOs are synthetic structures modeled after RNA, but with modifications purported to improve pharmacologic properties. PMOs have the same nucleic acid bases found in RNA or DNA, but they are bound to morpholine rings instead of ribose rings and are linked through phosphorodiamidate rather than phosphodiester or phosphorothioate groups, which are purported to eliminate ionization in physiologic pH, making PMOs uncharged. AVI-6003 utilizes the manufacturer's PMOplus™ technology to add position-specific, molecular charges into the PMO backbone, which is purported to improve targeted cell penetration to improve efficacy in the presence of viral mutations. PMOs could be created in a very short (i.e., days or weeks) timeframe. AVI BioPharma, Inc., Bothell, WA (now Sarepta Therapeutics, Inc., Cambridge, MA), with support from the U.S. Army Medical Research Institute for Infectious Diseases, Frederick, MD Phase I trial completed; manufacturer to file for approval through the animal efficacy rule after completing studies in healthy human subjects	Supportive care	Improved symptom resolution Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
BAL30072 for treatment of serious gram-negative infections	Patients in whom serious gram-negative infection has been diagnosed	Beta-lactam antibiotics are a mainstay of antimicrobial therapy, but their use is increasingly compromised by acquired resistance, especially in gram-negative bacteria. A recent survey of thousands of patients from hospitals globally revealed gram-negative bacteria in 60% of clinical isolates in intensive care units. A need exists for novel gram-negative antibiotics with broad coverage against clinically relevant pathogens; purportedly no compounds are currently in late-stage development in this space. BAL30072 is a novel siderophore (iron-binding) sulfactam antibiotic with a unique mode of action; BAL30072 is purported to have potent bactericidal activity against gram-negative pathogens including *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Klebsiella* spp. and *Enterobacter* spp.; BAL30072 is purported to exploit natural nutrient uptake systems of pathogens to gain access to its intracellular target; BAL30072 is stable towards many types of beta-lactamase enzymes and metallo-beta-lactamases, which can deactivate most of the currently marketed beta-lactam antibiotics such as cephalosporins and carbapenems; may be used for treating hospital-acquired pneumonia (including ventilator-associated pneumonia), complicated intra-abdominal infections, or complicated urinary tract infections. Basilea Pharmaceutica, Ltd., Basel, Switzerland Phase I trial ongoing	Aminoglycosides Carbapenems	Improved clinical response Improved microbiologic response Shorter hospital stays Reduced mortality
Bavituximab for treatment of chronic hepatitis C virus infection	Patients in whom chronic HCV infection has been diagnosed	Many patients treated with the current standard of care remain chronically infected with HCV. Bavituximab is a monoclonal antibody directed against phosphatidylserine (PS) exposed on the surface of cells infected by HCV; PS expression is believed to be immunosuppressive; bavituximab is thought to bind to PS and block the immunosuppressive signals, improving immune responses to HCV; it could potentially effectively treat HCV irrespective of the viral genotype or drug resistance; bavituximab is being administered in various dose regimens of 0.3–6.0 mg/kg of body weight, weekly, for 8 or 12 weeks, in clinical trials as a monotherapy and combination therapy with ribavirin. Peregrine Pharmaceuticals, Inc., Tustin, CA Phase I/II trial completed	Boceprevir Pegylated interferon/ribavirin Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bedaquiline (TMC207) for treatment of drug-resistant tuberculosis	Patients in whom drug-resistant tuberculosis (TB) is inspected	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. Bedaquiline (TMC207) is an experimental diarylquinoline antituberculosis drug; intended to achieve clinical response rates twice as fast as standard treatment. Tibotec BVBA, Beerse, Belgium Phase III trial ongoing: new drug application submitted to FDA Jun 2012 for treating pulmonary, multi-drug resistant tuberculosis (MDR-TB) in adults as part of combination therapy; FDA granted priority review Sept 2012	Ethionamide Ethambutol Isoniazid Kanamycin Ofloxacin Pyrazinamide Rifampicin	Resolution of active TB infection Reduced time to clinical response Improved patient adherence with therapy Reduced spread of infection Improved quality of life
BI-201335 (NS3/4 protease inhibitor) for treatment of chronic hepatitis C virus infection	Patients in whom chronic infection with hepatitis C virus (HCV) has been diagnosed	Current standard of care for HCV infection is ineffective in more than half of infected patients; effective treatments that improve clinical outcome in a shorter period of time are needed. BI-201335 is a NS3/4 protease inhibitor intended to block the activity of HCV protease preventing the cleavage and maturation of functional viral particles. 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 BI-207127 (polymerase inhibitor). Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials ongoing; granted FDA fast track status in combination with standard of care and in IFN-free combination with BI-207127	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
BI-207127 (non-nucleoside NS5B polymerase inhibitor) for treatment of chronic hepatitis C virus infection	Patients in whom chronic infection with hepatitis C virus (HCV) 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. 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, and 1,200 mg, 3 times a day. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase II trial completed; granted FDA fast track status in combination with BI-201335 (NS3/4 protease inhibitor) in interferon (IFN)-free combination	Boceprevir Sofosbuvir (in development) Pegylated interferon/ribavirin Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
BIT225 (viroporin inhibitor) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C infection (HCV) has been diagnosed	Existing HCV drugs have limited effectiveness and can be toxic; fewer than half of infected patients do not respond to current therapies, demonstrating the need for new treatments that directly target and halt replication and reproduction of the virus. BIT225 is a 1st-in-class drug candidate designed to specifically target the p7 membrane polypeptide of HCV; part of a new group of small-molecular compounds that inhibit a new class of antiviral targets known as viroporins. By blocking the ion channel activity of viroporins, these compounds are able to inhibit viral budding and replication; BIT225 is being investigated in combination with standard-of-care pegylated interferon plus ribavirin (IFN/RBV); preclinical studies have shown BIT225 to be highly synergistic with IFN/RBV as well as with NS5B (polymerase) inhibitors. Currently administered orally, 200 or 400 mg. Biotron Ltd., Sydney, Australia Phase II trial complete	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
BMS-914143 (pegylated interferon lambda) 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 ineffective in more than half of infected patients, and the presence of pegylated interferon (IFN) alpha-2a (IFNa-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. Bristol-Myers Squibb, New York, NY Phase II trials ongoing	IFN-free HCV drug combinations (in development) Pegylated IFN alpha-2a or Pegylated IFN alpha-2b/ribavirin	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
BTA798 for treatment of human rhinovirus infection	Patients who are immunocompromised or have respiratory complications such as asthma or chronic obstructive pulmonary disease (COPD)	Human rhinoviruses are highly prevalent and cause the common cold besides being a frequent cause of upper respiratory tract infections, which can cause complications and hospitalization in high-risk patients who are immunocompromised or have asthma or COPD. Only supportive care is available to these patients. BTA798 is an oral antiviral compound purported to inhibit attachment of the virus to host cells in the respiratory tract, preventing viral entry and replication. Administered twice daily. Biota Holdings, Ltd., Notting Hill, Victoria, Australia Phase II trial ongoing	Supportive care	Reduced exacerbations and hospitalization for asthma and COPD from rhinovirus infection Improved quality of life
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. CB-183,315 is a novel cyclic lipopeptide, which is purported to disrupt bacterial membrane potential, inhibiting bacterial metabolism. Administered orally, 125–250 mg, twice daily, for 10 days. Cubist Pharmaceuticals, Inc., Lexington, MA Phase II trial completed	Fecal microbiota transplant Fidaxomicin Metronidazole Vancomycin	Reduced CDI recurrence rate Shorter hospitalization time Faster time to resolution of diarrhea
Clostridium difficile vaccine (ACAM-CDIFF) for prevention of infection 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 hospital-acquired infection the can lead to significant morbidity, mortality, lengthened hospital stays and cost methods 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. Sanofi, Paris, France Phase II trials ongoing	Hospital infection control programs	Reduced *C. difficile* infection rates Reduced use of antibacterial drugs Reduced hospitalization time Reduced isolation

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
CMX001 for prevention of cytomegalovirus infection after hematopoietic stem cell transplant	Patients who recently received a hematopoietic stem cell transplant (HSCT)	In immunocompromised patients, such as those who have undergone HSCT, cytomegalovirus (CMV) infections are recognized as a significant cause of morbidity and mortality. Immunocompromised pediatric HSCT patients are particularly susceptible to serious and/or fatal CMV infections, for which no treatments are approved. CMX001 is purported to be a broad spectrum, oral antiviral for the treatment or prevention of life-threatening double-stranded DNA (dsDNA) viral diseases. CMX001 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 cytomegalovirus infection. PIM technology covalently modifies the cidofovir molecule so that it mimics a naturally occurring phospholipid metabolite that can utilize natural uptake pathways to achieve oral availability. Additionally, CMX001 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 of body weight in pediatric or adult patients. Chimerix, Inc., Durham, NC Phase II trial completed; FDA granted fast track status	Cidofovir (off label)	Reduced morbidity from adenovirus infection Reduced mortality from adenovirus infection
Collaborative care model (HITIDES) for treatment of depression secondary to HIV	Patients in whom depression secondary to HIV has been diagnosed	HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES) is a collaborative care model to support HIV and mental health clinicians in delivering evidence-based depression treatment. Depression care team (registered nurse depression care manager, a clinical pharmacist, and a psychiatrist) works with treating (for HIV) clinicians, delivering the following components: participant education and activation, assessment of treatment barriers and possible resolutions, depression symptom and treatment monitoring, substance abuse monitoring, and instruction in self-management (e.g., encouraging patients to exercise and participate in social activities). Veterans Affairs Medical Centers Trial completed	Usual HIV care without depression care team	Depression improvement Improved care implementation process Improved quality of care Improved health status Decreased HIV symptom severity Improved HIV medication adherence Improved antidepressant adherence Improved patient satisfaction Improved health-related quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Copper surfaces in the intensive care unit for prevention of hospital-acquired infections	Patients admitted to an intensive care unit (ICU)	Health care–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 is purported to control bacterial growth and lower the rates of infections acquired in the ICU; bacterial reduction rates are intended to achieve the same outcome as current "terminal cleaning" practices. International Copper Association, New York, NY Commercially available; studies at hospitals ongoing	Terminal cleaning of standard surfaces	Reduced infection rates Reduced bacteria isolated from surfaces Reduced morbidity and mortality from HAIs
Crofelemer 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 have chronic diarrhea, which can reduce adherence to antiretroviral regimens. Effective antidiarrheals that do not cause adverse reactions with antiretrovirals are needed. Crofelemer purported to treat diarrhea by inhibiting the cystic fibrosis transmembrane conductance regulator ion channel, which is responsible for the transport of chloride ions into the intestinal lumen, which subsequently draws water into the bowel. Crofelemer is purported to have poor systemic absorption, thus limiting the development of adverse events. In trials, crofelemer has been administered orally, 125 mg, twice daily. Salix Pharmaceuticals, Ltd., Raleigh NC Napo Pharmaceuticals, Inc., San Francisco, CA Phase III trial ongoing; FDA granted fast track status; new drug application submitted to FDA for treating HIV-associated diarrhea; decision date extended until 2013	Absorbents containing attapulgite or polycarbophil Antibiotics Diphenoxylate Loperamide	Reduced number of watery bowel movements Relief of diarrhea

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cyclophilin inhibitor 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 period of time are needed. Cyclophilin A is a host cell protein involved in protein folding and transport, and it has been shown to be essential in HCV replication; cyclosporine A inhibits cyclophilin activity but is immunosuppressive; alisporivir (Debio-025) is an oral modified form of cyclosporin A, that is purported to act as a host-targeted antiviral with enhanced cyclophilin binding but no immunosuppressive activity, which is purported to be due to the inability of the alisporivir-cyclophilin complex to bind calcineurin which modulates proinflammatory lymphocyte signaling. Debiopharm, S.A., Lausanne, Switzerland Novartis International AG, Basel, Switzerland Phase III trials ongoing; FDA granted fast track status	Boceprevir Pegylated interferon/ribavirin Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Cytosine nucleoside analog mericitabine (RG7128; RO5024048) 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 period of time are needed. Mericitabine is a cytosine nucleoside analog purported to inhibit virus genome replication. The drug may or may not be used in combination with standard-of-care pegylated interferon plus ribavirin (IFN/RBV). Pharmasset, Inc., Princeton, NJ F. Hoffmann-La Roche Ltd., Basel, Switzerland Phase II trials ongoing	Boceprevir Sofosbuvir (in development) IFN/RBV Telaprevir	Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
DAS181 (Fludase) for treatment and prevention of influenza-like illness	Patients at high risk of influenza-like illness (ILI)	Resistance to current neuraminidase inhibitors may leave patients at risk of ILI; treatments with new mechanisms of action may help treat existing and emerging mutant strains of the virus. ILI is caused by all types and strains of influenza and parainfluenza viruses; DAS181 (Fludase®) is a recombinant protein purported to be a broad spectrum agent against ILI. It targets host cell receptors and is purported to prevent the entry of influenza and parainfluenza viruses into host cells by binding to and inactivating sialic acid of the surface of cells lining the respiratory tract. DAS181 consists of 2 parts, a sialidase and a cell-surface anchoring domain, that are designed to attach to the respiratory epithelium and increase retention time and potency. Agent is administered via oral inhalation, as a single 10 mg dose or 10 mg, once daily for 3 days. NexBio, Inc., San Diego, CA Phase II trials ongoing	Laninamivir (in phase III trials) Oseltamivir Peramivir Zanamivir	Reduced viral loads in respiratory secretions Shorter time to achieve a sustained reduction in viral shedding Reduced transmission and incidence of influenza Reduced incidence of ILI
Disinfection of high-touch surfaces with peracetic acid disinfectant to prevent transmission of hospital-acquired infections	Patients in a hospital or other health care setting in which where health care–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 the most frequently touched surfaces (i.e., bed rails, bedside tables, call buttons, telephones) in patient rooms daily with a surface sporicidal and disinfectant containing peracetic acid is purported to reduce the transmission of the bacteria *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* more than standard terminal-cleaning procedures using bleach. Cleveland VA Medical Center, Cleveland, OH	Antimicrobial copper touch surfaces Terminal cleaning procedures using bleach and cleaning of visibly soiled surfaces as necessary Ultraviolet light	Reduced infection rates Reduced bacteria isolated from surfaces Reduced morbidity and mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
DNA vaccine (INO-3510) for prevention of H1N1 and H5N1 influenza	Patients at risk of H1N1 and H5N1 influenza	Influenza continues to cause significant morbidity and mortality in susceptible populations; improper strain selection and viral mutations continue to challenge vaccine developers. INO-3510 is a SynCon® DNA vaccine intended to prevent H1N1 influenza and avian H5N1 influenza; administered using intradermal electroporation; SynCon vaccines are designed through a proprietary method with the intention of achieving cross-strain protection against the natural and frequent mutations of influenza strains within subtypes; vaccine product is intended to eventually be broadly protective and induce effective antibody and T-cell responses against influenza infection. Inovio Pharmaceuticals, Inc., Blue Bell, PA Phase I trial ongoing	Pandemic influenza vaccines Seasonal inactivated flu vaccines Seasonal live flu vaccines	Protection against influenza Reduced morbidity and mortality
Duct tape Red Box safe zone to prevent transmission of hospital infections and improve care	Patients with infections requiring isolation	Patients with infections requiring isolation sometimes have simple communication needs, yet, hospital infection control procedures require that personnel gown-up to enter the patient's room prior to communicating, thus introducing a barrier to communication. A duct tape Red Box safe zone can be applied to the floor extending 3 feet outside of the patient's room signifying the barrier to entry of an isolated room and providing a clear boundary where a health care provider can communicate with a patient regarding simple requests such as getting a glass of water; this intervention is intended to decrease the need for excessive gowning and to increase the frequency with which health care providers check on patients in isolation. Trinity Medical Center, Rock Island and Moline, IL, and Bettendorf and Muscatine, IA	Standard infection control procedures	Improved frequency of communication Improved patient experience/satisfaction Reduced staff hours/costs spent gowning
Entry inhibitor (ITX-5061) to prevent chronic hepatitis C reinfection after liver transplantation	Patients with chronic hepatitis C virus (HCV) infection who are undergoing liver transplantation	Reinfection with HCV is a concern for patients with chronic HCV infection who have received liver transplants. Current treatments for chronic HCV infection are associated with a long duration of therapy and adverse events, and new options to prevent HCV reinfection after undergoing liver transplantation are needed. ITX-5061 is purported to be an entry inhibitor that binds a host-cell receptor to prevent HCV from entering host cells. ITX-5061 is administered before transplantation, immediately after transplantation, and daily thereafter for 1 week. iTherX, Inc., San Diego, CA Phase I trials ongoing	Boceprevir Pegylated interferon/ribavirin combination Telaprevir Other HCV treatments in development	Increased graft survival Increased patient survival Reduced HCV reinfection after transplantation

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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) has been contraindicated in patients with serious infections; however, recent trials in patients with H1N1 influenza suggested some utility for the procedure. ECMO involves cannulas placed in large blood vessels to provide access to the patient's blood. The ECMO machine continuously pumps blood from the patient through a membrane oxygenator that imitates the gas exchange process of the lungs. Oxygenated blood is then returned to circulation. Management of the ECMO circuit requires a specially trained team. Far Eastern Memorial Hospital, Taipei, Taiwan, and National Taiwan University Hospital, Taipei Could be implemented readily	Ventilation support Treatment of comorbidities	Reduced morbidity Reduced mortality
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. Multiple trials ongoing at various U.S. medical centers	Fidaxomicin Metronidazole Vancomycin	Reduced diarrhea Reduced dehydration Reduced reinfection
Fidaxomicin (Dificid) for treatment of *Clostridium difficile* infection	Patients in whom *Clostridium difficile* associated diarrhea has been diagnosed	Because of antibiotic resistance, new antibacterials that can improve clinical cure rates and reduce (*Clostridium difficile* infection) CDI recurrence are needed. Fidaxomicin (Dificid®) is an antibiotic that is 1st in a new class called macrocyclics, which inhibit bacterial RNA polymerase, resulting in rapid killing; fidaxomicin has a narrow spectrum and selectively eradicates CDI with minimal disruption to the normal intestinal flora, which may lower recurrence rates. Administered orally, 200 mg, twice a day. Optimer Pharmaceuticals, Inc., San Diego, CA FDA approved May 2011	Fecal microbiota transplant Metronidazole Vancomycin	Increased clinical cure rates Reduced CDI recurrence

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fluoroketolide (CEM-101) for treatment of gonorrhea	Patients in whom gonorrhea has been diagnosed	Resistance to fluoroquinolones has made cephalosporins the recommended and last-line treatment for gonorrhea infection. Cephalosporin-resistant gonorrhea has been detected in Europe, Japan, and Australia, and new treatment options are needed for emergent resistant infections. CEM-101 is a novel fluoroketolide (macrolide) antibiotic that exerts its antibacterial activity by reversibly binding to the 50S subunit of the bacterial ribosome, blocking protein synthesis. Administered orally, 1,200 mg, once daily. Cempra, Inc., Chapel Hill, NC Phase II trial ongoing	Cephalosporins Fluoroquinolones	Bacterial eradication at end of therapy Reduced transmission Resolved symptoms
Hemopurifier blood filter for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C infection has been diagnosed	Hemopurifier blood filter works with standard hemodialysis or other conventional blood pump technology to capture and remove hepatitis C particles from general circulation; intended as an adjunct therapy to accelerate viral load reduction at the outset of standard of care drug regimens. Aethlon Medical, Inc., San Diego In initial trials; commercialization planned for India	Boceprevir Pegylated interferon/ribavirin Telaprevir	Reduced viral load Improved efficacy of drug therapy Resolution of chronic infection Improved quality of life
Hemopurifier blood filter for treatment of HIV infection	Patients in whom HIV infection has been diagnosed	Hemopurifier blood filter works with standard hemodialysis or other blood pumping devices to remove viral particles from circulating blood. Intended as a potential therapeutic option for HIV-infected individuals to manage disease progression once they become resistant to antiviral drug regimens. Aethlon Medical, Inc., San Diego, CA In initial clinical trials; commercialization planned for India	Antiretroviral therapy Therapeutic vaccines (investigational)	Reduced viral load Improved efficacy of drug therapy Improved symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Hemopurifier blood filter to capture infectious agents from bloodstream during pandemics and bioterrorism	Patients affected by pandemic disease or bioterrorism agents	Hemopurifier blood filter works with conventional dialysis systems or other blood pumping technology using a broad-spectrum approach to attract and capture infectious agents from the bloodstream during pandemics or bioterrorism events; in vitro studies have shown that Hemopurifier effectively captures Dengue hemorrhagic virus, Ebola hemorrhagic virus, Lassa hemorrhagic virus, West Nile virus, H5N1 avian influenza virus, 2009 H1N1 influenza virus, the reconstructed Spanish flu of 1918 virus, and monkeypox virus, which serves as a model for human smallpox infection. Aethlon Medical, Inc., San Diego, CA In initial clinical trials; commercialization planned for India	Standard public health measures for containing and treating pandemic disease and/or biologic weapon threats	Reduced severity of pandemic disease
Histone deacetylase inhibitor (vorinostat, Zolinza) for treatment of HIV infection	Patients in whom HIV infection has been diagnosed	HIV infection is a chronic disease with no cure. This is partially due to sequestration of latent virus in memory compartments throughout the body that can be reactivated throughout life. Drugs that could target latent HIV might contribute to a “cure” for the infection. Vorinostat (Zolinza®) is a histone deacetylase inhibitor; histone deacetylase is responsible for forming chromatin and inhibiting gene expression. By inhibiting histone deacetylase, vorinostat activates HIV-provirus transcription and the virus replication cycle, thus ending viral latency in the cell. Vorinostat is intended to be used in combination with antiretroviral therapy, which is intended to inhibit further replication of the newly activated virus. Administered 200, 400, or 600 mg, orally, as needed, to activate the virus. University of North Carolina, Chapel Hill Phase I/II trial ongoing; FDA approved for treating cutaneous T-cell lymphoma	Antiretroviral therapy Therapeutic vaccination Zinc finger nuclease product in development	Better long-term control of the virus Reduced HIV load Long-term undetectable HIV

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
INSTI rapid HIV antibody test for the detection of HIV-1 and HIV-2 infection	Patients who wish to determine their HIV-1 or HIV-2 status	Current HIV-infection diagnostics require 15–30 minutes for preliminary results, which must be confirmed by more costly and time-consuming Western blot and indirect fluorescent antibody tests. Using a multi-test rapid algorithm may eventually provide quick and definitive HIV testing at the point of care. INSTI™ rapid HIV antibody test includes a unique antigen construct comprised of recombinant transmembrane proteins from HIV-1 (gp-41) and HIV-2 (gp-36), which is purported to provide greater than 99% sensitivity and specificity and can add to the predictive power of any rapid testing algorithm currently in use. INSTI uses a novel flow-through technology that purportedly allows more rapid detection of HIV, within 60 seconds, compared with the lateral-flow technology currently used in rapid HIV detection kits. INSTI also includes a unique procedural control using a true human immunoglobulin G which purportedly will allow the test to react only when the correct quantity of human blood is added, which may reduce user error. The test is purported to be highly stable and does not require refrigeration or specialized storage. By combining pretest and posttest counseling into a single visit, INSTI may increase the capacity of a health care facility to provide HIV testing to more patients and promote prompt treatment. BioLytical™ Laboratories, Inc., Richmond, British Columbia, Canada FDA approved Dec 2010 under premarket approval application for detection of antibodies to HIV-1 in whole blood, finger stick blood, or plasma specimens	OraQuick Advance® Uni-Gold Recombigen® Clearview® Complete HIV 1/2 and Clearview® HIV 1/2 Stat-Pak Reveal™ HIV	Improved HIV counseling Improved HIV detection Improved treatment outcomes Increased rates of HIV testing
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 purported to target the HCMV terminase enzyme. The terminase enzyme is crucial for concatemeric HCMV DNA cleavage during the replication process and its subsequent packaging into the HCMV virions. This is purported to be a novel mechanism of action that should remain effective against strains resistant to current therapy targeting the HCMV DNA polymerase. In a clinical trial, letermovir was administered orally, 120 or 240 mg, once daily. AiCuris GmbH & Co. KG, Wuppertal, Germany Phase II trial complete; FDA granted orphan drug status and fast track designation	Ganciclovir	Decreased rate of organ rejection Increased time to organ rejection Reduced HCMV load

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Live attenuated rabies virus vaccine for treatment and prevention of rabies	Patients at risk of rabies or who are suspected to be infected with rabies	Rabies can be effectively treated or prevented only if it has not infected the central nervous system (CNS), after which time survival outcomes are poor. Live attenuated rabies vaccine is purported to prevent rabies infection. It is also purported to generate effective cellular immune responses to the virus in patients infected with rabies virus even after it has infected the CNS and progressed to the brain. Thomas Jefferson University, Philadelphia, PA Pilot trial ongoing	Prophylactic rabies vaccine Rabies immune globulin	Improved survival
Microbicide (NVC-422) for treatment of adenoviral conjunctivitis	Patients in whom adenoviral conjunctivitis has been diagnosed	Adenoviral conjunctivitis is a highly contagious ocular infection with no effective treatment. NVC-422 is an Aganocide® microbicide that is purportedly derived from natural substances found in the immune system said to help resolve infections while minimizing resistance. It is delivered as an ophthalmic solution, 0.33%. NovaBay Pharmaceuticals, Inc., Emeryville, CA Phase II trial planned	Supportive care	Reduced transmission Relieved symptoms Resolved infection
Modified vaccinia virus Ankara vector-encoding influenza nucleoprotein and matrix protein 1 for prevention of influenza	Patients at risk of influenza	Influenza strains mutate each year, requiring a new vaccines annually for protection. A long-lasting, effective, universal vaccine is sought. Modified vaccinia virus Ankara (MVA) vector vaccine encoding nucleoprotein and matrix protein 1 (MVA-NP+M1) of influenza virus has been designed to induce broad T-cell responses in patients. The NP and M1 antigens are naturally expressed inside viruses and virus-infected cells and do not mutate annually, unlike the neuraminidase and hemagglutinin antigens targeted in traditional antibody-based influenza vaccines. Thus, the investigators purport, this vaccine is not expected to need annual reformulations. The MVA vector is purported to express NP and M1 proteins resulting in the generation of T-cell–based immunity in the absence of a productive viral infection. Jenner Institute (a partnership between Oxford University and the Institute for Animal Health), Oxford, UK Phase I trial completed against the H3N2/Wisconsin influenza strain	Pandemic influenza vaccines Seasonal inactivated flu vaccines Seasonal live flu vaccines	Prevention of influenza infections Reduced hospitalizations Reduced length of hospitalization Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Monoclonal antibody entry inhibitor (ibalizumab) for treatment of HIV infection	Patients in whom HIV infection has been diagnosed	HIV infection remains a chronic illness resulting in high morbidity and mortality. HIV drug resistance, poor tolerance of existing treatments, and high lifelong costs of therapy indicate a need for improved therapeutic options. Ibalizumab is purported to be a nonimmunosuppressive monoclonal antibody that binds CD4, the major HIV receptor expressed on the surface of T cells and macrophages. Ibalizumab is purported to compete with HIV for CD4-binding sites, slowing the HIV infectious cycle. Administered intravenously, 800 mg, every 2 weeks or 2,000 mg, every 4 weeks, in combination with the optimized background regimen. TaiMed Biologics, Inc., Taipei, Taiwan Phase II trials ongoing	Antiretroviral therapy Enfuvirtide Maraviroc Therapeutic vaccines (investigational)	Decreased viral load Slower development of resistance Reduced morbidity Reduced mortality
Nano-stat-based intranasal vaccine for prevention of respiratory syncytial virus	Infants and children, especially 2–3 years of age and the elderly in whom respiratory syncytial virus (RSV) has been diagnosed	The number 1 cause of childhood hospitalization both in the U.S. and around the world is RSV infection. Approved vaccines to prevent it do not exist. The vaccine is being developed as an intranasal vaccine for RSV using the company's Nano-stat®-based technology. The company asserts that "the nanoemulsion is uniquely capable of permeating the nasal mucosa, where it loads vaccine antigen into immune-presenting cells. These cells then carry the antigen to areas of the body that initiate an immune response, including the lymph nodes, thymus and spleen producing both mucosal immunity and systemic immune response." NanoBio Corporation, Ann Arbor, MI Phase I trial planned	Palivizumab (Synagis®)	Improved adherence with vaccination (no needles) Reduced incidence of bronchiolitis and pneumonia Reduced hospitalizations Reduced mortality
Nitro-dihydro-imidazooxazole (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, besides standard TB regimens. Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan Phase III trial ongoing	Bedaquiline, a diarylquinoline in development Ethionamide (Trecator®) Kanamycin Ofloxacin (Floxin®) PA-824, a nitroimidazole in development Pyrazinamide	Improved patient adherence with therapy Reduced spread of infection Reduced time to clinical response Resolution of active TB infection Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nitazoxanide and therapeutic hepatitis C virus vaccine (IC41) for chronic hepatitis C virus infection	Patients in whom hepatitis C virus (HCV) infection has been diagnosed	HCV infection in many infected patients is resistant to treatment or has a suboptimal response to available treatments. 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; oral nitazoxanide will be combined with IC41, a therapeutic HCV vaccine containing 5 HCV-derived peptides adjuvanted with synthetic poly-L-arginine (IC-30). The vaccine is administered intradermally. Romark Laboratories, L.C., Tampa, FL; Intercell AG, Vienna, Austria Phase II trials completed	Boceprevir Pegylated interferon/ribavirin Telaprevir	Rapid virologic response Sustained virologic response Slowed or halted disease progression to liver failure Improved quality of life
Nitazoxanide 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 drug is administered orally, 300 mg, twice a day. Romark Laboratories, L.C., Tampa, FL Phase II/III trial completed	Oseltamivir (Tamiflu®) Zanamivir (Relenza®)	Reduced complications of influenza infection Shorter duration of symptoms
Nitazoxanide for treatment of viral respiratory infections in children	Pediatric patients in whom a respiratory viral infection has been diagnosed	No effective treatments are available for viral respiratory infections (rhinovirus, coronavirus, influenza, parainfluenza, adenovirus, and respiratory syncytial virus). Only supportive care can be offered. Nitazoxanide is purported to be the 1st agent in a new class of broad-spectrum antiviral drugs called the thiazolides. The drug is intended to interfere with the maturation of viral proteins. In trials, nitazoxanide was administered orally, 100–200 mg, twice daily. Romark Laboratories, L.C., Tampa, FL Phase II trial completed	Oseltamivir (Tamiflu®; for influenza) Supportive care Zanamivir (Relenza®; for influenza)	Reduced duration of symptoms Reduced morbidity Viral resolution

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nitroimidazole (PA-824) for treatment of pulmonary tuberculosis	Patients in whom multidrug-resistant/drug susceptible tuberculosis 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, which has activity in vitro against all tested drug-resistant clinical isolates; intended to shorten treatment time and simplify treatment. Given orally. Novartis International AG, Basel, Switzerland Bayer AG, Leverkusen, Germany Phase II trials ongoing	Ethionamide Ethambutol Isoniazid Kanamycin Ofloxacin Pyrazinamide Rifampicin	Shorter duration of therapy Simpler dosing Improved adherence Safer method of action Lower cost of overall treatment
Nonnucleoside NS5B polymerase inhibitor (setrobuvir) 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 generally ineffective in more than half of infected patients. Effective treatments are needed. Setrobuvir is a HCV nonnucleoside, NS5B polymerase inhibitor intended to limit viral replication when used in combination with pegylated interferon plus ribavirin (IFN/RBV) for both treatment-naive patients and patients whose HCV infection has failed to respond to a prior course of therapy with IFN/RBV. Administered orally, 200–400 mg. Anadys Pharmaceuticals, Inc., San Diego, CA Phase II trial ongoing; FDA granted fast track status	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
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, even with the newly approved agents telaprevir and boceprevir. HCV treatment is also associated with frequent adverse events and a long duration of therapy. ABT-333 is a nonnucleoside NS5B polymerase inhibitor intended to bind HCV RNA-dependent RNA polymerase and inhibit replication of the viral genome. It could be used in combination with ABT450/r and ribavirin in an interferon (IFN)-free regimen. Administered orally, once daily. Abbott Laboratories, Abbott Park, IL Phase II trial ongoing	Boceprevir NS5A inhibitors in development Nonnucleoside polymerase inhibitors in development Nucleoside polymerase inhibitors in development Telaprevir	Decreased need for liver transplant Slowed or halted disease progression Sustained virologic response (defined as undetectable virus at 24 weeks) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
NS5A inhibitor (daclatasvir, BMS-790052) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C infection (HCV) 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. BMS-790052 is a 1st-in-class inhibitor of 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 BMS-790052 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. Administered orally, 60 mg, once daily. Bristol-Myers Squibb, New York, NY Phase III trials ongoing	Boceprevir Sofosbuvir (investigational) Pegylated interferon/ribavirin Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
NS5A inhibitor (IDX-719) for treatment of chronic hepatitis C infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Standard of care for HCV infection has a long dosing schedule and poor tolerability. Better-tolerated treatments with more convenient dosing are needed. IDX-719 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. IDX-719 purportedly inhibits the activity of all HCV genotypes and has been administered up to 50 mg, once daily, in a clinical trial. Idenix Pharmaceuticals, Inc., Cambridge, MA Phase I/II trial ongoing	Boceprevir NS5A inhibitors in development Nonnucleoside polymerase inhibitors in development Nucleoside polymerase inhibitors in development Pegylated interferon/ribavirin combination Telaprevir	Slowed or halted disease progression Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
NS5A inhibitor (PPI-461) 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 generally ineffective in more than half of infected patients; effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. PPI-461 is an HCV NS5A inhibitor; NS5A is a multifunctional, nonenzymatic endoplasmic reticulum 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 PPI-461 destabilizes N5A interactions thus inhibiting the formation of functional virions; it may be used in combination with other HCV treatment options. Administered orally, 50 to 100 mg, once daily. Presidio Pharmaceuticals, Inc., San Francisco, CA Phase I trial completed	Boceprevir Pegylated interferon/ribavirin Telaprevir	Early virologic response Rapid virologic response (HCV RNA undetectable at week 4) Sustained virologic response (HCV RNA undetectable after 24 weeks of followup) Slowed or halted disease progression Reduced need for liver transplant Improved quality of life
Nucleoside polymerase inhibitor (TMC649128) 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 generally ineffective in more than half of infected patients and the presence of pegylated interferon (IFN) alpha-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. TMC649128 is an oral nucleoside analog polymerase inhibitor; HCV polymerase is a virally encoded enzyme necessary for replication of the viral genome. TMC649128 is purported to have a high genetic barrier to resistance and antiviral activity across multiple HCV genotypes. Administered 1,000 mg, once daily. Medivir AB, Huddinge, Sweden Phase I trial completed	Boceprevir Sofosbuvir (investigational) Pegylated interferon/ribavirin Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Reduced need for liver transplant Slowed or halted disease progression Sustained virologic response (HCV RNA undetectable after 24 weeks of followup) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nucleotide polymerase inhibitor (ALS-2200) for treatment of chronic hepatitis C infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Standard of care for HCV infection has a long dosing schedule and poor tolerability. Better-tolerated treatments with more convenient dosing are needed. ALS-2200 is an oral nucleoside analog purported to block the activity of HCV polymerase, which is essential for replicating the viral genome, and ultimately functional virus particles. ALS-2200 purportedly inhibits the activity of all HCV polymerase genotypes, and it can be dosed once daily. Vertex Pharmaceuticals, Inc., Cambridge, MA Phase I trial ongoing	Boceprevir NS5A inhibitors in development Nonnucleoside polymerase inhibitors in development Nucleoside polymerase inhibitors in development Pegylated interferon/ribavirin combination Telaprevir	Slowed or halted disease progression Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Nucleotide polymerase inhibitor (IDX-184) for treatment of chronic hepatitis C infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Standard of care for HCV infection has a long dosing schedule and poor tolerability. Better-tolerated treatments with more convenient dosing are needed. IDX-184 is an oral nucleotide analog purported to block the activity of HCV polymerase, which is essential for replicating the viral genome, and ultimately functional virus particles. IDX-184 purportedly inhibits the activity of all HCV polymerase genotypes and incorporates proprietary liver-targeting of the nucleotide prodrug to minimize dosing and reduce systemic side effects. IDX-184 has been administered at 50, 100, 150, and 200 mg, once daily. Idenix Pharmaceuticals, Inc., Cambridge, MA Phase II trials completed; FDA placed on partial clinical hold Aug 16, 2012, to review cardiovascular safety	Boceprevir NS5A inhibitors in development Nonnucleoside polymerase inhibitors in development Nucleoside polymerase inhibitors in development Pegylated interferon/ribavirin combination Telaprevir	Slowed or halted disease progression Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label neurokinin-1 receptor antagonist aprepitant (Emend) for treatment of HIV infection	Patients in whom HIV infection has been diagnosed	HIV infection remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments. HIV drug resistance, poor tolerance to existing treatments, and high lifelong cost of therapy continue to suggest that improved therapeutic options be pursued to treat patients. Additionally, patients with successfully managed HIV infection frequently develop neurocognitive impairment that is associated with residual chronic inflammation. Aprepitant (Emend®), a drug already approved for treating chemotherapy-induced nausea and vomiting (CINV), is purported to have immunomodulator and antiviral activity. That activity is intended to target residual inflammation by acting on host cells and not the virus, thus leading to prevention of inflammatory and neurocognitive events associated with HIV infection. Aprepitant is purported to be a neurokinin-1 receptor antagonist, inhibiting HIV replication in macrophages by decreasing expression of the chemokine receptor type 5 coreceptor which is needed for HIV to infect cells and possibly other mechanisms. Aprepitant is also purported to improve natural killer cell function, which may help patients better control the virus. Aprepitant is purported to act synergistically with HIV protease inhibitors. In trials, aprepitant was administered orally, 125 or 250 mg, once daily. Merck & Co., Inc., Whitehouse Station, NJ (manufacturer) University of Pennsylvania, Philadelphia, and National Institute of Mental Health, Bethesda, MD (trial sponsors) Phase I trial ongoing for HIV-1 treatment; FDA approved in 2003 for preventing acute and delayed CINV and preventing postoperative nausea and vomiting	Antiretroviral therapy Therapeutic vaccines (investigational)	Delayed onset of AIDS Increased T-cell counts Reduced cognitive impairment Reduced viral load
Oligonucleotide (miravirsen) for treatment of chronic hepatitis C infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Treatment for HCV infection, including with recently approved protease inhibitors, requires a long duration of therapy and is associated with poor adherence to treatment and a high frequency of adverse events. Better treatment options are needed. Miravirsen is an oligonucleotide targeting the microRNA miR-122, a liver-specific microRNA that HCV requires for replication. Miravirsen is purported to recognize and sequester miR-122, making it unavailable to HCV, thereby inhibiting viral replication. By blocking the expression of a host protein needed for viral replication, miravirsen could reduce the development of viral resistance. The drug is administered by subcutaneous injection. Santaris Pharma a/s, Hørsholm, Denmark Phase II trial completed	Boceprevir Pegylated interferon/ribavirin Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Sustained virologic response (HCV RNA undetectable after 24 weeks of followup) Reduced need for liver transplantation Reduced symptoms

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ozonated water disinfectant to prevent health care-acquired infections	Patients in a hospital or other health care setting in which where health care–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 is purported to clean as effectively as other chemicals used for terminal cleaning, but 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 is purported to react with microorganisms leading to efficient killing. After reacting, elemental oxygen is thought to remain. Windsor Regional Hospital, Windsor, Ontario, Canada	Antimicrobial copper touch surfaces Terminal cleaning procedures using bleach and cleaning of visibly soiled surfaces as necessary Ultraviolet light	Reduced bacteria isolated from surfaces Reduced infection rates Reduced morbidity and mortality
Ozone and hydrogen peroxide-based sterilization system (AsepticSure) to reduce health care–acquired infections	Patients in a hospital or other health care setting in which where health care–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. The AsepticSure™ device is a small portable device purported to sterilize hard and fabric surfaces in a health care or hospital room or surgical suite in about 80–90 minutes. The device is placed in the center of the room, and the room is evacuated and sealed off with tape. Then with a remote control, the device is activated to release ozone and hydrogen peroxide (1%) at a specific humidity into the room for sterilization. After the cycle is run the device purportedly returns the air to U.S. Environmental Protection Agency standards and the room (air, surfaces, and textiles) is sterilized and ready for use. Medizone International, Inc., Sausalito, CA Beta testing in U.S. hospitals planned	Antimicrobial copper touch surfaces Terminal cleaning procedures using bleach and cleaning of visibly soiled surfaces as necessary Ultraviolet light	Reduced bacteria isolated from surfaces Reduced infection rates Reduced morbidity and mortality
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 around 40% in many health care settings, leading to the transmission of deadly and costly infections. It is purported that many health care workers have expressed that because they are frequently exposed to infections, they are more immune to infection and, thus, do not wash their hands. Signage 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. University of North Carolina at Chapel Hill	Standard hand-washing practices Radiofrequency identification hand-washing systems	Reduced costs associated with health care–acquired infections (HAIs) Reduced HAI incidence Reduced HAI morbidity and mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Peramivir for treatment of influenza	Patients in whom H1N1 influenza has been diagnosed or is suspected	Because of resistance to existing antiviral agents used for flu, new antiviral therapies are needed. Additionally, therapies that provide broad coverage against different strains of influenza virus are needed. Peramivir is a cyclopentane neuraminidase inhibitor, which is intended to bind the active site of the protein and inhibit viral budding; peramivir has activity against influenza A and B viruses as well as in patients refractory to oseltamivir. Administered as an intravenous drug, 600 mg, once daily, for 5–10 days. BioCryst Pharmaceuticals, Inc., Research Triangle Park, NC Phase III trials terminated due to administrative reasons; approved for emergency use in patients with confirmed or suspected H1N1 influenza	Oseltamivir (Tamiflu®; for influenza) Zanamivir (Relenza®; for influenza)	Decreased length of hospitalization Reduction in virus titers Relief of symptoms
Pharmacist-provided medication therapy management for patients with HIV/AIDS	Patients in whom HIV infection/AIDS has been diagnosed	A significant correlation between improved antiretroviral therapy (ART) adherence and reduced viral load and therapeutic outcomes has been demonstrated; ART regimens comprise multiple classes of medications; treatment options are limited once resistance occurs, and resistance can be associated with poor treatment adherence; programs to optimize treatment adherence are needed to optimize outcomes. Pharmacist-provided medication therapy management services are being provided to California residents with HIV/AIDS as part of a Medi-Cal pilot program; participating pharmacies and pharmacists select various services offered above and beyond standard counseling, such as the following: evaluating patients' ability to adhere to medications, in consultation with doctors and case managers; identifying and managing adverse drug reactions; tailoring drug regimens to fit patient lifestyle or special needs; scheduling individual appointments with pharmacists to discuss medication therapy; adherence packaging beyond any provided by manufacturer (e.g., personalized blister packs for all ART medications); identifying peer advocates to assist in medication adherence; and making weekly telephone call or home visit after initiation of therapy. School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego	Medication therapy management in another care setting Nurse care coordinator	Decreased cost of care Decreased incidence of opportunistic infections Reduced need for inpatient services Reduced need to change treatment regimen Improved treatment adherence Reduced viral load

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Plant-derived virus-like particle vaccine for prevention of H5N1 avian influenza	Patients at risk of avian influenza	Influenza continues to cause significant morbidity and mortality in susceptible populations; improper strain selection and viral mutations continue to challenge vaccine developers. Vaccines that are safe, effective, and generated quickly are needed. The H5N1 vaccine candidate is composed of recombinant virus-like particles manufactured in *Nicotiana benthamiana*, a relative of the tobacco plant. The vaccine is purported to protect against the H5N1 Indonesian influenza virus. The vaccine can purportedly be manufactured within 4 weeks of obtaining the sequence of the circulating influenza strain instead of 6–9 months with current methods. Medicago, Inc., Quebec, Quebec, Canada Phase II trial ongoing	Pandemic influenza vaccines Seasonal inactivated flu vaccines Seasonal live flu vaccines	Faster production of pandemic vaccine Reduced incidence of influenza Lower morbidity and mortality Vaccine option for people allergic to eggs
PMX-30063 for treatment of acute bacterial skin infections	Patients in whom acute bacterial skin and skin structure infection has been diagnosed	Drug resistant bacteria and the shrinking clinical pipeline of new agents to treat serious skin infections will continue to pose issues for effectively managing patients. Antibiotics with new mechanisms of action are needed. PMX-30063 is a novel, synthetic defensin-mimetic antibiotic; defensins are proteins that are part of the human innate immune system that target and disrupt bacterial cell membranes, leading to lysis; by targeting bacterial membranes, PMX-30063 is purported to avoid current resistance mechanisms and is less likely to develop future resistance; PMX-30063 is composed of biomimetic compounds that mimic key biologic properties of proteins, but are purported to be more stable and inexpensive to produce than natural proteins; PMX-30063 is purported to have broad-spectrum activity; PMX-30063 has been shown to kill *Staphylococcus aureus* in human blood samples in vitro. Administered intravenously. PolyMedix, Inc., Radnor, PA Phase II trial completed	Linezolid Vancomycin	Complete clinical response Complete microbiologic response Infection resolution/cure

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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. MD Innovate, Inc., Decatur, GA Exempt from FDA regulatory clearance processes; classified as a class I device	Sputum and culture detection methods	Improved accuracy of diagnosis Improved treatment plan Reduced duration of symptoms through appropriate treatment
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. Multiple manufacturers: Blaze Venture Technologies, Ltd., Ware, UK Enigma Diagnostics, Ltd., Salisbury, UK InstantLabs Medical Diagnostics Corp., Reston, VA QuantaLife, Inc., Pleasantville, CA Smiths Group, plc, London, UK TwistDx, Ltd., Cambridge, UK Early trials ongoing; devices and test kits expected to be cleared through 510(k) pathway with no requirement for clinical evidence of efficacy	MRSA culture Conventional 1st-generation polymerase chain reaction (PCR) assay 2nd-generation quantitative PCR	Reduced transmission of MRSA Increased sensitivity and specificity of MRSA detection Increased speed of MRSA detection

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Polymerase inhibitor (BMS-791325) 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 generally not effective in more than half of infected patients, the nonadherence rate with medication regimens is high, and even treatments approved since 2011 have side effects and nonadherence issues. Effective treatments that patients will adhere to are needed. BMS-791325 is an HCV nonnucleoside, NS5B polymerase inhibitor intended to limit viral replication when used in combination with standard-of-care pegylated interferon plus ribavirin (IFN/RBV) for both treatment-naive patients and patients whose HCV infection has failed to respond to a course of therapy with IFN/RBV. Administered orally, 75–150 mg, twice daily. Bristol-Myers Squibb, New York, NY Phase IIb trials ongoing	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Polymerase inhibitor (GS-9190, tegobuvir) 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 generally ineffective in more than half of infected patients; effective treatments that improve clinical outcome in a shorter period of time are needed. Tegobuvir is a nonnucleoside NS5B polymerase inhibitor intended to block the activity of HCV polymerase, preventing replication of the viral genome. Administered orally, 40 mg, twice daily in various combinations with GS-9256 (protease inhibitor), pegylated interferon (IFN), and ribavirin. Gilead Sciences, Inc., Foster City, CA Phase IIb trials ongoing	Boceprevir Pegylated IFN/ribavirin Telaprevir	Early virologic response Reduced need for liver transplant Slowed or halted disease progression Sustained virologic response (HCV RNA undetectable after 24 weeks of followup) Improved quality of life
Polymerase inhibitor (sofosbuvir, GS-7977) 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. 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 interferon free regimens which include ribavirin, daclatasvir, simeprevir, and other agents. Administered orally 400 mg once daily. Gilead Sciences, Inc., Foster City, CA Phase III trial ongoing; received FDA fast track status	Boceprevir Pegylated interferon/ribavirin Telaprevir	Cured infection (sustained virologic response with no detectable virus) Reduction of symptoms Delayed or halted progression to end-stage liver disease Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Polymerase inhibitor (VX-222) 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. VX-222 is a non-nucleoside NS5B polymerase inhibitor which may limit viral replication by inhibiting viral genome replication. VX-222 could be used in combination with telaprevir and ribavirin in an interferon-free regimen. Vertex Pharmaceuticals, Inc., Cambridge, MA Phase II trials ongoing	Boceprevir Sofosbuvir (investigational) Pegylated interferon/ribavirin Telaprevir	Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Prime-boost vaccine with DNA and modified vaccinia virus Ankara for prevention of HIV infection	Persons who are at risk of HIV infection	HIV remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments; HIV drug resistance, poor tolerance to existing treatments, and high lifelong cost of therapy continue to suggest that prophylactic HIV vaccination be pursued for individuals whom are not infected with the virus. This vaccine protocol consists of prime-boost strategy where 2 doses of a DNA vaccine (pGA2/JS7) are administered followed by 2 doses of a recombinant modified vaccinia virus Ankara (MVA) vector expressing HIV clade B Gag, Pol, and Env proteins (MVA/HIV62); the expressed proteins form onco-infectious virus-like particles with the intention of generating protective antibody and cellular responses; clade B is the most common clade in North America. GeoVax Labs, Inc., Smyrna, GA Phase I trial ongoing	Condoms Harm reduction campaigns Pre-exposure prophylaxis (tenofovir/emtricitabine; investigational) Prophylactic vaccines (investigational) Vaginal microbicide gels (investigational)	Improved antibody and T-cell responses Decreased incidence of infection
Pro 140 monoclonal antibody for treatment of HIV infection	Patients chronically infected with HIV	HIV remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments; HIV drug resistance, poor tolerance to existing treatments, and high lifelong cost of therapy present opportunities for the development of novel and effective HIV therapies. Pro 140 is a monoclonal antibody directed against the CCR5 chemokine receptor that serves as the coreceptor for HIV infection; by binding to CCR5, Pro 140 is purported to reduce the rate of viral replication, increasing the efficacy of current antiretrovirals; expected to have better tolerability than current antiretrovirals (not metabolized in the liver); purported to not affect normal CCR5 function. Administered by subcutaneous injection on days 1, 8, and 15. Progenics Pharmaceuticals, Inc., Tarrytown, NY Phase II trial ongoing	Antiretroviral therapy Enfuvirtide Maraviroc Therapeutic vaccines (investigational)	Decreased viral load Decreased morbidity Increased survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Prophylactic vaccine Pennvax-B (VGX-3300) for prevention of HIV infection	Patients at high risk of chronic HIV-1 infection	HIV remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments; HIV drug resistance, poor tolerance to existing treatments, and high lifelong cost of therapy continue to suggest that prophylactic HIV measures be pursued for individuals who are not infected with the virus, but are at high risk. Pennvax™-B is a SynCon DNA vaccine that encodes sequences from the gag, pol, and env proteins of HIV-1; the DNA vaccine is administered with Inovio's Cellectra® electroporation device; the vaccine is intended to be then taken up by local antigen presenting cells, which express the antigens and induce antibody and T-cell responses to the HIV-1 proteins and may provide protection against infection. Inovio Pharmaceuticals, Inc., Blue Bell, PA ChronTech Pharma AB, Huddinge, Sweden Phase I trial ongoing	Condoms Harm reduction campaigns Pre-exposure prophylaxis (tenofovir/emtricitabine; investigational) Prophylactic vaccines (investigational) Vaginal microbicide gels (investigational)	Lower incidence of HIV-1 infection Improved B- and T-cell responses to HIV antigens
Prophylactic vaccine recombinant vesicular stomatitis virus expressing HIV-1 gag protein (VSV_{IN} HIV-1 gag) for HIV-1	Patients at risk of HIV-1 infection	HIV remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments; HIV drug resistance, poor tolerance to existing treatments, and high lifelong cost of therapy continue to suggest that prophylactic HIV measures be pursued for individuals who are not infected with the virus. Recombinant vesicular stomatitis virus HIV-1 gag vaccine ($rVSV_{IN}$ HIV-1 gag) uses the negative-strand, nonsegmented RNA virus vector to deliver the HIV gag immunogen; this vector was selected for immunogenicity (naturally activating toll-like receptor-7 signaling), safety (cytoplasmic replication, incapable of integration within the host's genome), and a lack of previously existing natural immunity; intended to be used in combination with plasmid vaccines under investigation by Profectus. Profectus BioSciences, Inc., Baltimore, MD Phase I trial ongoing	Condoms Harm reduction campaigns Pre-exposure prophylaxis (tenofovir/emtricitabine; investigational) Prophylactic vaccines (investigational) Vaginal microbicide gels (investigational)	Lower incidence of HIV-1 infection Improved T-cell responses to Gag

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Protease inhibitor (ABT-450/r) 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 HCV protease inhibitor. Abbott Laboratories, Abbott Park, IL Phase II trials ongoing	Boceprevir Pegylated interferon/ribavirin Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Protease inhibitor (asunaprevir) for treatment of chronic hepatitis C virus infection	Patients in whom chronic infection with hepatitis C virus (HCV) has been diagnosed	Current standard of care for HCV infection is generally ineffective in more than half of infected patients and is poorly tolerated in many patients; effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. BMS-650032 is a 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 BMS-914143 (NS5A inhibitor) with or without the standard-of-care pegylated interferon plus ribavirin (IFN/RBV). Bristol-Myers Squibb, New York, NY Phase III trial ongoing	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Protease inhibitor (boceprevir, Victrelis) for treatment of hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) genotype 1 infection has been diagnosed	Current standard of care for HCV infection is generally ineffective in more than half of infected patients; effective treatments that improve clinical outcome in a shorter period of time are needed. Boceprevir (Victrelis™) is a NS3/4 protease inhibitor intended to block the activity of HCV protease, preventing the cleavage and maturation of functional viral particles. Administered orally, 800 mg, 3 times daily, in combination with pegylated interferon and ribavirin (IFN/RBV). Merck & Co., Inc., Whitehouse Station, NJ FDA approved May 2011	IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Protease inhibitor (danoprevir) for treatment of chronic hepatitis C virus infection	People chronically infected with hepatitis C virus (HCV) infection	Current standard of care (pegylated interferon plus ribavirin [IFN/RBV]) for HCV infection is generally ineffective in more than half of patients; effective treatments that improve clinical outcome in a shorter period of time are needed. Danoprevir is an orally administered NS3/4A protease inhibitor intended to block the activity of HCV protease, preventing the cleavage and maturation of functional viral particles. In trials, the drug has been administered at various doses such as 100 mg, twice daily, orally, for 24 weeks in combination with IFN/RBV. F. Hoffmann-La Roche Ltd., Basel, Switzerland Phase II trials completed	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Protease inhibitor (GS-9256) 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. GS-9256 is a NS3 protease inhibitor intended to block the activity of HCV protease, preventing the cleavage and maturation of functional viral particles. Administered orally, 75 mg, twice daily, in various combinations with tegobuvir (polymerase inhibitor) and pegylated interferon plus ribavirin (IFN/RBV). Gilead Sciences, Inc., Foster City, CA Phase IIb trials ongoing	Boceprevir IFN/RBV Telaprevir	Early virologic response Reduced need for liver transplant Slowed or halted disease progression Sustained virologic response (HCV RNA undetectable after 24 weeks of followup) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Protease inhibitor (MK-5172) for treatment of chronic hepatitis C 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. MK-5172 is an 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. Administered orally, 100–800 mg, once daily; may be used in combination with pegylated interferon plus ribavirin (IFN/RBV). Merck & Co., Inc., Whitehouse Station, NJ Phase II trials ongoing	Boceprevir IFN/RBV Telaprevir	Early virologic response Reduced need for liver transplant Slowed or halted disease progression Sustained virologic response (HCV RNA undetectable after 24 weeks of followup) Improved quality of life
Protease inhibitor (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). Administered 150 mg, once daily. Tibotec BVBA, Beerse, Belgium Phase III trials ongoing; FDA fast track status	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Protease inhibitor (sovaprevir) 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; intended to be used in combination with standard-of-care pegylated interferon plus ribavirin (IFN/RBV). Administered orally, 200–800 mg, once daily. Achillion Pharmaceuticals, Inc., New Haven, CT Phase II trial ongoing; FDA granted fast track status for treating chronic HCV	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Protease inhibitor (telaprevir, Incivek) for treatment of hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) genotype 1 infection has been diagnosed	HCV treatment with pegylated interferon plus ribavirin (IFN/RBV) is generally ineffective in more than half of infected patients; effective treatments that improve clinical outcome in a shorter period of time are needed. Telaprevir (Incivek™) is a NS3/4 protease inhibitor intended to block the activity of HCV protease, preventing the cleavage and maturation of functional viral particles. Administered orally, 750 mg, 3 times daily, in combination with IFN/RBV. Vertex Pharmaceuticals, Inc., Cambridge, MA FDA approved May 2011	Boceprevir IFN/RBV	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Protease inhibitor (vaniprevir, MK7009) 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. Vaniprevir (MK7009) is a next-generation is a NS3/4 protease inhibitor intended to block the activity of HCV protease, preventing the cleavage and maturation of functional viral particles. Vaniprevir is used in combination with pegylated interferon plus ribavirin (IFN/RBV). Administered orally 300 mg, twice daily. Merck & Co., Inc., Whitehouse Station, NJ Phase III trials ongoing	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Rapid molecular detection test (Xpert MTB/RIF) for *Mycobacterium tuberculosis* infection with rifampin resistance	Patients suspected of having *Mycobacterium tuberculosis* infection	Automated molecular test (Xpert® MTB/RIF) for *M. tuberculosis* infection that also simultaneously tests for resistance to rifampin. Cepheid, Sunnyvale, CA Expected to become available in the U.S. in 2012 or 2013; Conformité Européene (CE) marked	Microscopy Tuberculin skin test (Mantoux test) Ziehl-Neelsen microscopy	Less training time Rapid detection Improved treatment Better control of antibacterial resistance

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Recombinant fusion protein–derived vaccine (RSV-F) for preventing respiratory syncytial virus	Children at risk of respiratory syncytial virus (RSV) infection	The number 1 cause of childhood hospitalization both in the U.S. and around the world is RSV infection. No vaccines are available to prevent RSV. This investigational vaccine (RSV-F) comprises recombinant particles of fusion (F) protein and an adjuvant. The vaccine is intended to generate neutralizing antibodies against the RSV-F protein, preventing infection with the virus. Administered at days 0 and 30. Novavax, Inc., Rockville, MD Phase I trial completed	Palivizumab (Synagis®)	Improved lung function Reduced infection rate Reduced progression of bronchiolitis obliterans syndrome Fewer hospitalizations Shorter hospital stays
Recombinant interleukin-7 (CYT107) for immune reconstitution in treatment of HIV infection	Patients with HIV whose immune system has decreased function and whose tests show CD4 counts remaining between 101 and 350 cells after at least 2 years of highly active antiretroviral therapy (HAART)	CYT107 is a recombinant form of human interleukin-7; treatment is expected improve and prolong immune reconstitution and stabilize patient CD4+ T-cell counts of less than 500; intended to decrease activation/inflammation markers. Cytheris SA, Issy-les-Moulineaux, France Phase II trials ongoing	Antiretroviral therapy Therapeutic vaccines (investigational)	Improved immune response Reduced need for other medications Increased survival Improved quality of life
Recombinant interleukin-7 (CYT107) for treatment of chronic hepatitis C virus infection	Patients with chronic hepatitis C virus (HCV) infection unresponsive to pegylated interferon plus ribavirin (IFN/RBV) treatment	Current HCV-infection treatments, even the newer ones, do not effectively treat all HCV patients and require long and complicated courses of therapy (up to 48 weeks) that sometimes result in low adherence to treatment. Effective and shorter-duration treatment regimens are needed. CYT107 is a recombinant form of human interleukin-7 that is purported to increase production of lymphocytes and immune response. CYT107 is administered as a weekly subcutaneous injection for 4 weeks in conjunction with standard-of-care IFN/RBV therapy to improve viral response rates. Cytheris S.A., Issy-les-Moulineaux, France Phase I/II trials ongoing	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Reduced need for liver transplantation Reduced symptoms Sustained virologic response (HCV RNA undetectable after 24 weeks of followup) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
RHB-104 for treatment of Crohn's disease due to *Mycobacterium avium paratuberculosis* infection	Patients with Crohn's disease that shows evidence of *Mycobacterium avium paratuberculosis* infection	No cure for Crohn's disease is available. Existing treatments aim only to suppress inflammation and provide symptomatic relief for a limited period of time. To reduce the frequency of surgery and morbidity, better treatments are needed. RHB-104 is an antibiotic purported to have activity against *M. avium paratuberculosis*, which has been implicated in the development of Crohn's disease. The manufacturer claims the bacterium can be found in 40% to 50% of patients with Crohn's disease. Licensed to RedHill Biopharma, Ltd., Tel Aviv, Israel, by UCF Research Foundation, Inc., Orlando, FL Phase III trial planned	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (e.g., prednisone) Helminthic therapy Immunomodulators (e.g., azathioprine) Low-dose naltrexone Monoclonal antibodies (e.g., natalizumab, infliximab)	Avoidance of surgery Complete microbiologic response Resolved symptoms
Routine anal Pap smear screening at HIV clinics to prevent anal cancer	Patients in whom HIV infection has been diagnosed	Patients with HIV have a higher risk of developing anal cancer, yet national or international guidelines do not exist for anal dysplasia screening. Anal Pap (Papanicolaou) screening can be incorporated into routine visits when patients attend HIV clinics for treatment and monitoring, and some clinicians recommend screening regardless of history of anal intercourse. University of Miami Miller School of Medicine, Miami, FL	Anal Pap screening or anoscopy by other physician during regular intervals (after 50 years of age) or during routine gynecologic visits for women	Earlier detection of suspicious polyps Reduced anal cancer incidence in patients with HIV Reduced anal cancer mortality in patients with HIV

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
RTS,S 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. Current treatments to the *Plasmodium falciparum* parasite can be ineffective, particularly in young children and immunosuppressed individuals. The lack of effectiveness results in high morbidity and mortality. RTS,S 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 in a particle expressed in yeast that also includes unfused S antigen. The vaccine is also administered with the AS02A adjuvant (proprietary oil-in-water emulsion with the immunostimulants monophosphoryl lipid A and QS21). The vaccine is purported to target the pre-erythrocytic stage of *P. falciparum* by inducing protective immune responses against the parasite when it 1st enters the human host's bloodstream and/or when it infects liver cells, thus inhibiting the infection cycle. Administered in 3 intramuscular injections at 0, 1, and 2 months. GlaxoSmithKline, Middlesex, UK PATH Malaria Vaccine Initiative, Washington, DC Phase III trials completed; phase II/III trial ongoing	Chloroquine phosphate Mosquito nets	Reduced incidence of malaria infection Increased overall survival
SB-728 for treatment of HIV infection	Patients in whom chronic HIV infection has been diagnosed	Many patients (30%) infected with HIV who have controlled their infection with antiretroviral therapy (ART) still have low T-cell counts; therapies to increase T-cell counts in these patients are needed to prevent HIV-related morbidity. CR5 is a major coreceptor required for HIV to infect CD4+ cells; a naturally occurring mutation of the CCR5 gene, CCR5-delta32 has been shown to provide protection against HIV infection; SB-728 is an autologous T-cell product that uses zinc finger nuclease technology to generate CCR5-permanently modified T cells that are resistant to HIV infection and are capable of replicating in the gut mucosa, which serves as a reservoir for HIV. An apheresis is taken from patients, cells are modified in vitro, and readministered into patients 1 time. Sangamo BioSciences, Inc., Richmond, CA Phase I/II trials ongoing	Antiretroviral therapy Maraviroc Pro140 (investigational) Therapeutic vaccines (investigational)	Improved CD4:CD8 ratio Persistence of modified T cells in the circulation Increased T-cell counts Reduced viral load Reduced HIV/AIDS morbidity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
SCY-635 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 for more than half of infected 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. Cyclophilin A is a host cell protein involved in protein folding and transport, it has also been shown to be essential in HCV replication; cyclosporine A inhibits cyclophilin activity but is immunosuppressive; SCY-635 is a novel cyclosporine analog that was developed to be nonimmunosuppressive and, like other inhibitors in this class, is not associated with an increased risk of hyperbilirubinemia; SCY-635 may also have an antifibrotic effect independent of demonstrated anti-HCV activity. Administered 300–400 mg, twice a day, for 28 days with pegylated interferon plus ribavirin (IFN/RBV). SCYNEXIS, Inc., Durham, NC Phase II trial ongoing	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Tenofovir and emtricitabine (Truvada) for prevention of HIV infection	People at risk of HIV infection	Truvada® is a combination of 2 reverse transcriptase inhibitors Viread® (tenofovir disoproxil fumarate) and Emtriva® (emtricitabine) given as pre-exposure prophylaxis for people at high risk of HIV infection. Preliminary studies have shown that daily prophylactic use of tenofovir and emtricitabine may prevent the acquisition of HIV in men who have sex with men and heterosexual men. Data for prophylactic use in women have been confounding due to lack of efficacy. The 2 drugs are combined into 1 oral tablet taken daily. Gilead Sciences, Inc., Foster City, CA FDA approved the drug 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 part of the approval, Gilead had 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 Harm reduction campaigns Pre-exposure prophylaxis (tenofovir/emtricitabine; investigational) Prophylactic vaccines (investigational) Vaginal microbicide gels (investigational)	Reduced transmission and incidence of HIV

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Therapeutic vaccine (DermaVir) for HIV infection	Patients in whom chronic HIV infection has been diagnosed	HIV remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments; HIV drug resistance, poor tolerance to existing treatments, and high lifelong cost of therapy continue to suggest that improved therapeutic options be pursued to treat patients. DermaVir therapeutic vaccine is designed to induce T-cell responses against HIV-1 capable of controlling viral load; the vaccine is comprised of "pathogen-like" nanomedicine particles formulated using a novel synthetic polymer, mannosylated linear polyethyleneimine, a synthetic polymer, purported to have the size and the shape of infectious virus particles capable of delivering nucleic acids to antigen-presenting dendritic cells (APCs), without the risk of actual infection; the vaccine is administered topically using a patch placed by a health care practitioner; once applied to the skin and taken up by APCs, the single DNA plasmid immunogen, expresses 15 HIV antigens and up to 3,000 T-cell epitopes, which are purported to safely self-assemble into virus-like particle immunogens that are targeted to generate immunity. Genetic Immunity, LLC, McLean, VA Phase II trials ongoing	Antiretroviral therapy Therapeutic vaccines (investigational)	T cell precursors with high proliferative capacity Reduced viral load Reduction of medication regimen Reduced HIV-related morbidity
Therapeutic vaccine (GI-5005) for chronic hepatitis C virus infection	Patients with chronic hepatitis C virus (HCV) infection whose disease has failed to respond to standard treatment	Effective treatment for chronic HCV infection is needed. Therapeutic vaccine GI-5005 is composed of a recombinant fusion protein composed of sequences from HCV nonstructural protein 3 (NS3) and core antigens expressed on the surface of the yeast *Saccharomyces cerevisiae*; these proteins are highly conserved regions from HCV; immunization with the recombinant yeast is intended to induce cellular immunity against HCV to resolve chronic infection. GlobeImmune, Inc., Louisville, CO Phase IIb trial ongoing	Boceprevir Pegylated interferon/ribavirin Telaprevir	Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Therapeutic vaccine (HerpV) for genital herpes infection	Patients infected with herpes simplex virus 2 (HSV-2)	One in 6 people from age 14–49 years are infected with HSV-2, greatly affecting quality of life; additionally, some evidence exists to suggest that resistance to existing herpes treatments is increasing. HerpV is a recombinant, off-the-shelf, therapeutic vaccine for treating genital herpes that is caused by HSV-2; HerpV is comprised of recombinant heat shock protein-70 complexed with 32 distinct 35-mer synthetic peptides from the HSV-2 proteome; intended to allow for more accurate immune targeting and surveillance, reducing the likelihood of immune escape and providing adequate epitope diversity in diverse genetic populations; the addition of heat shock protein-70 is intended to increase antigen presentation and immunogenicity of the peptides; the vaccine also contains Agenus' proprietary adjuvant QS-21 Stimulon. Agenus, Inc., Lexington, MA Phase II trial planned	Acyclovir Valacyclovir	Reduced duration of outbreaks Reduced frequency of outbreaks Reduced transmission of HSV-2
Therapeutic vaccine (Vacc-4x) for chronic HIV-1 infection	Patients in whom chronic HIV-1 infection has been diagnosed	HIV infection remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments. HIV drug resistance, poor tolerance to existing treatments, and high lifelong cost of therapy suggest that new therapeutic options are needed. Vacc-4x is a therapeutic vaccine comprised of 4 synthetic peptides with slight modifications to increase immunogenicity. Vacc-4x is believed to encode 2 conserved regions from the HIV gag (p24) protein in which mutations in these regions lead to defective virus. Sustained immune responses to p24 have been associated with delayed disease progression. Investigators purport that Vacc-4x may be the 1st HIV treatment that is not vulnerable to viral escape mutants. Bionor Pharma ASA, Oslo, Norway Phase I/II trial completed	Antiretroviral therapy Therapeutic vaccines (investigational)	Reduced viral load Reduced medication regimen Reduced morbidity and mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Therapeutic vaccine (V5) for 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. Therapeutic vaccine (V5) intended for use as adjunctive TB immunotherapy in combination with standard drugs. Oral pill. Immunitor USA, Inc., College Park, MD Phase II trial completed	Ethionamide Ethambutol Isoniazid Kanamycin Ofloxacin Pyrazinamide Rifampicin	Improved treatment adherence Resolution of active TB Reduced treatment failures Reduced antibacterial resistance Reduced spread of TB infection Improved quality of life
TKM-Ebola for treatment of Ebola infection	Patients infected with Ebola virus	Ebola infection has an 80% mortality rate. Only supportive care is available. TKM-Ebola comprises a cocktail of modified small, interfering RNAs targeting the Zaire Ebola virus L polymerase, viral protein 24, and viral protein 35. It is delivered in proprietary lipid nanoparticles that are purported to inhibit expression of these proteins, which are essential for viral replication. Tekmira Pharmaceuticals Corp., Burnaby, British Columbia, Canada Phase I trial ongoing	AVI-6002	Increased symptom resolution Reduced mortality
Topical microbicide (VivaGel) for treatment of bacterial vaginosis	Patients in whom bacterial vaginosis (BV) has been diagnosed	BV is common and is associated with complications in the female reproductive tract such as premature labor and increased risk of sexually transmitted infections. Current treatments are purported to have low cure rates and be associated with high BV recurrence and complication rates, as well as antibacterial resistance. VivaGel® is a topical lubricant and microbicide gel containing a proprietary dendrimer (polymer), SPL7013. It purportedly inhibits the activity of many viruses and bacteria. Because it is not an antibiotic, the gel might limit development of antibiotic-resistant infections. VivaGel might then be used more frequently or prophylactically without concerns about developing antibiotic resistance. The gel is self-administered at bedtime for treating BV. Dendritic Nanotechnologies, Inc., unit of Starpharma Holdings, Ltd., Melbourne, Australia Phase III trials ongoing	Clindamycin cream (Cleocin®) Metronidazole (Flagyl®) Metronidazole gel (Metrogel®) Tinidazole (Tindamax®)	Increased clinical cure rates Reduced antibiotic-resistance rates Reduced recurrence rates

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Universal vaccine (N8295) for prevention of influenza	Patients at risk of influenza	Influenza strains mutate each year requiring a new vaccine annually for protection. A long-lasting, effective, universal vaccine is sought. N8295 is purported to be a universal vaccine composed of a recombinant fusion protein of the influenza nucleoprotein and matrix protein 2e of influenza virus fused to a toll-like receptor 9 agonist purported to increase immunogenicity. The vaccine is intended to induce broad T-cell and cytotoxic antibody responses to the NP and M2e antigens, respectively, which do not mutate annually like the neuraminidase and hemagglutinin antigens targeted in traditional antibody-based influenza vaccines. Additionally, the vaccine contains an investigational H5N1 avian influenza vaccine. Dynavax Technologies Corp., Berkeley, CA Phase I trials completed	Pandemic influenza vaccines Seasonal inactivated flu vaccines Seasonal live flu vaccines	Reduced incidence of influenza Reduced morbidity and mortality
Vancomycin powder for prevention of surgical site infections following spinal arthroplasty	Patients in whom spinal arthroplasty is required	Surgical site infections can result in significant morbidity, mortality, and cost. Better methods to reduce surgical site infections are needed. Applying 1 g of powdered vancomycin (Vancocin®) to the surgical site following arthroplasty in addition to standard of care intravenous antibiotics is purported to reduce the risk of infections following spine arthroplasty. ViroPharma, Inc., Exton, PA Unphased trials ongoing; can be used off label	Standard of care with intravenous antibiotics only	Reduced rate of surgical site infections
VAX125 vaccine for prevention of seasonal influenza	Persons at risk of influenza infection or complications	Influenza is 1 of the most communicable diseases, resulting in significant morbidity and mortality each year; changes in seasonal flu strains can leave even immunized patients poorly protected; vaccines that can be rapidly produced to relevant strains are needed. VAX125 is a recombinant fusion protein that consists of *Salmonella typhimurium* flagellin type 2, a toll-like receptor 5 ligand designed to enhance immunogenicity, fused to the globular head domain of the hemagglutinin influenza A HA1 protein; VAX125 is purported to be the 1st recombinant bacterial expressed vaccine for influenza, which will increase the speed and decrease the cost of seasonal influenza vaccine development. Administered as a single intramuscular injection. VaxInnate, Inc., Cranbury, NJ Phase II trial completed	Seasonal inactivated flu vaccines Seasonal live flu vaccines	Decreased transmission rates of viral influenza Improved immunogenicity in older patients Lower morbidity and mortality from influenza

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Virus-like particle seasonal flu vaccine for prevention of influenza	People who are eligible for influenza vaccination	Seasonal flu vaccine composed of virus-like particles containing hemagglutinin, neuraminidase, and M1 matrix proteins from seasonal influenza viruses produced in recombinant insect cells; commercial quantities of the virus-like particle vaccine can be produced in 10–14 weeks; standard vaccines produced in chicken eggs require production times of 4–6 months. Novavax, Inc., Rockville, MD Phase II trials completed	Seasonal inactivated flu vaccines Seasonal live flu vaccines	Faster production and distribution of vaccine Reduced incidence of viral influenza Vaccination option for people who are allergic to eggs
Virus-like particle vaccine for prevention of Norovirus infection	Patients at risk of Norovirus infection	Norovirus is the most common cause of acute gastroenteritis in the U.S. Investigators have not found a vaccine or treatment other than supportive therapy. The vaccine consists of recombinant virus-like particles derived from the virus combined with chitosan and a monophosphoryl lipid A adjuvant (GlaxoSmithKline, Middlesex, UK), which is purported to increase immunogenicity of the vaccine. The vaccine is delivered in a dry powder intranasally. The vaccine is purported to provide protection against the Norwalk strain (genotype GI.1) Norovirus only. LigoCyte Pharmaceuticals, Inc., Bozeman, MT Phase I trial ongoing; phase I/II trial ongoing	Supportive care	Reduced frequency of gastroenteritis
VP 20621 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. VP 20621 consists of nontoxin producing spores of *C. difficile* which are orally administered following initial treatment of acute CDI with an antibiotic such as vancomycin; following initial treatment of CDI with antibiotic therapy, VP 20621 is used to recolonize the gastrointestinal (GI) tract and prevent the wild-type toxin producing strains from recolonizing colon until normal GI flora returns and the patient is no longer susceptible to disease. ViroPharma, Inc., Exton, PA Phase II trial ongoing	Fecal microbiota transplant Fidaxomicin Metronidazole Vancomycin	Reduced hospitalization time Reduced presence of toxin-producing *C. difficile* in stool Reduced use of additional antibacterial drugs

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
VPM1002 vaccine for prevention of tuberculosis infection	People at risk of tuberculosis (TB) infection	Antibiotic resistance and long duration of TB treatment can lead to poor treatment outcomes; better methods of TB prevention are needed. VPM1002 TB vaccine is a genetically modified form of the bacterium *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG) strain TB vaccine that has been modified to express the altered *a* gene from the *Listeria* bacterium. This allows the vaccine to escape the phagosome, gain access to the cytosol of the antigen-presenting cell, and potentially improve immunogenicity. Vakzine Projekt Management GmbH, Hannover, Germany Phase II trial ongoing	Antibacterial therapy: Ethionamide Ethambutol Isoniazid Kanamycin Ofloxacin Pyrazinamide Rifampicin Current BCG vaccine	Protection against multidrug-resistant TB Reduced infection rates
XF-73 for prevention of postsurgical infections due to *Staphylococcus aureus*	Patients undergoing surgery who may be at risk of infection	Antibacterial drugs with a low propensity for inducing bacterial resistance are needed to prevent and treat multidrug-resistant bacteria in health care settings. XF-73 is a novel dicationic porphyrin, purported to have rapid bactericidal activity against gram-positive bacteria including *Staphylococcus aureus*, the number 1 global cause of hospital-acquired bacterial infections. XF-73 has also shown activity against drug-resistant strains of methicillin-resistant *S. aureus* (MRSA). XF-73, is purported to be less likely to develop antibacterial resistance than currently available antibiotics commonly used to treat MRSA infections; its mechanism of action remains to be elucidated, however XF-73 may interact with bacterial membranes in a way distinct from any other antibiotic; because of the low propensity of developing resistance, XF-73 may be used to prophylactically in patients undergoing surgery who may be at risk of developing serious postsurgical infections. Destiny Pharma, Ltd., Brighton, UK, in collaboration with National Institute of Allergy and Infectious Disease, Bethesda, MD Phase I trials completed	Daptomycin Fluoroquinolones Minocycline Vancomycin	Reduction in bacterial infections

Table 10. AHRQ Priority Condition: 10 Obesity: 15 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Controlled-release phentermine-topiramate (Qsymia, formerly Qnexa) for treatment of obesity	Overweight adults with body mass index (BMI) >27 kg/m^2 with a comorbidity or obese adults (BMI >30 kg/m^2)	Long-term weight loss drugs on the U.S. market (Belviq® and Orlistat) in the U.S. result in relatively small amounts of weight loss in only a portion of patients taking them. The drugs also have side effects that often lead to cessation of therapy. Controlled-release phentermine-topiramate (Qsymia™, formerly Qnexa) 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 resulted in more weight loss by more patients than other available antiobesity drugs. Vivus, Inc., Mountain View, CA FDA approved Jul 2012 for "for chronic weight management in adults who are obese, or overweight with at least 1 weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia" with diet and lifestyle modifications. Obese is defined as BMI 30 kg/m^2 or higher; overweight is BMI 27 kg/m^2 or higher. 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.	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Excess weight loss Decreased rate of obesity-related comorbidities (e.g., prediabetes, high blood pressure) Improved quality of life
Endoluminal sleeve (EndoBarrier) for preoperative weight loss or treatment for obesity	Adults with body mass index (BMI) >35 kg/m^2 who need to lose weight before bariatric surgery	Gastrointestinal (GI) liner (EndoBarrier®) is a 60-cm impermeable sleeve intended to allow partially digested food to move through GI tract without allowing nutrients to be absorbed in order to achieve weight loss. GI Dynamics, Inc., Lexington, MA Medtronic, Inc., Minneapolis, MN U.S. pilot trial completed; several trials completed in Europe, South America; marketed in Europe	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Preoperative weight loss Improved patient safety Reduced side effects Reduced morbidity

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
FGFR4 antagonist (ISIS-FGFR4Rx) for treatment of obesity	Adults with body mass index (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, all approved drugs have significant potential side effects and work in only a proportion of patients taking them. Additional pharmacologic options are needed. ISIS-FGFR4Rx is a new candidate intended to block production of fibroblast growth factor receptor 4 (FGFR4) in the liver and fat tissue. FGFR4 seems to underlie fatty liver disease with a chronic high fat intake diet and obesity. ISIS-FGFR4 is purported to not reduce FGFR4 expression in the central nervous system or heart, therefore avoiding side effects associated with many pharmacologic products developed for obesity. ISIS Pharmaceuticals, Inc., a unit of Johnson & Johnson, New Brunswick, NJ Phase I trial ongoing	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Total weight loss Excess total weight loss
Food-based polymer (Attiva) for treatment of obesity	Adults with body mass index (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, all approved drugs have significant potential side effects and work in only a proportion of patients taking them. Additional pharmacologic options are needed. Attiva™ is a polymer that may promote weight loss without any unwarranted central nervous system effects. Attiva is a highly absorbent hydrogel containing polymer particles solely comprised of food materials that expand when in contact with liquid in the stomach; the polymer expands into numerous hydrogel beads in the stomach, giving a “full” feeling to suppress hunger; the hydrogel keeps food in the stomach longer, giving stomach acid more time to break down both the food and the hydrogel, which begins to release its water; everything then moves to the small intestine where the gel can re-expand to some extent, slowing the absorption of fatty materials and sugars. Attiva capsules may be taken orally, after meals. Gelesis, Inc., Boston, MA Pilot study completed; company pursuing FDA 510(k) clearance	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Total weight loss Excess weight loss Decline in obesity-associated comorbidities (e.g., prediabetes, high blood pressure)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gastric pacemaker (Abiliti) for treatment of obesity	Adults with body mass index (BMI) ≥40 or ≥35 kg/m^2 with comorbidity	Current surgical options for treating obesity are often effective, but some of them alter the size, shape, and/or architecture of the gastrointestinal (GI) tract, potentially leading to side effects such as nausea, digestive issues, and nutritional deficits. The Abiliti® gastric pacemaker is proposed as an alternative that does not alter the structure of the GI tract, but senses the ingestion of food and stimulates the stomach with electrical pulses to try to induce satiety, which might lead to weight loss. IntraPace, Inc., Mountain View, CA One unphased trial completed and another ongoing; Conformité Européene (CE) marked Mar 2011; IntraPace was discussing with FDA requirements for a U.S. investigational device exemption pivotal trial by early 2012	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Percentage excess weight loss Percentage total weight loss Decreased obesity-associated comorbidities (e.g., prediabetes, high blood pressure) Improved quality of life
Liraglutide (Victoza®) for treatment of obesity	Patients at risk for diabetes with a body mass index (BMI) greater than 30 or between 27 and 30 with an associated comorbidity	Pharmacologic options have expanded with new drug approvals in 2012, however, all approved drugs have significant potential side effects and work in only a proportion of patients taking them. Liraglutide (Victoza) is approved for treatment of T2DM and acts as a glucagon-like peptide 1 analog; drug acts to reduce 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. Novo Nordisk A/S, Bagsværd, Denmark Phase III trial ongoing	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Total weight loss Excess weight loss Decline in obesity-associated comorbidities (e.g., prediabetes, high blood pressure) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lorcaserin (Belviq) for treatment of obesity	Overweight adults (BMI >27 kg/m^2) with a comorbidity or obese adults (BMI >30 kg/m^2)	Lorcaserin (Belviq®) is in a new class of selective serotonin 2C receptor agonists. It is taken twice daily in a 10 mg dose tablet. If 5% weight loss is not achieved by week 12 of therapy, labeling requires that the drug therapy be discontinued. Arena Pharmaceuticals, Inc., San Diego, CA (manufacturer) Eisai, Inc., U.S., a subsidiary of Eisai Co., Ltd., Tokyo, Japan (U.S. distributor) FDA approved Jun 2012 on the basis of 3 completed phase III trials. Approved indication is "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 one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes)." The drug is being classified by the U.S. Drug Enforcement Administration (DEA) as a schedule IV drug, which means DEA will review FDA's recommendation and determine the final scheduling designation, a process estimated to take 4–6 months. After that Eisai, which is marketing the drug in the U.S., will announce when it will be available for prescribing. No Risk Evaluation and Mitigation Strategy required, as is required for the antiobesity drug, Qsymia, approved Jul 2012.	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Weight loss Decreased comorbidities Adverse events Improved quality of life
Melanin concentrating hormone 1 antagonist (ALB-127158[a]) for treatment of obesity	Overweight adults	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, all approved drugs have significant potential side effects and work in only a proportion of patients taking them. Additional pharmacologic options are needed. The melanin concentrating hormone 1 (MCH-1) signaling pathway is a neuropeptide-based pathway that promotes food intake. ALB-127158(a) is an MCH-1 antagonist that purportedly acts as an appetite suppressant. AMRI, Albany, NY Phase I trial completed	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Excess weight loss Total weight loss Reduced obesity-related comorbidities (e.g., cardiovascular, diabetes)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Methionine aminopeptidase 2 inhibitor (beloranib) for treatment of obesity	Adults with body mass index (BMI) ≥32 to ≤45 kg/m^2 with or without comorbidities	The World Health Organization estimates that more than 500 million are considered obese or severely obese. Pharmacologic options have expanded with new drug approvals in 2012, however, all approved drugs have significant potential side effects and work in only a proportion of patients taking them. Additional pharmacologic options are needed. Pharmacologic options to treat severe obesity are very limited and severely obese patients who are not candidates for bariatric procedures and cannot lose and maintain weight loss with lifestyle changes want other options. ZGN-433 inhibits methionine aminopeptidase 2, which reduces blood flow to fatty tissues, starving them; researchers purport that this can potentially induce weight loss. Given as a subcutaneous injection in ongoing trials (previous trials gave intravenously prior to reformulation as a subcutaneous injection). Zafgen, Inc., Cambridge, MA Phase IIa trials planned for 1st half of 2012	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Weight loss Decreased comorbidities Fewer adverse events Improved quality of life
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, all 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 is purported to act on weight control by stimulating the POMC neuron. Naltrexone is purported to prevent inhibition of POMC neurons by blocking the action of beta-endorphin. Naltrexone and bupropion extended release (Contrave SR®) is taken orally, once a day. Orexigen Therapeutics, Inc., La Jolla, CA FDA rejected new drug application Feb 2011; requested additional trial on cardiovascular effects; company announced in Jul 2012 that the trial began enrolment in Jun 2012 and had enrolled more quickly than anticipated and that it expects to complete data collection by end of 2013. The company anticipates a resubmission of data in early 2014.	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Weight loss Adverse events Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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)	One 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 reduces BMI, waist circumference, and body weight in addition to improving the glycemic index. Exenatide purportedly increases satiety sensation and appetite suppression. In this trial, exenatide was administered subcutaneously twice daily at 5 mcg/dose for the 1st month and increased to 10 mcg/dose for 2 months. University of Minnesota, Minneapolis Pilot trial completed; phase II trials ongoing	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Total weight loss Excess weight loss Reduced glycosylated hemoglobin levels Decline in obesity-associated comorbidities (e.g., prediabetes, high blood pressure)
Oral volume restriction device (Sensor Monitored Alimentary Restriction Therapy) for treatment of obesity	Overweight or obese adults with a body mass index (BMI) of 27.0–29.9 kg/m^2 and minor comorbidity or BMI of 30–33 kg/m^2 with or without comorbidity	The World Health Organization estimates that more than 1.5 billion adults are overweight, and 500 million are considered obese. Pharmacologic options have expanded with new drug approvals in 2012, however, all approved drugs have significant potential side effects and work in only a proportion of patients taking them; more novel weight loss devices are needed to treat obesity and prevent associated health complications. The oral volume restriction device (Sensor Monitored Alimentary Restriction Therapy) is custom-made from palatal molds designed to fit directly against the upper palate and is secured by metal clasps around the teeth. This device is designed to slow eating rate by displacing oral volume, restricting the size of each bite of food while simultaneously slowing the eating rate to improve the satiety mechanism in the body. A microchip within the device measures the device temperature and is later removed to upload information pertaining to patient adherence to use of the device. Scientific Intake Ltd. Co., Atlanta, GA Several early- to mid-phase trials completed	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Weight loss Decreased obesity-associated comorbidities (e.g., prediabetes, high blood pressure) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
PRX00933 (5-HT2C serotonin receptor agonist) for treatment of obesity	Patients in whom obesity has been diagnosed	Pharmacologic options have expanded with new drug approvals in 2012, however, all approved drugs have significant potential side effects and work in only a proportion of patients taking them. PRX00933 is in a new class of antiobesity drugs in development; it is an agonist of the 5-HT2C serotonin receptor, which is involved in appetite control; preclinical studies have demonstrated that stimulation of the 5-HT2C receptor results in appetite suppression. Proximagen Group, plc, London, UK Phase II trial completed	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Percentage excess weight loss Reduced rate of obesity-associated comorbidities (e.g., prediabetes, high blood pressure) Improved quality of life
Restorative obesity surgery (endoluminal ROSE) for treatment of postgastric-bypass weight regain	Patients who have undergone gastric bypass, but regained weight and stretched the stomach pouch or stoma	The World Health Organization estimates that more than 1.5 billion adults are overweight, and 500 million are considered obese. Invasive surgical options have severe health outcomes, warranting the need for less invasive options. Restorative obesity surgery (endoluminal ROSE) is intended to restore the stomach or stoma to its original postsurgical (i.e., smaller) size in patients who have undergone gastric bypass surgery and regained weight. The procedure is minimally invasive and incisionless because it is performed through the mouth. Van Den Bossche and Elemental Healthcare, Ltd., Berkshire, UK Pilot study ongoing	Bariatric revision surgeries	Reduction in stoma Weight loss Quicker recovery than open revision surgery No scarring
Vagus nerve blocking (Maestro system VBLOC) for treatment of obesity	Adults with body mass index (BMI) of ≥40 to ≤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 pharmacological and surgical options can have severe adverse events, warranting the need for more novel approaches for treating obesity. High frequency, low-energy electrical impulses are emitted to block the vagus nerve (VBLOC™) in an effort to inhibit gastric motility and increase feelings of fullness; electrical impulses are delivered by an implanted neuroregulator which is powered either by an external controller (Maestro™ RF System) or an integrated rechargeable battery (Maestro RC System); implanted laparoscopically. EnteroMedics, Inc., St. Paul, MN Pivotal ReCharge trial ongoing; phase III EMPOWER™ trial ongoing, expected completion in 2013	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Amount of weight loss Duration of weight loss Resolution of comorbidity (cardiovascular, diabetes)

Table 11. AHRQ Priority Condition: 11 Peptic Ulcer Disease and Dyspepsia: 20 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Acetylcholinester-ase inhibitor (acotiamide) for treatment of functional dyspepsia	Patients in whom functional dyspepsia (FD) has been diagnosed	FD is a highly prevalent condition, but currently, no efficacious treatments are available. Acotiamide represents a novel drug class for this indication; it is a muscarinic receptor antagonist and acetylcholinesterase inhibitor under development for treating FD; intended to inhibit peripheral acetylcholinesterase (an important neurotransmitter for gastrointestinal motility) activities; intended to increase acetylcholine release in the enteric nervous system, thereby enhancing gastric contractility and accelerating gastric emptying (etiology of FD is still unclear, but delayed gastric emptying is closely associated with FD); also known as Z-338 or YM443. Administered orally, 100 mg, 3 times daily. Zeria Pharmaceutical Co., Ltd., Tokyo, Japan, in collaboration with Astellas Pharma, Inc., Tokyo, Japan Phase III trial completed in Japan; phase II trial completed in U.S.; submitted application for marketing authorization in Japan Sept 2010	Antacids Antibiotics Antispasmodic agents Behavioral therapy Gas remedies H_2 receptor blockers Low-dose antidepressants Prokinetic agents Proton pump inhibitors	Postprandial fullness Early satiety Decreased upper abdominal bloating Improved rate of gastric emptying Improved gastric accommodation Improved quality of life
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 currently approved. Remestemcel-L (Prochymal®) consists of allogeneic, bone marrow–derived human mesenchymal stem cells, which are purported to 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. Administered in a clinical trial 3 times, 200 million cells per infusion, 42 days apart. Osiris Therapeutics, Inc., Columbia, MD Phase III trials ongoing; FDA granted fast track status	Autologous bone marrow–derived mesenchymal stromal cells (in development) Teduglutide (in development)	Increased disease remission Improved disease symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Allogeneic stem cells (MultiStem) for treatment of ulcerative colitis	Patients in whom moderate to severe ulcerative colitis (UC) has been diagnosed	Current therapies for UC have not achieved desired results, especially for moderate to severe cases, and have undesirable side effects; no stem cell products for UC are currently available. MultiStem® is a proprietary allogeneic stem cell product made from nonembryonic stem cells obtained from bone marrow donors; the cells are intended to exert their effects through the production of therapeutic proteins and other molecules produced in response to inflammation and tissue damage; the company states that MultiStem is designed for off-the-shelf use because it can be used without the need for either tissue matching or immunosuppressive drugs. Administered by injection. Athersys, Inc., Cleveland, OH Pfizer, Inc., New York, NY Phase II trial ongoing	Tissue regrowth: Autologous bone marrow–derived mesenchymal stromal cells (in development) Teduglutide (in development) UC treatment: Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (prednisone, etc.) Immunomodulators (azathioprine, etc.) Monoclonal antibodies (natalizumab, infliximab, etc.)	Reduced relapse rates Healing of colon Reduced UC-related complications Improved quality of life
Elobixibat (A3309) oral agent to treat chronic idiopathic constipation	Patients with chronic idiopathic constipation	Effective treatments for chronic constipation are lacking. Elobixibat (A3309) is an oral drug that is intended to inhibit ileal bile acid transporter to increase fluid secretion and colonic motility without disrupting the lower intestinal tract. Albireo AB, Gothenburg, Sweden Phase II trials completed ; phase III program planned for 2012	Enemas Laxatives Lubiprostone	Relief of constipation with fewer side effects Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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. Phase II trial ongoing; procedure may be adopted by gastroenterologists who are using the procedure for treating recurrent *Clostridium difficile* infection	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (prednisone, etc.) Immunomodulators (azathioprine, etc.) Monoclonal antibodies (natalizumab, infliximab, etc.)	Reduction in the frequency of relapses Reduction in the use of medications reduction of symptoms Reduced or postponed need for surgery Improved quality of life
GSK1605786 (Traficet-EN) for treatment of Crohn's disease	Patients who have been given a diagnosis of moderate to severe Crohn's disease	GSK1605786 (Traficet-EN™) 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, GSK'786 selectively impairs the movement of activated T cells that are involved in causing inflammation of the digestive tract. GlaxoSmithKline, Middlesex, UK Phase III trials ongoing	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (prednisone, etc.) Immunomodulators (azathioprine, etc.) Monoclonal antibodies (natalizumab, infliximab, etc.	Delayed or avoided surgery Improved quality of life Reduced flare-ups Reduced side effects Remission Symptom improvement
Helminthic therapy (pig whipworm) for treatment-resistant ulcerative colitis	Patients in whom treatment-resistant ulcerative colitis has been diagnosed	Patients ingest 2,500 pig whipworm eggs every 2 weeks for 3 months; rationale is that inflammatory bowel diseases are uncommon in developing countries where helminths are common, and people with helminth infection have an altered immunological response to antigens. Parasites obtained from U.S. Department of Agriculture. In animal models, helminths prevent or improve colitis by the induction of regulatory T cells and modulatory cytokines. University of California, San Francisco One trial ongoing at NYU School of Medicine; 2 trials completed; 1 for ulcerative colitis and 1 for Crohn's disease	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (prednisone, etc.) Immunomodulators (azathioprine, etc.) Monoclonal antibodies (natalizumab, infliximab, etc.)	Increased safety Reduced flare symptoms Maintained remission Reduced or postponed need for surgery Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
IntelliCap (formerly iPill) to deliver localized drug therapy in digestive tract	Patients with digestive tract diseases (e.g., colon cancer) or irritable bowel disease (Crohn's disease, ulcerative colitis)	The iPill, recently renamed IntelliCap, is the size of an average pill; capsule includes a microprocessor, battery, pH sensor, temperature sensor, radiofrequency wireless transceiver, fluid pump, and drug reservoir. It communicates navigational feedback by measuring the local acidity (pH) of its environment via its wireless transceiver to a control unit outside the body; the internal pump, under control of the microprocessor, releases drugs to the programmed target. Drugs can be given with a bolus, progressive release, or multi-location dosing; it is also designed to pass through the digestive tract naturally. Royal Philips Electronics, Amsterdam, the Netherlands Prototype developed in 2008, redesigned and renamed in 2009; platform would be used by other companies to develop specific medications delivered by IntelliCap	No direct comparators	Reduced medication side effects Improved efficacy due to local delivery of drugs
JAK 3 kinase inhibitor (tofacitinib) 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. 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. Pfizer, Inc., New York, NY Phase III trial ongoing	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (prednisone, etc.) Immunomodulators (azathioprine, etc.) Monoclonal antibodies (natalizumab, infliximab, etc.)	Improved clinical response Reduced flare symptoms Reduced or postponed need for surgery Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Linaclotide (Linzess) for treatment of irritable bowel syndrome with constipation	Patients in whom irritable bowel syndrome (IBS) with constipation has been diagnosed	Linaclotide (Linzess™) is a peptide agonist of guanylate cyclase 2C located on the luminal surface of the intestine. In preclinical models, linaclotide was purported to reduce visceral hypersensitivity, increased fluid secretion, and accelerate intestinal transit. Linaclotide is taken orally once daily in a dose of 290 micrograms. Ironwood Pharmaceuticals, Cambridge, MA FDA approved Aug 30, 2012 to treat chronic idiopathic constipation and to treat irritable bowel syndrome with constipation (IBS-C) in adults; approval included a boxed warning that it should not be given to patients age 16 years and younger	Antispasmodic drugs Laxatives Serotonin agonists Tricyclic antidepressants	Reduced abdominal pain and constipation symptoms Long-term relief
Magnetically guided capsule endoscopy for diagnosis of gastrointestinal disorders	Patients appropriate for gastrointestinal (GI) endoscopic examinations	Current GI endoscopic procedures are invasive, require sedation, and have low rates of patient acceptance and satisfaction; existing capsule endoscopy technology does not enable clinicians to guide the capsule as it travels through the GI tract to ensure images of desired areas are captured. Magnetically guided capsule endoscopy is intended to allow the clinician more control of where the capsule travels and captures images; the patient swallows a capsule, which wirelessly transmits images to processing system, as the clinician navigates the capsule via a joystick and a magnetic field. The procedure is noninvasive and requires no sedation. Siemens Healthcare, Munich, Germany Olympus Medical Systems, Center Valley, PA Unphased trial ongoing	Endoscope procedure Pill Cam	Increased sensitivity and specificity Positive and negative predictive values Improved diagnostic accuracy Impact on clinical decision making for managing symptoms
MuDelta (JNJ-27018966) for treatment of diarrhea-predominant irritable bowel syndrome	Patients who have been given a diagnosis of diarrhea-predominant irritable bowel syndrome (IBS-d)	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. Furiex Pharmaceuticals, Morrisville, NC Phase III trials ongoing; received fast track status from FDA Jan 2011	Antispasmodic drugs Opioids Serotonin agonists Tricyclic antidepressants	Reduced abdominal pain and bloating symptoms Long-term relief

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
PerOral endoscopic myotomy 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 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 is purported to be less invasive, thereby potentially reducing complications, recovery time, and pain. Northwestern Memorial Hospital, Chicago, IL Phase IV trial ongoing	Heller myotomy	Improved Esophageal Function Tests (upper endoscopy, barium swallow, esophageal manometry, pH test) scores Improved quality of life
Plecanatide (SP-304) for treatment of chronic idiopathic constipation	Patients in whom chronic idiopathic constipation has been diagnosed	Current treatments for constipation are ineffective or poorly tolerated in some patients. Effective, well tolerated therapies are needed. Plecanatide is a synthetic peptide uroguanylin analog that targets guanylate cyclase C receptors in the gastrointestinal (GI) tract. Uroguanylin is a natural peptide hormone that regulates ion and fluid transport in the GI tract. Plecanatide is purported to be more potent than uroguanylin. It may be used to treat chronic constipation or constipation-predominant irritable bowel syndrome. In trials, it is being administered orally, 0.3–9.0 mg, once daily. Synergy Pharmaceuticals, Inc., New York, NY Phase II/III trial ongoing	Enemas Laxatives Lubiprostone	Decreased straining and abdominal discomfort Increased frequency of bowel movements Improved stool consistency 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 currently approved for treating traveler's diarrhea. Salix Pharmaceuticals, Inc., Morrisville, NC Phase III trial completed; company received complete response letter from FDA Mar 2011, received advice from FDA advisory committee	Antispasmodic drugs Opioids Serotonin agonists Tricyclic antidepressants	Reduced abdominal pain and bloating symptoms Long term relief

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Spherical carbon adsorbent (AST-120, Zysa) 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. AST-120 (Zysa™) is an oral spherical carbon adsorbent purported to bind to and neutralize 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. Ocera Therapeutics, Inc., San Diego, CA Phase II trial completed; FDA granted fast track status	Antispasmodic drugs Opioid receptor agonist in development Opioids Serotonin agonists Tricyclic antidepressants	Reduced abdominal pain and bloating Long-term relief
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 is purported to increase nutrient absorption and intestinal cell growth in patients with SBS. NPS Pharmaceuticals, Bedminster, NJ Phase III trials ongoing; new drug application submitted to FDA Dec 2011 for treating SBS; FDA approval date Dec 2012	Intravenous fluids Parenteral nutrition	Improved hydration Improved nutritional status Weight gain Reduced diarrhea Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tight junction regulator (larazotide acetate, AT-1001) for treatment of celiac disease	Patients in whom celiac disease has been diagnosed	Managing celiac disease consists mainly of following a gluten-free diet, which is difficult to follow for many patients. Additional treatment options are needed to minimize complications and improve the quality of life for patients with celiac disease. Larazotide acetate is an 8-amino-acid peptide purported to be part of a new drug class, tight junction regulators. Tight junctions comprise proteins intended to hold cells together to form an impermeable barrier except to shed dead cells. The presence of gluten in gastrointestinal tract of patients with celiac disease opens tight junctions, which creates a destructive inflammatory reaction in the bowel that destroys intestinal villi. In theory, larazotide acetate taken before a meal could help keep the tight junctions closed, which could reduce inflammation when gluten is ingested. Administered orally 0.5, 1.0, or 2.0 mg, 3 times daily. Alba Therapeutics Corp., Baltimore, MD Phase IIb trial ongoing	Corticosteroids Gluten-free diet Immunosuppressants	Improved ratio of intestinal villous height to crypt depth Reduced signs and symptoms Improved quality of life
Tumor necrosis factor-alpha kinoid for treatment of Crohn's disease	Patients in whom moderate to severe Crohn's disease has been diagnosed (Crohn's Disease Activity Index of between 220 and 400)	Tumor necrosis factor alpha-kinoid is a novel immunotherapy platform technology that uses inactivated cytokines, conjugated to a carrier protein and delivered with an adjuvant, or immune stimulant, to elicit a natural polyclonal antibody response. Delivered by 3-part injections. Neovacs S.A., Paris, France Phase II trial ongoing	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (prednisone, etc.) Immunomodulators (azathioprine, etc.) Monoclonal antibodies (natalizumab, infliximab, etc.)	Delayed or avoided surgery Improved quality of life Reduced flareups Reduced side effects Remission Symptom improvement
Vedolizumab for treatment of moderate to severe ulcerative colitis	Patients in whom moderate to severe ulcerative colitis (UC) has been diagnosed	Vedolizumab is an infused monoclonal antibody; current treatments for UC have limited effectiveness; the only cure is surgery. This may provide an alternative treatment. Millennium Pharmaceuticals, a unit of Takeda Pharmaceutical Co., Ltd., Osaka, Japan Phase III trials completed	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (prednisone, etc.) Immunomodulators (azathioprine, etc.) Monoclonal antibodies (natalizumab, infliximab, etc.)	Reduced flare symptoms Maintained remission Reduced or postponed need for surgery Improved quality of life

Table 12. AHRQ Priority Condition: 12 Pregnancy, Including Preterm Birth: 18 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Blood test to predict spontaneous preterm birth	Pregnant women	About 1 in 10 pregnant women have a spontaneous preterm birth in the U.S. each year; however, no diagnostic test is currently available to identify women at risk of preterm birth early in pregnancy to plan preterm birth prevention strategies. Sera Prognostics has developed a panel of proteomic markers that purportedly indicate the likelihood of spontaneous preterm birth. The proteomic assay is performed on a blood sample taken at 28 weeks of pregnancy. Sera Prognostics, Salt Lake City, UT Clinical trial ongoing; company states it is developing a commercial assay	Home uterine activity monitoring Salivary estriol testing Fetal fibronectin Detection of bacterial vaginosis Assessment of cervical length	Earlier intervention for women at risk of preterm birth Reduced incidence of preterm birth Reduced neonatal complications Reduced use of neonatal intensive care services
Cell-free fetal DNA test (MaterniT21 PLUS) for prenatal trisomy 13, 18, and 21 screening	Pregnant mothers at risk of trisomy 21 mutation	Trisomy 21 test (MaterniT21™) examines fetal DNA from the expectant mother's blood in 1st trimester. Massively parallel sequencing is performed to detect excess chromosome 21 DNA of fetal origin, which is indicative of trisomy 21 (Down syndrome). This test might replace invasive tests that pose a risk of miscarriage and allow earlier definitive screening to enable pregnant women to make decision earlier about continuing the pregnancy. Sequenom, Inc., San Diego, CA Late phase clinical trials completed; as of Oct 2011, lab-developed test has been made available to physicians in the U.S.; Sequenom planned to submit premarket approval application to FDA in late 2012 with hope for approval in 2013	Amniocentesis Blood serum markers for trisomy 21 Chorionic villus sampling Ultrasound detection of fetal abnormalities	Increased sensitivity and specificity Improved predictive values Avoided invasive procedures Earlier diagnosis for earlier decision making
C-Jun-N-terminal kinase inhibitor (bentamapimod) for treatment of endometriosis	Women in whom endometriosis has been diagnosed	Bentamapimod (PGL5) is a c-Jun-N-terminal kinase inhibitor being developed as the 1st oral drug to prevent recurrence of endometriosis; preclinical data have demonstrated PGL5 has anti-inflammatory and antifibrotic properties. Preglem SA, Geneva, Switzerland Phase IIa trial ongoing	Pharmacotherapy (e.g., anti-inflammatories) Surgical intervention (e.g., laparoscopy, hysterectomy [severe cases])	Improved treatment of endometriosis, potential avoidance of surgical treatment.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
C-Jun-N-terminal kinase inhibitor (bentamapimod) to prevent abdominal surgery adhesions from gynecologic pelvic surgery	Women undergoing gynecologic surgery in the pelvic or abdominal area	Bentamapimod (PGL5) is a c-Jun-N-terminal kinase inhibitor purportedly demonstrating anti-inflammatory and antifibrotic properties; this oral drug is being developed to prevent postsurgical abdominal adhesions in patients undergoing tubal ligation, surgery for endometriosis. PregLem, Geneva, Switzerland Phase IIa trial ongoing	Physical adhesion barriers Sprayed adhesion barriers	Fewer postsurgical adhesions compared with conventional treatments Less pain from adhesions
Copolymer styrene maleic anhydride/dimethyl sulfoxide (Vasalgel) for male contraception	Male patients pursuing contraception	Vasalgel™ is a male contraceptive intended to inhibit sperm under guidance. It is a copolymer styrene maleic anhydride/dimethyl sulfoxide that becomes hydrated in seminal fluid and degrades sperm cell membrane as sperm attempts to pass through vas deferens. It is purported to provide a safer, less costly alternative to contraception and is intended to be reversible. One dose injected into vas deferens every 10 years. Indian Institute of Technology, Powai, Mumbai, India Phase III clinical trials ongoing (in India); has secured a U.S. patent with intent to bring to U.S. market	Condoms Vasectomy	Long-acting male contraception
Daily text messaging to encourage oral contraceptive continuation	Patients using an oral contraceptive pill (OCP)	Sixty-three percent of reproductive-age women who practice contraception use nonpermanent methods, with OCP as the leading method for women younger than 30 years of age. On average, 6-month OCP continuation rates in young women range from 12% to 58%. In the U.S., OCP discontinuation and misuse cause about 1 million unintended pregnancies a year. The OCP daily text messaging study evaluates the efficacy of a 2-way text messaging program intended to deliver educational content on OCP continuation; this intervention is intended to reduce OCP discontinuation rates, especially for women in urban settings. Columbia University Medical Center Department of Obstetrics and Gynecology, New York, NY Pilot trials completed	Educational therapy Routine care	Increased OCP continuation Decreased risk of pregnancy

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Donor human milk program to feed very-low-birthweight infants	Very-low-birthweight infants (less than 1,501 g weight at birth)	Women who give birth to very-low-weight infants who must remain in the intensive care unit often are unable to supply sufficient breast milk. Donated breast milk for very-low-birthweight infants whose mothers cannot supply sufficient breast milk is purported to lead to better health and neurodevelopmental outcomes than observed in preterm infants fed formula. The milk is collected from lactating volunteers and screened for safety before administration to infants. University of Iowa, Iowa City Phase III trial ongoing	Standard infant formula	Reduced health care costs Normal Bayley Scales of Infant Development, III (at 18–22 months of age)
Electronic early physiologic response test (PhysiScore) to predict risk of illness in preterm infants	Preterm infants	One of every 8 births in the U.S. is categorized as preterm. Novel devices to more rapidly predict risk of preterm birth are needed to improve an infant's short- and long-term health outcomes. PhysiScore is an electronic version of the APGAR score; collects physiologic data (heart rate, respiratory rate and oxygen saturation) during 1st 3 hours of life in a neonatal intensive care unit. The software would enable PhysiScore to be displayed on existing bedside monitors. Stanford University School of Medicine, Stanford, CA Pilot phase trial ongoing	APGAR score	Increased sensitivity Improved predictive value for risk of life-threatening events Avoided invasive testing Improved health outcomes Decreased long-term disabilities
Endoglin urine screening test to screen for preeclampsia in pregnancy	Pregnant women at risk of preeclampsia	Urine test intended to detect endoglin, a cell surface glycoprotein that has been shown to be elevated in pregnant women who develop preeclampsia. Miraculins, Inc., Winnipeg, Manitoba, Canada Inverness Medical Professional Diagnostics, Princeton, NJ Assay development and optimization ongoing	Screening pregnant women for elevated blood pressure and high levels of protein in the urine	More specific and earlier detection of preeclampsia Earlier management of secondary preeclampsia symptoms

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fetal programming to prevent metabolic disorders	Pregnant women	Many metabolic abnormalities may stem from the fetal environment and how the fetus' metabolism becomes established during pregnancy; measures taken to ensure healthy fetal development include adherence to prenatal vitamin intake and routine prenatal care. Fetal programming (FP) is a comprehensive concept that aims to enhance a child's metabolism into adulthood by using drug therapy, nutritional supplements, and enhanced nutrition during pregnancy. FP aims to decrease risk of many adult diseases, including coronary artery disease, breast cancer, and diabetes, by improving the uterine environment through programming of hormone-production levels with intention of maintaining healthy organ function throughout life. An example of FP is treating obese pregnant women with metformin even if they do not have a diagnosis of diabetes because blood glucose levels tend to be higher during pregnancy and glucose may pass through the placenta to the fetus. University of Edinburgh, Scotland, UK Pilot trial ongoing	Nutritional programs alone for pregnant women Prenatal vitamins alone Routine prenatal care	Improved health in newborns Decreased risk of development of metabolic disorders
Gonadotropin-releasing hormone antagonist (Elagolix) for treatment of endometriosis	Patients in whom endometriosis has been diagnosed	Elagolix is the 1st oral nonpeptide gonadotropin-releasing hormone (GnRH) antagonist that, unlike currently used 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 made it possible to maintain appropriate levels of estrogen, thus preventing menopausal-like hormonal levels and the need for management of bone loss while treating endometriosis. Neurocrine Biosciences, Inc., San Diego, CA Phase III trial ongoing	Pharmacotherapy (e.g., hormonal contraceptives, steroids) Surgical intervention (e.g., endometrial growth and scar tissue excision, hysterectomy)	Improved composite pelvic signs and symptoms score (measures dysmenorrhea, non-menstrual pelvic pain, dyspareunia, pelvic tenderness and induration) Maintained bone mineral density Improved patient global impression of change Less pain (visual analog scale)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 do not completely develop (i.e., aorta, aortic valve, mitral valve). 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. Texas Children's Fetal Center of Texas Children's Hospital, Houston, TX 4-patient surgical trial completed	Neonatal surgery	Increased oxygenation to fetus Increased survival to live birth Increased postnatal survival
N-acetylcysteine for treatment of intra-amniotic infection and inflammation during pregnancy	Pregnant women in whom intra-amniotic infection and/or inflammation has been diagnosed	Intra-amniotic inflammation in utero early in gestation is thought to possibly trigger a cascade of events that lead to preterm birth (i.e., premature rupture of membranes, cervical ripening, uterine contractions). N-acetylcysteine (NAC), an antioxidant, is a derivative of amino acid, L-cysteine, and mucolytic agent. It is proposed for treating pregnant women with intra-amniotic infection to prevent adverse neonatal outcomes by potentially reducing intracellular concentration of free radicals and cell damage. Administered intravenously. Yale University, New Haven, CT Phase II trial ongoing	Standard pharmacotherapy without NAC	Reduced early onset neonatal sepsis Prevention of neonatal death

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nurse home visits to reduce second pregnancies in high-risk mothers	Low-income, high-risk mothers	Nurse home-visitation programs in which information on women's health, preconception health, and family planning is provided to low-income women who have delivered 1 child and are at high risk of a 2nd unplanned pregnancy. Children's Hospital of Philadelphia, Philadelphia, PA Pennsylvania Department of Public Welfare Pilot trial completed	Family planning clinics Healthy Start (Health Resources & Services Administration) Lay women home visitation programs (e.g., Resource Mothers, Promotoras)	Improved health outcomes for mother and child Improved planning of subsequent pregnancies
Oral androgen (dimethandrolone undecanoate) for male contraception	Male patients pursuing contraception	Dimethandrolone undecanoate (DMAU) is a potent, orally active androgen with progestational activity that might act as a single-agent oral hormonal contraceptive (given its dual androgenic and progestational activity). DMAU purportedly suppresses the hypothalamic-pituitary-gonadal axis, resulting in severe oligospermia. DMAU purportedly decreases levels of follicle-stimulating hormone, luteinizing hormone, and testosterone. DMAU may be administered orally at 25, 50, 100, 200, 400, or 800 mg per dose. Los Angeles Biomedical Research Institute, Los Angeles, CA, in collaboration with the National Institutes of Health, Bethesda, MD, and University of Washington, Seattle Phase I trial ongoing	Condoms Vasectomy	Long-acting male contraception Decreased risk of unplanned pregnancy Changes in use of condoms
Ulipristal acetate (CDB-2914) 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 (CDB-2914; EllaOne®) is a selective P receptor modulator with antiprogestin effects. Given orally, 10 or 20 mg, once daily. Laboratoire HRA Pharma, SA, Paris, France Phase IIb and phase III trials ongoing	Cryomyolysis ExAblate Gonadotropin-releasing hormone agonists Hysterectomy Uterine artery embolization	Avoided or delayed hysterectomy Reduced total fibroid volume Prevention of anemia due to heavy menstrual bleeding Reduced symptoms (e.g., pain) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vaginal progesterone gel (Prochieve) to prevent preterm birth in women with a short cervix	Pregnant women in whom a sonographic short cervix (10–20 mm) has been diagnosed	A sonographic short cervix has been demonstrated to be a good predictor of preterm birth (a major cause of perinatal morbidity and mortality). Current interventions for short cervix include hospital care, bed rest, surgery, and removable devices. According to investigators, progesterone appears to relax the myometrium by repressing the expression of genes that promote labor; micronized vaginal progesterone gel is being investigated to reduce the risk of preterm birth and associated neonatal complications in women with a sonographic short cervix; women self-administer the drug once daily in the morning using a vaginal progesterone capsules kit to prevent dispensing errors; Prochieve 8%, also known as Crinone 8%, is an off-white gel, in a single use, 1-piece, disposable polyethylene vaginal applicator. Watson Pharmaceuticals, Parsippany, NJ FDA advisory panel voted Jan 2012, to not recommend for approval citing trial had not met efficacy endpoint; Feb 2012, FDA issued complete response letter; Watson requested end-of-review meeting with FDA to determine if a viable path forward is possible	Bed rest (hospital admission or at-home) Cervical cerclage Tocolytic therapy Steroids Vaginal pessary	Sustained pregnancy to full-term Reduced preterm (delivery at <3 weeks before term) birth rate Fewer admissions to neonatal intensive care unit Reduced neonatal morbidity Reduced perinatal mortality Shorter length of neonatal stay
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' perception, and cost are several determinants in emergency contraceptive use. Shippensburg University in Pennsylvania has incorporated an emergency contraceptive, or "morning after pill," vending machine into the student health center, charging $25 for each dose for students 17 years of age or older. The vending machine also includes other reproductive health products, including condoms and pregnancy test kits. Shippensburg University, Shippensburg, PA Not yet subject to FDA approval	Over-the-counter access to emergency contraceptives	Decreased risk of pregnancy Increased emergency contraceptive use Increased risk of adverse events associated with emergency contraception

Table 13. AHRQ Priority Condition: 13 Pulmonary Disease, Asthma: 36 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
APD811 (oral prostacyclin) 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. Prostacyclin is an approved therapy for treating PAH, but no orally dosed prostacyclin therapy is available in the U.S.; available prostacyclin therapies are intravenous, subcutaneous injection, or inhaled. APD811 would be the 1st oral, once-daily, selective agonist of the prostacyclin receptor that regulates vascular smooth muscle tone. It is believed to have the potential to reduce mortality in patients with advanced PAH. Arena Pharmaceuticals, Inc., San Diego, CA Phase I trial completed; phase Ib trial planned	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalization
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 U.S. and EU cases and more than 50% of CF cases in Israel. Ataluren is intended to improve lung function, which could lead to improved survival. PTC Therapeutics, Inc., South Plainfield, NJ Phase III trials ongoing; FDA granted orphan drug status	Antibiotics Bi-level positive airway pressure ventilators Bronchodilators (albuterol or salmeterol) Chest physiotherapy DNase (such as Pulmozyme®) Gene therapies (viral vector or liposome delivery of normal *CFTR*; investigational) Hypertonic saline Mucolytics (acetylcysteine)	Improved lung function Increased survival Reduced need for additional therapies Improved quality of life
BIO-11006 inhalation solution for treatment of chronic obstructive pulmonary disease	Patients in whom chronic obstructive pulmonary disease (COPD) has been diagnosed	COPD is the 3rd leading cause of death in the U.S. and is characterized by airway obstruction, inflammation, and excess mucus production. Currently no COPD medications directly inhibit excess mucus production. BIO-11006 is an inhaled, soluble, small peptide consisting of 10 amino acids purported to inhibit the myristoylated alanine-rich C kinase substrate, which has been shown to be involved in the secretion of mucus and inflammatory mediators. Administered 75 mg, twice daily. BioMarck Pharmaceuticals, Ltd., Durham, NC Phase II trial completed	Glucocorticoids Long-acting anticholinergic agents Long-acting beta2-agonists Roflumilast	Decreased cough frequency Decreased inflammation Decreased sputum production Improved pulmonary function

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
CFTR corrector (VX-661) for treatment of cystic fibrosis	Patients in whom cystic fibrosis (CF) has been diagnosed	Current therapies for CF have improved median survival, but patients with CF still have a shorter-than-normal life expectancy and require extensive treatment over a lifetime to optimize health outcomes. Novel, effective medications to improve outcomes are needed. VX-661 is considered a corrector of the cystic fibrosis transmembrane regulator (CFTR) gene in patients with the F508del mutation. VX-661 is intended to increase the regulator's function by increasing its movement to the cell surface. Administered orally as monotherapy, once daily, or in combination with ivacaftor. Vertex Pharmaceuticals, Inc., Cambridge, MA Phase II trial ongoing	Antibiotics Bi-level positive airway pressure ventilators Chest physiotherapy Gene therapies (viral vector or liposome delivery of normal CFTR) Transplantation (lungs) VX-809	Improved lung function Increased survival Improved quality of life
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, one-way valves in targeted airways to direct the flow of air out of diseased portions of the lung." Three to 4 valves per lobe are typically placed during a procedure, and the total procedural time is purported to take 15–30 minutes, depending on the number of valves placed. The valves are coated with medical-grade silicone to prevent tissue growth through the nitinol retainer. Pulmonx, Inc. (formerly Emphasys), Redwood City, CA Phase III trial ongoing	Antibiotics Bronchodilators Corticosteroids Oxygen Pulmonary rehabilitation program Surgery: lung-reduction volume surgery, bullectomy, lung transplantation	Improved lung function Improved activities of daily living Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
GPS and Wi-Fi-enabled inhaler (Spiroscout) for treatment of asthma	Patients in whom asthma has been diagnosed	The few alternatives available for asthma patient data recording may introduce patient error, leading to less accurate and more subjective judgments about when inhaler doses are needed. The GPS and Wi-Fi-enabled inhaler (Spiroscout®) is a device that attaches to the top of a metered-dose inhaler, using GPS and Wi-Fi to accurately record time, geographic location, and frequency of inhaler use; this information is sent to a central server/database for analysis, and physicians and epidemiologists can use the information to make determinations about events and environments correlating to patients' inhaler use; if implemented, Spiroscout might provide an affordable and more accurate way for both physicians and patients to decrease triggers to asthma and consequent dependence on asthma inhalers. Spiroscout takes 1 reading per inhaler use. Asthmapolis, Madison, WI Received 510(k) clearance Jul 2012	Self-recorded logs (hand-written, mobile, Web)	Reduced need for recording logs for patients with asthma Enhanced detection of triggers for asthma Reduced health disparities Improved quality of life
Heparin (VR-496) dry inhaled powder for treatment of cystic fibrosis	Patients in whom cystic fibrosis (CF) has been diagnosed	Current CF inhaled therapies target only 1 disease element, such as infection or viscid mucus; furthermore, not all patients respond well to currently available mucolytics. VR-496, a proprietary formulation of dry powder heparin sodium; intended to be the 1st agent to treat CF that can potentially provide anti-inflammatory, mucolytic, antibronchoconstrictor, and anti-infective activity; active component is heparin, which acts on multiple sites in the coagulation pathway. VR-496 is to be administered (inhaled) twice daily; in trials it was given for 4 weeks. Vectura Group, Wiltshire, UK Phase II trial completed; FDA granted orphan drug status	Antibiotics Bilevel positive airway pressure ventilators Bronchodilators (albuterol or salmeterol) Chest physiotherapy DNase (such as Pulmozyme®) Gene therapies (viral vector or liposome delivery of normal *CFTR*; investigational) Hypertonic saline Mucolytics (acetylcysteine)	Reduced chest infections Reduced anti-inflammatory activity Improved mucolysis

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Human monoclonal antibody (FG-3019) for treatment of idiopathic pulmonary fibrosis	Patients in whom idiopathic pulmonary fibrosis (IPF) has been diagnosed	FG-3019 is a human monoclonal antibody against connective tissue growth factor; could potentially reduce collagen deposition and slow/reverse progressive scarring of lung tissue that occurs in IPF; currently available anti-inflammatory agents and immune modulators have shown minimal effectiveness in modifying the natural course of IPF and are associated with many side effects. FibroGen, Inc., San Francisco, CA Phase II trial ongoing	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Intedanib (investigational) Methotrexate Penicillamine Pirfenidone (investigational) Pulmonary rehabilitation Supplemental oxygen	Improved lung function Improved survival
Imatinib (Gleevec) 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. Imatinib (Gleevec®) is a small-molecule, ABL kinase inhibitor that is purported to inhibit cellular processes that are responsible for uncontrolled growth of arterial smooth muscle cells. Imatinib has been administered orally, 200–400 mg, once daily in clinical trials. Novartis International AG, Basel, Switzerland Phase III trials ongoing	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalization
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 designed for administration via inhalation once daily 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. Arikace is approved for other indications and is sometimes used off-label for NTM indication, but existing formulation is not intended for that use and trials are ongoing for the NTM indication. Insmed, Inc., Richmond, VA Phase II recruiting with results expected in 2013; FDA granted orphan drug status	Amikacin (injectable) Other antibiotics such as: Amoxicillin/clavulanate Capreomycin Clarithromycin Clofazimine Ethambutol Ethionamide Fluoroquinolones Imipenem/cilastatin Isoniazid Kanamycin Linezolid p-Aminosalicylic acid Prothionamide Pyrazinamide Streptomycin Terizidone Thioacetazone	Resolved abnormalities as seen on computed tomographic scan Higher rate of culture conversion to negative Improved 6-minute walk distance and improved oxygen saturation Extended time before need for “rescue” antimycobacterial drugs

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Inhaled interferon beta (SNG001) for treatment of respiratory infections in patients with asthma	Patients with asthma who have a respiratory infection	Respiratory infections are a major trigger for exacerbation of asthma and a cause of hospitalization for severe asthma attacks. Treatment options for viral infections in patients with asthma are limited. SNG001 is an inhaled interferon-beta formulation intended to be used during a respiratory infection's early stages to limit viral replication and asthmatic complications. Interferon beta is a cytokine naturally produced as part of the immune system's early response to limit the spread of a viral infection. SNG001 is purported to be the 1st treatment aimed at increasing host responses to the virus instead of targeting viral replication with a direct-acting agent. Administered by nebulizer, once daily, for 14 days. Synairgen, plc, Southampton, UK Phase II trial completed	BTA798 (in clinical development) N6022 (in clinical development) Supportive therapy	Improved asthma symptoms Preserved lung function Reduced medication use Reduced severe exacerbations Improved quality of life
Inhaled mannitol (Bronchitol) for treatment of mucus in noncystic-fibrosis bronchiectasis and cystic fibrosis	Patients in whom cystic fibrosis (CF) or non-CF bronchiectasis has been diagnosed	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. Bronchitol is a new approach, a proprietary formulation of mannitol administered as a dry powder through a handheld inhaler. It is being developed to reduce the amount of mucus build-up in the lungs. Restoration of airway surface liquid by hydration of the lungs could help restore normal lung clearance and clear excess mucus. Pharmaxis, Ltd., Frenchs Forest, Australia Phase III trial completed; FDA granted fast track and orphan drug status; company has indicated it will submit FDA application	Cystic fibrosis: Antibiotics Bilevel positive airway pressure ventilators Bronchodilators (albuterol or salmeterol) Chest physiotherapy DNase (such as Pulmozyme®) Gene therapies (viral vector or liposome delivery of normal *CFTR*; investigational) Hypertonic saline Mucolytics (acetylcysteine) Noncystic-fibrosis bronchiectasis: Oxygen supplementation	Improved lung function Reduced pulmonary exacerbations Reduced antibiotic use Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interleukin-5 antagonist (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 is purported to play 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, and 750 mg, every 4 weeks. GlaxoSmithKline, Middlesex, UK Phase III trial ongoing	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long-acting beta agonists Omalizumab (Xolair) Theophylline Reslizumab (in development) Short-acting beta agonists	Improved asthma control Improved asthma exacerbation rate Reduced emergency room visits Reduced hospitalization Improved quality of life
Interleukin-5 antagonist (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 is purported to play 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. Cephalon, Inc., acquired by Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, Oct 2011 Phase III trials ongoing	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long-acting beta agonists Mepolizumab (in development) Omalizumab (Xolair) Short-acting beta agonists Theophylline	Improved asthma control Improved asthma exacerbation rate Reduced emergency room visits Reduced hospitalization Improved quality of life
Ivacaftor (Kalydeco) for treatment of cystic fibrosis in patients with G551D-CFTR mutation	Patients 6 years of age and 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. Vertex Pharmaceuticals, Inc., Cambridge, MA Phase III trial ongoing; FDA approved Jan 2012 for patients with CF who are age 6 years and older with the G551D mutation	Currently, no treatment exists to treat the cause of the gene mutation	Reduced lung damage Improved lung function Slowed disease progression

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
KIT tyrosine kinase inhibitor 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 is purported to target 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 of body weight daily, in clinical trials. AB Science S.A., Paris, France Phase III trial ongoing	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long-acting beta agonists Omalizumab (Xolair) Short-acting beta agonists Theophylline	Improved asthma control Improved asthma exacerbation rate Reduced emergency room visits Reduced hospitalization Improved quality of life
KL4 synthetic lung surfactant (Aerosurf and Surfaxin [lucinactant]) for prevention of neonatal respiratory distress syndrome	Very-low- and low-birthweight premature infants at risk of respiratory distress syndrome	KL4 surfactant is a synthetic peptide-containing surfactant intended to closely mimic the essential attributes of human lung surfactant; 2 forms in development. Aerosurf® is a combination drug/device administered in conjunction with noninvasive nasal continuous positive airway pressure (nCPAP); Surfaxin® is delivered through other ventilation modalities; purported to be the 1st potential opportunity to deliver a clinically relevant dose of synthesized surfactant with key polypeptides missing in existing synthetic surfactant. Discovery Laboratories, Inc., Warrington, PA FDA approved Mar 2012 for preventing respiratory distress syndrome; phase IIa trial for aerosolized Aerosurf formulation completed	Animal-derived surfactants delivered by endotracheal intubation with or without mechanical ventilation	Improved survival Reduced pulmonary complications Reduced intubation and mechanical ventilation Prevention of risks associated with intubation and mechanical ventilation
Lebrikizumab for treatment of moderate to severe uncontrolled asthma	Patients in whom moderate to severe uncontrolled asthma has been diagnosed	Despite currently available therapies some patients with asthma remain unable to control their symptoms. Lebrikizumab is a humanized monoclonal antibody designed to block the activity of interleukin-13 (IL-13), a contributor to asthma which is produced by T-helper type 2 cells; lebrikizumab may be more effective in patients with elevated serum periostin levels (a surrogate marker for elevated IL-13). Biologic is administered subcutaneously. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials ongoing	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long-acting beta agonists Omalizumab (Xolair) Short-acting beta agonists Theophylline	Improved asthma control Improved asthma exacerbation rate Reduced emergency room visits Reduced hospitalization Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lung volume reduction coil (RePneu) for treatment of emphysema	Patients in whom upper and/or lower lobe heterogeneous emphysema and/or multiple emphysematous lobes with focal tissue defects has been diagnosed	Treatment for advanced emphysema involves lung volume reduction (LVR) surgery, and a less invasive approach to LVR 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 the healthier lung tissue to function; RePneu is a wire-like 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 to improve breathing. PneumRx, Inc., Mountain View, CA Pivotal phase II/III trials ongoing; Conformité Européene (CE) marked Oct 2010	Antibiotics Bronchodilators Corticosteroids Oxygen Pulmonary rehabilitation program Surgery: lung-reduction volume surgery, bullectomy, lung transplantation	Improved lung function, physical endurance and activities of daily living Improved scores in St. George's Respiratory Questionnaire (measures impaired health and perceived well-being in airways disease)
Milrinone lactate for treatment of persistent pulmonary hypertension of the newborn	Newborns (up to 10 days) in whom persistent pulmonary hypertension of the newborn (PPHN) has been diagnosed	The current standard of care is treatment with inhaled nitric oxide for PPHN; however, for many babies this treatment does not provide sufficient improvement in oxygenation, and the condition is associated with high morbidity and mortality. In PPHN pulmonary vasculature fails to relax after birth resulting in severe hypoxemia (decreased partial pressure of oxygen in blood); milrinone lactate will be given as an intravenous infusion for 24 hours in addition to nitric oxide (NO) to try to improve oxygenation. Milrinone is indicated for the short-term intravenous treatment of acute decompensated heart failure. Children's Hospital of Philadelphia, Philadelphia, PA, and Bedford Laboratories, Bedford, OH (maker of generic milrinone), are collaborating Pilot study of 18 newborns ongoing; to be followed by a randomized controlled trial	Assisted ventilation Extracorporeal membrane oxygenation High frequency oscillatory ventilation NO Oxygen	Improved oxygenation index Decreased signs of pulmonary hypertension Improved safety profile

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multikinase inhibitor (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 currently exist. BIBF-1120 (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. Nintedanib is under study for treating IPF and slowing of disease progression and symptoms. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials ongoing	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Methotrexate Penicillamine Pirfenidone (investigational) Pulmonary rehabilitation Supplemental oxygen	Improved lung function measured by forced vital capacity Improved ability to perform activities of daily living Slowed disease progression Improved quality of life
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. University of Colorado Denver Health Sciences Center Phase III trials ongoing; FDA approved in 1992 for treating community-acquired respiratory infections and skin infections	Glucocorticoids Long-acting anticholinergic agents Long-acting beta2-agonists Roflumilast	Reduced cost due to exacerbations Reduced incidence of exacerbations Increased survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label rituximab for treatment of systemic sclerosis-associated pulmonary arterial hypertension	Patients in whom systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) has been diagnosed	One-year survival for patients with SSc-PAH ranges from 50% to 81%, and treatment is limited to vasodilator therapy. Rituximab, a genetically engineered anti-CD20 antibody for treating B-cell lymphoma, is being investigated for immune mechanisms associated with B-cell dysregulation and pathogenic autoantibody response in SSc-PAH. It is being administered in 2 infusions, 1,000 mg each, 14 days apart. National Institute of Allergy and Infectious Diseases, Bethesda, MD (trial sponsor) Phase II trial ongoing	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalization
Oral sustained-release prostacyclin (treprostinil UT-15C) 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. No approved oral prostacyclin therapies are available in the U.S.; only intravenous, injected, or inhaled formulations are available. Sustained release oral treprostinil, if approved, could be the 1st oral prostacyclin for PAH, and is intended for use early in the PAH disease continuum; treprostinil diethanolamine vasodilates pulmonary and systemic arterial vascular beds and inhibits platelet aggregation; intended as an add-on therapy to current oral therapies. United Therapeutics Corp., Silver Spring, MD Phase III trials ongoing	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalization
Pirfenidone 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 currently exist. Pirfenidone is a small molecule that inhibits the synthesis of transforming growth factor-beta, which is purported to be involved in fibrosis, and tumor necrosis factor alpha, which is involved in mediating inflammation. The drug is administered orally. InterMune, Inc., Brisbane, CA Phase III trials ongoing; FDA granted fast track and orphan drug status	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Intedanib (investigational) Methotrexate Penicillamine Pulmonary rehabilitation Supplemental oxygen	Improved ability to perform activities of daily living Improved lung function measured by forced vital capacity Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
PL-3994 for treatment of acute exacerbations of asthma	Patients with asthma who experience acute exacerbations	Some patients are unresponsive to beta-2 adrenergic receptor agonists and improvement after an acute exacerbation of asthma in these patients usually takes several hours. PL-3994 is being developed as a self-administered subcutaneous injection for rapid treatment and resolution of acute exacerbations of asthma; a synthetic molecule and natriuretic peptide receptor A (NPR-A) agonist that activates NPR-A, a receptor involved in cardiovascular homeostasis; PL-3994 induces a pharmacologic response consistent with the effects of endogenous natriuretic peptides (smooth muscle relaxation, blood pressure decrease, sodium excretion); PL-3994 works through a different pathway from beta-2 adrenergic receptor agonists and other approved bronchodilators, which are used to treat acute exacerbations of asthma. Palatin Technologies, Inc., Cranbury, NJ Phase II trial ongoing	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long-acting beta agonists Omalizumab (Xolair) Short-acting beta agonists Theophylline	Improved asthma control Improved asthma exacerbation rate Reduced emergency room visits Reduced hospitalization Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Portable inhaled nitric oxide device (Nitrosyl) for treatment of pulmonary diseases	Patients in whom pulmonary hypertension secondary to idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension has been diagnosed	No medications are currently approved for treating pulmonary hypertension associated with IPF. Portable nitric oxide (NO) device (Nitrosyl) delivers NO therapy for pulmonary indications and is the 1st portable device to enable ambulatory delivery of NO. Intended to enhance pulmonary vasodilation. GeNO, LLC, Cocoa, FL Phase II trials ongoing	Pulmonary arterial hypertension: Calcium channel blockers Endothelin receptor antagonists Lung transplantation Phosphodiesterase type 5 inhibitors Prostanoids Pulmonary rehabilitation Supplemental oxygen IPF: Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Intedanib (investigational) Methotrexate Penicillamine Pirfenidone (investigational) Pulmonary rehabilitation Supplemental oxygen	Improved exercise capacity Reduced mortality Reduced hospitalizations
Riociguat (BAY63-2521) 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. Riociguat is purported to stimulate the soluble guanylate cyclase pathway that is involved in nitric oxide signaling and vasodilation, which may relieve symptoms of PAH. In ongoing trials, riociguat is administered orally, 1.0, 1.5, 2.0, or 2.5 mg, 3 times daily. Bayer AG, Leverkusen, Germany One phase III trial completed; extension phase III trial ongoing	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalizations

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Selective prostacyclin (PGI2) receptor agonist (selexipag) 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. 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 an oral tablet taken twice daily. Actelion Pharmaceuticals, Ltd., Allschwil, Switzerland Phase III trials ongoing	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalization
Surface-enhanced Raman spectroscopy for rapid diagnosis of *Mycoplasma pneumoniae* infection	Adults, older children, and young adults suspected of having *Mycoplasma pneumoniae* infection	A throat swab is taken and evaluated using enhanced Raman spectroscopy signals to detect bacteria in the specimen. The spectroscopy detects spectral signatures of a near-infrared laser as it scatters off a biologic specimen. University of Georgia, Athens Pilot trial planned	Existing tests for possible *M. pneumoniae* infection Serology and nucleic acid amplification tests	Early diagnosis Avoided unnecessary antibiotic treatment Reduced transmission
TC-6987 oral neuronal nicotinic receptor alpha-7 modulator for treatment of asthma	Patients in whom persistent mild to moderate asthma has been diagnosed	Although several effective inhaled anti-inflammatory treatments are available for chronic asthma, adherence with therapy is an issue. TC-6987 is an oral therapy that is a modulator of alpha-7 neuronal nicotinic receptor (NNR), which has been shown to play a role in controlling inflammation pathways. Chronic inflammation of the bronchial tubes is thought to be the underlying cause of asthma. Modulation of NNR alpha-7 has been shown to lead to a reduction in the production and release of proinflammatory cytokines. Administered orally, as a 50 mg, hard-gel capsule. Targacept, Inc., Winston Salem, NC Phase II trial completed.	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long-acting beta agonists Omalizumab (Xolair) Short-acting beta agonists Theophylline	Improved asthma control Improved asthma exacerbation rate Reduced emergency room visits Reduced hospitalization Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Temperature controlled laminar air-flow device (Protexo) 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. Protexo® is a temperature-controlled laminar air-flow device that is positioned over the patient while he or she sleeps. The device is purported to create a downward flow of filtered air that surrounds the sleeping patient's breathing zone with the intention of providing air in convection currents that is free of allergens and irritants. Airsonett AB, Ängelholm, Sweden Phase III trials completed	Air purifiers Antiallergenic pillow/mattress encasements Home heating, ventilation, and air conditioning systems	Reduced asthma symptoms Improved peak nasal inspiratory flow Improved sleep quality Improved quality of life
Therapeutic oral vaccine (HI-164OV) for chronic obstructive pulmonary disease	Patients in whom chronic obstructive pulmonary disease (COPD) has been diagnosed	Immunotherapy (HI-164OV) using *Haemophilus influenza*; intended to treat moderate to severe exacerbations (those that would require corticosteroid therapy) of COPD. Taken orally. Probiomics Ltd., Gordon, NSW, Australia Phase IIb trial completed	Glucocorticoids Long-acting anticholinergic agents Long-acting beta2-agonists Roflumilast	Reduced duration of episodes Fewer hospitalizations for exacerbations Reduced number and severity of exacerbations
Tissue-engineered donor trachea for trachea replacement	Patients who need replacement of irreversibly damaged respiratory tract	Tissue-engineered trachea made from a donor trachea in which a tissue scaffold of fibrous protein collagen is prepared and then repopulated with the recipient's cells (cells lining the windpipe and adult stem cells) in laboratory; once cultivated with recipient's cells, the donor trachea is transplanted to recipient. Paolo Macchiarini and colleagues, Barcelona, Spain Ministerio de Sanidad y Consumo, Madrid, Spain First transplant reported in late 2010	None	Restored trachea Restored respiratory function/capacity Increased or restored lung capacity Improved quality of life
TPI ASM8 for treatment-resistant asthma	Patients with severe asthma that has not responded to current standard of care	Treatments for asthma that is not well controlled with existing medications are needed. ASM8 is a proprietary oligonucleotide technology intended to reduce the recruitment and persistence of chronic inflammatory cells and their associated release of cytokines. It inhibits multiple targets associated with inflammation in asthma. Pharmaxis, Ltd., Sydney, Australia Three phase II trials completed	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long-acting beta agonists Omalizumab (Xolair) Short-acting beta agonists Theophylline	Improved asthma control Improved asthma exacerbation rate Reduced emergency room visits Reduced hospitalization Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
VX-809 for treatment of cystic fibrosis	Patients with cystic fibrosis (CF) who have the delta F508-*CFTR* gene mutation	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). Vertex Pharmaceuticals, Inc., Cambridge, MA Phase II trial ongoing; FDA granted orphan drug status	Antibiotics Bilevel positive airway pressure ventilators Bronchodilators (albuterol or salmeterol) Chest physiotherapy DNase (such as Pulmozyme®) Gene therapies (viral vector or liposome delivery of normal *CFTR*; investigational) Hypertonic saline Mucolytics (acetylcysteine)	Improved lung function Increased survival Improved quality of life Reduced need for additional therapies

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Buprenorphine implants (Probuphine) for treatment of opioid dependence	Patients in whom opioid dependence has been diagnosed	Sublingual buprenorphine-naloxone tablet induction followed by buprenorphine implants; 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. Titan Pharmaceuticals, Inc., South San Francisco, CA Phase III confirmatory trial completed; held pre-NDA (new drug application) meeting with FDA in Oct 2011; NDA to be submitted in 3rd quarter of 2012	Methadone maintenance treatment Naltrexone Sublingually administered buprenorphine	Resolution problems with adherence, diversion Reduced illicit use of opioids
GABA transaminase inhibitor (CPP-109, vigabatrin) for treatment of cocaine dependence	Patients in whom cocaine dependence has been diagnosed	No pharmacotherapies for cocaine dependence are approved. CPP-109 (vigabatrin) is a gamma aminobutyric acid (GABA) transaminase inhibitor. By inhibiting GABA transaminase, GABA levels in the brain are increased, thereby suppressing dopamine release and reducing the pleasurable feelings associated with cocaine use. Vigabatrin is approved for use in patients with epilepsy, but is being redeveloped for cocaine-addiction treatment by a different company. For this indication, the drug is intended to be administered dissolved in orange juice. Catalyst Pharmaceutical Partners, Inc., Coral Gables, FL Phase II/III trial ongoing	Behavioral intervention Off-label pharmacotherapy (e.g., disulfiram)	Reduced reward associated with cocaine use Prevented relapse Long-term abstinence Improved health outcomes associated with abstinence
GABA transaminase inhibitor (CPP-115) for treatment of cocaine dependence	Patients in whom cocaine dependence has been diagnosed	No pharmacotherapies for cocaine dependence have been approved. CPP-115 is a gamma-aminobutyric acid (GABA) transaminase inhibitor. When GABA transaminase is inhibited, GABA levels in the brain are increased, suppressing dopamine release and reducing the pleasurable feelings associated with cocaine use. CPP-115 is a derivative of vigabatrin, which is approved for use in patients with epilepsy but is being redeveloped by its manufacturer for treating cocaine addiction. Chronic administration of vigabatrin is associated with visual field defects, and the manufacturer claims that CPP-115 may not cause these visual field defects. For this indication, the drug is intended to be administered by dissolving it in orange juice. Catalyst Pharmaceutical Partners, Inc., Coral Gables, FL Phase I trial ongoing	Psychotherapy	Improved abstinence rates Improved health outcomes Reduced reward associated with cocaine use

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Handheld, portable fingerprinting device (Intelligent Fingerprinting Technology) to detect substance abuse	Individuals suspected of illicit drug use	Detection of drugs and their metabolites in body fluids (e.g., blood, urine, saliva) is limited by invasiveness, biohazard risks, cross reactivity with other substances in the samples, a requirement for cold or frozen sample transport and storage, susceptibility to contamination leading to false positives, and the potential for a person to undermine the test. To address these limitations, a manufacturer has developed Intelligent Fingerprinting Technology, a handheld fingerprint drug testing device that analyzes the minute traces of sweat deposited in subjects' fingerprints. According to the manufacturer, the technology detects drug metabolites, not the drug itself. Additionally, the company purports that samples are quick and easy to collect, are impossible to cheat, are stable at room temperature, and do not require additional sample preparation. The company is positioning this product for use by law enforcement and in workplaces and institutions (e.g., prisons, the military). SmartStart, Inc., Irving, TX U.S. launch planned for 2013	Other body fluid testing (urine, saliva, blood) Field sobriety tests	Improved detection of illicit substances Reduced invasiveness of drug testing Reduced turnaround time for drug testing Reduced biohazard risk Reduced risk of cross reactivity Improved health outcomes
Interactive text message program (Text2Quit) for smoking cessation	Patients attempting smoking cessation	About 20% of the adult population in the U.S. smoke, and more than 1/3 of adult smokers (17 million of 46 million) smokers try to quit each year, but only 1.3 million succeed with currently available interventions. Text2Quit is an interactive text-messaging program based on the same platform as Text4Baby (please see Table 42, "Cell phone bi-directional communication educational program") and intended to aid smokers in stopping smoking; the messaging system is intended to deliver customized educational content based on the user's own quit date; the program enables users to complete surveys to receive advice, play games to fight off cravings, select the best possible prescription or over-the-counter therapies as cessation aids, and collect data to help user monitor their achievement towards their own goals; it is designed to be especially useful for reaching underserved communities. The company intends to make the program available publicly and also through employers, health plans, and public health departments. Voxiva, Inc., and the George Washington University School of Public Health, both of Washington, DC Initial trials completed; program launched Jun 2011	One-way text messaging smoking cessation plans (not diffused) Hardcopy patient education Internet-based patient education Patient support groups	Increased number of successful smoking cessation attempts Reduced number of relapses Improved long-term health outcomes Reduced health disparities and improved access to cessation program

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 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. Merck & Co., Inc., Whitehouse Station, NJ (manufacturer) National Institute on Alcohol Abuse and Alcoholism (investigator) Phase II trial ongoing	Off-label pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone)	Abstinence from alcohol use Prevented relapse Improved long-term health outcomes associated with prevention of relapse
Off-label aripiprazole (Abilify) 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. Aripiprazole is a dopamine partial agonist. Because dopamine is involved in the reward pathway that follows alcohol consumption, off-label use of aripiprazole may reduce the positive effects a person associates with consuming alcohol, thereby potentially reducing alcohol consumption. Additionally, this agent is associated with fewer negative side effects than other atypical antipsychotics, which are full agonists. In clinical trials, this drug is administered orally, daily. It is approved for treating bipolar disorder, schizophrenia, and major depressive disorder and is marketed as Abilify®. Its manufacturers do not appear to be seeking a labeling expansion for this indication, and it would be used off label. Bristol-Myers Squibb, New York, NY, and Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan (manufacturers) Medical University of South Carolina, Charleston (investigator) Phase III trial ongoing	Pharmacotherapy (e.g. acamprosate, disulfiram, naltrexone)	Reduced alcohol consumption Improved morbidity Decreased mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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. It does not appear that the manufacturer of the equipment used in these studies is seeking a labeled indication change for this product. Medtronic, Inc., Minneapolis, MN (manufacturer) University of Cologne, Cologne, Germany (investigator) Several small pilot studies completed internationally	Pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone) Psychotherapy	Reduced craving for alcohol Reduced alcohol consumption Reduced morbidity Reduced mortality Improved quality of life
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. 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 and, thus, it would be used off label for this indication. New York State Psychiatric Institute, New York The Scripps Research Institute, La Jolla, CA Phase II/III trial ongoing	Behavioral intervention Off-label pharmacotherapy (e.g., disulfiram)	Reduced stress sensitivity Increased cocaine abstinence Improved health outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label olanzapine (Zyprexa) 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 efficacy of pharmacotherapy is linked to genetic variants, leading researchers to conclude that no single agent will be found effective in the majority of individuals with alcohol dependence. Olanzapine (Zyprexa®) is an atypical antipsychotic that is approved for treating schizophrenia and bipolar disorder. Olanzapine is a D2/D4 antagonist, and research suggests that given the potential importance of the dopamine pathways (particularly the D4 receptor) in alcohol dependence and craving, the agent may have the ability to reduce craving for and consumption of alcohol, particularly patients with a variant in the gene that expresses D4 receptors. It does not appear that the drug's manufacturer is seeking this labeled indication change. Eli Lilly and Co., Indianapolis, IN (manufacturer) Various academic centers, including The Mind Research Network, Albuquerque, NM (acquired Jan 2012 by Lovelace Respiratory Research Institute, also of Albuquerque); and University of Colorado, Boulder (investigators) Phase III trial completed	Pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone) Psychotherapy	Reduced craving for alcohol Reduced alcohol consumption Reduced morbidity Reduced mortality 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 currently available pharmacotherapy; serotonin 5-HT3 receptors are a novel therapeutic target for this population. Ondansetron is a serotonin 5-HT3 receptor antagonist, approved for treating chemotherapy-induced nausea and vomiting and 1st marketed by GlaxoSmithKline (Middlesex, UK) as Zofran®; 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. Under study at Johns Hopkins University, Baltimore, MD; NIDA, Bethesda, MD; University of Virginia, Charlottesville; and Medical University of South Carolina, Charleston. (No ondansetron manufacturers are sponsoring these studies.) Phase II and phase III trials ongoing	Pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone) Psychotherapy	Decreased severity of alcohol consumption (e.g., drinks per drinking day) Reduced preference for alcohol Reduced craving for alcohol Sustained abstinence Improved long-term health Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label quetiapine (Seroquel) 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. Researchers have recently begun exploring a novel approach to improving medication efficacy, involving the identification of subtypes of patients with alcohol dependence that may respond preferentially to specific medications. One such subpopulation is type B alcohol-dependent patients, characterized by an early age of onset of alcohol problems, high severity of dependence, polydrug use, a high degree of concomitant psychopathology, and a poor prognosis after alcoholism treatment. Selective serotonin reuptake inhibitors have been tried in this population, but showed poor efficacy, leading researchers to suggest that adding dopamine blockade (dopamine is associated with the reward pathway for alcohol) may improve outcomes. Quetiapine is an atypical antipsychotic with activity at both the dopaminergic and serotonergic receptors and a favorable safety profile. This class of drugs has shown improvement in patients with alcohol dependence and concomitant psychiatric illness, suggesting that they could have utility in Type B patients, who are more likely to have associated psychopathology. Quetiapine is marketed under the brand name Seroquel®; it does not appear that the manufacturer is seeking a labeled indication change for the drug, although the company has supplied medication for off-label trials. AstraZeneca, London, UK (manufacturer) University of Pennsylvania, Philadelphia (investigator) Phase III trial completed	Pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone) Psychotherapy	Reduced craving for alcohol Reduced alcohol consumption Reduced morbidity Reduced mortality Improved quality of life
Therapeutic synthetic vaccine (SEL-068) for treatment of nicotine dependence	Patients in whom nicotine dependence has been diagnosed	Although 75% of smokers want to quit smoking, fewer than 5% who attempt to quit are successful. Vaccines represent a new potential treatment for nicotine addiction. SEL-068 is described by the developer as a synthetic vaccine intended to absorb inhaled nicotine, thereby potentially preventing it from reaching the brain and triggering the addictive response. The company purports that because the vaccine is synthetic, it may avoid off-target responses to biologic carriers that other vaccines use. Selecta Biosciences, Watertown, MA Phase I trial ongoing	Acupuncture “Cold-turkey” quitting Hypnosis Nicotine replacement aids Oral pharmacotherapy (e.g. bupropion)	Reduced nicotine dependence Decreased morbidity and mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Therapeutic vaccine (Nic002) for nicotine addiction	Patients in whom nicotine dependence has been diagnosed	Although 75% of smokers want to quit smoking, fewer than 5% who attempt to quit are successful. Vaccines represent a new potential treatment modality for this condition. Nic002, formerly named CTY002-NicQB, is a therapeutic vaccine in development for treating nicotine addiction. Nicotine is conjugated to a virus-like particle formed by recombinant expression of the protein coat of bacteriophage Qb; intended to induce nicotine-specific antibodies that bind to nicotine in the bloodstream; once nicotine is attached to an antibody, the molecule becomes too large to cross the blood-brain barrier, so nicotine uptake into the brain (and, therefore, the subsequent neuronal response) is reduced. Cytos Biotechnology, AG, Schlieren, Switzerland, in collaboration with Novartis International AG, Basel, Switzerland Phase II trial ongoing in collaboration with Duke University, Durham, NC, and Wake Forest University, Winston-Salem, NC; filing anticipated after 2015	Acupuncture "Cold-turkey" quitting Hypnosis Nicotine replacement aids Oral pharmacotherapy (e.g., bupropion)	Smoking cessation Decreased relapse rates Long-term abstinence
Therapeutic vaccine (TA-CD) for cocaine dependence	Patients in whom cocaine dependency has been diagnosed	Cocaine conjugate vaccine (TA-CD), consists of succinyl norcocaine covalently linked to recombinant cholera toxin B subunit protein and adsorbed onto aluminum hydroxide gel adjuvant; it is a large protein molecule that attaches to cocaine, stimulating antibody response, which then destroys the molecule. It also is intended to prevent cocaine from crossing the blood-brain barrier, intended to prevent high rewarding effect of cocaine caused by dopamine release, and believed to not affect desire for cocaine, only physical effects. Celtic Pharma Management L.P., Hamilton, Bermuda Phase II trial ongoing	Behavioral intervention Off-label pharmacotherapy (e.g., disulfiram)	Reduced self-administration of cocaine Prevented relapse Long-term abstinence from cocaine Improved health outcomes associated with abstinence from cocaine

Table 15. AHRQ Priority Condition: 15 Cross-Cutting: 13 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Barbershop-based medical screening and health education programs	Patrons of community barbershops	Health disparities in cardiovascular, diabetic, cancer, and mental health disease areas exist in minority areas. For example, African-American men have the highest death rate from hypertension of any race or ethnic group, or compared with women in the U.S. Furthermore, the U.S. Centers for Disease Control and Prevention has issued a new priority to develop novel hypertension-based outreach programs with community partners and deliver intervention messages that resonate with African-American men, because of a paucity of programs to address this need. Barbershops are being used as an access point to conduct screenings for hypertension, diabetes, prostate cancer, and mental health. One program, the Black Barbershop Health Outreach Program (BBHOP), uses medical and nonmedical volunteers (including barbers) to screen for hypertension and diabetes, because African-American-owned barbershops are considered a cultural institution within African-American communities. They provide an environment of trust and a means for disseminating health education. A 2nd program, the Barbershop Health Network, includes mental health screenings by physician and evening-hour clinics at UMass Memorial Medical Center, Worcester, MA, for patient followup. BBHOP: Diabetic Amputation Prevention Foundation, Inglewood, CA Barbershop Health Network, Worcester, MA Pilot program completed	Clinic-based health screenings	Improved health outcomes Improved access to care Reduced health disparities
Intelligent pills for chronic conditions requiring long-term drug therapy	Patients in whom long-term drug therapy is needed for various chronic conditions	Edible microchip affixed to oral drugs (tablets) to monitor patient adherence; wearable data recorder captures actual drug consumption and vital statistics, reminds patients of missed doses, and transmits patient data to clinicians. Proteus Biomedical, Inc., Redwood City, CA Trial registered (no phase listed), but not yet open for recruitment; external data recorder component FDA 510(k) cleared; Conformité Européene (CE) marked	Conventional oral drug therapy Patient medication reminders via telephone, text message, and/or email	Improved disease management by maintaining consistent oral drug dosing and reducing missed doses

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interactive kiosks (Ideal Life) for remote monitoring of patient health data	Patients in need of remote monitoring of health care data	Because of obstacles such as long waits for appointment times, lack of or insufficient insurance coverage, geographical dispersion, and transportation issues, many patients are unable or unwilling to routinely visit physicians for ongoing monitoring of symptoms. Also, physicians are backlogged because of the high number of routine cases they see in their offices. The Ideal Life® interactive wireless kiosk is intended to address this unmet need. The kiosk, placed in public areas (e.g., gyms, libraries) is intended to measure blood pressure, weight, blood glucose levels and other biometric readings, then wirelessly send the data to the patient's electronic health record. According to the manufacturer, the kiosk can detect when a patient experiences a sudden change in biometric parameters and in that case, will send the information to a physician or hospital emergency department for a quick decision on care. Ideal Life, Inc., Toronto, Ontario, Canada, and Sprint Corp., Overland Park, KS FDA approved for over-the-counter sales and launched in 2011; Health Insurance Portability and Accountability Act (privacy) compliant	Physical-presence appointments Phone-in data monitoring	Improved access to medical care Reduced health care disparities Decreased hospitalizations Fewer visits to emergency departments Improved health outcomes
Medical homes network (South Side Healthcare Collaborative) to link emergency department patients to community care	Patients who do not currently have a primary care medical home (PCMH)	Patients without PCMHs often adopt less preventative care, experience exacerbations of ambulatory-care-sensitive conditions, contract illnesses and health conditions earlier, and seek care in the emergency department (ED), placing an avoidable burden on the health care system (e.g., ED overcrowding) and negatively affecting their personal health; EDs are not intended to treat or manage chronic illness or to offer preventive care. South Side Healthcare Collaborative is a program intended to link ED patients with (18 hospital-affiliated) community providers via an ED-based patient navigator (i.e., patient advocate); patient advocates approach eligible patients who are flagged by an ED electronic tracking system and offer patients services provided by primary-care referral and appropriate dental, mental health, and substance-abuse facilities. Appointments are scheduled for the patient, and pertinent ED medical data is faxed to the outlying sites. University of Chicago Medical Center, Chicago, IL Pilot trial completed	Current use of ED system for nonurgent conditions ED-MC Connect (Primary Care Coalition of Montgomery County, MD— PCMH model) ED Diversion Project (District of Columbia Primary Care Association—PCMH model)	Appropriate primary care use Increased mental health, dental, substance abuse care use Improved health prevention and promotion Improved patient health outcomes Reduced ED use for nonemergent conditions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Motivational interviewing in the pharmacy setting to improve patient medication adherence	Patients who are at risk of nonadherence or nonadherence with prescribed medication regimen(s)	According to the New England Healthcare Institute, medication nonadherence is responsible for about $290 billion annually in avoidable medical spending. Motivational interviewing is a patient-centered style of counseling that has shown efficacy in many health issues, such as substance abuse, physical exercise, health screenings, and medication adherence. Motivational interviewing is intended to be positive, empathetic, and nonconfrontational and is designed to help patients resolve their ambivalence about (health behavior) change. Training pharmacists (either in pharmacy school or in the professional setting) to engage in brief (2–5 minutes) motivational interviews with patients may cultivate patient self-efficacy and improve medication adherence. Pharmacists are taught overall interviewing techniques and strategies for dealing with patient resistance to medication adherence. University of Missouri, Columbia; University of Pittsburgh School of Medicine, Pittsburgh, PA; Highmark Blue Cross Blue Shield, Pittsburgh, PA; Rite-Aid Pharmacies, Harrisburg, PA Trials completed	Current pharmacist-patient communication curriculum Medication review by pharmacist Nonpharmacy based adherence programs (e.g., reminder services)	Increased patient motivation to adhere to regimen Improved medication adherence Reduced costs of medical care from treating noncompliant patients
Natural orifice transluminal endoscopic surgery (NOTES)	Surgical patients undergoing thoracic, abdominal, gastrointestinal, gynecologic, or urologic procedures	Minimally invasive endoscopic surgery that avoids skin incisions by inserting instrumentation through the abdomen or thorax using natural orifices as entry points. Minos Medical, Inc., Irvine, CA USGI Medical, Inc., San Clemente, CA Ethicon Endo-Surgery, Inc., Cincinnati, OH Trials ongoing	Traditional open surgery Laparoscopic surgery Robot-assisted surgery	Less pain and reduced medication need Less external scarring Quicker recovery Less blood loss/need for transfusion Shorter hospital stay

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Partnering urban academic medical centers and rural primary care clinicians for treatment of complex chronic diseases	Patients with chronic or complex diseases living in rural or otherwise medically underserved areas (e.g., prisons)	For patients with chronic or complex diseases living in rural or medically underserved areas (e.g., prisons), receiving high-quality specialty care can be challenging, because of access barriers, specialist shortages, geographical isolation, and other factors. Project ECHO (Extension for Community Healthcare Outcomes) is a health care delivery model that is intended to help develop rural communities' capacity to treat chronic, common, and complex disease in rural and underserved areas. The program utilizes telehealth technology and clinical management tools to train and support rural primary care providers in developing knowledge on diseases that would normally fall within the realm of specialist care. Clinicians are organized into learning networks with specialists at academic medical centers, which are intended to aid the clinicians in developing knowledge of and capability to treat certain complex conditions. University of New Mexico Health Sciences Center, Albuquerque Trials ongoing	Current model of specialist care for rural or underserved patient populations Other telemedicine delivery systems (e.g., Indian Health Service and the Veterans Health Administration)	Expanded primary care physician knowledge of complex conditions Improved patient health outcomes Reduced health disparities
Postdischarge clinics to provide transition care after hospital stay	Patients who have been recently discharged from the hospital and require followup care, but who do not have access to timely primary care	One-third 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 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 readmission. 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. Various hospitals across the country, including Beth Israel Deaconess Medical Center, Boston, MA; University of California, San Francisco; and University of New Mexico Health Sciences Center, Albuquerque Several clinics have been launched in the U.S.	Outpatient followup care (e.g., with primary care physician)	Improved patient outcomes Reduced hospital readmissions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Primary care house calls by paramedics	Patients in need of primary care appointments who have barriers to obtaining primary care	Several factors have converged in recent years that pose barriers in certain patient groups (e.g., incapacitated elderly) to going out to obtain primary care at a primary care office. Furthermore, part of the Federal Health Reform Act was intended to enable establishment of innovative primary care programs, which could include emergency medical service workers as providers of primary care. Several states have repurposed their emergency paramedics to make primary care house calls to patients who otherwise would not be able to seek care in a clinical setting. Patients are referred to paramedic personnel by their primary care physicians to receive services at home. Paramedics see patients during the downtime when they are not responding to emergency calls. Services include hospital discharge followup, blood draws, medication reconciliation, and wound care. Some of these initiatives are being funded by State grants, but eventually are intended to be services covered by 3rd-party payers. Pilot programs ongoing in several states, including Colorado, Texas, and Minnesota	No care due to lack of access House calls by physicians Care in a clinical setting	Improved access to care Lower morbidity Improved health outcomes Increased survival Improved patient satisfaction
Remote monitoring project (Improving Healthcare One Patient at a Time) to improve access to care for rural residents	Patients in rural or otherwise underserved areas who have suboptimal access to health care	Patients in rural or otherwise underserved areas are unable to reach traditional care facilities regularly and easily. The Improving Healthcare One Patient at a Time remote monitoring project is intended to improve access to care for this population. The project uses kiosks (placed in rural schools and churches) and home touch-screen devices to monitor patients' vital signs and other information (e.g., blood pressure, blood sugar, symptoms, weight). Clinicians can access both the home and the kiosk information via the Internet to review patient information, monitor vital signs, manage care plans and medication reminders, and further enhance in-person visits. University of Utah and the Utah Telehealth Network, Salt Lake City Pilot demonstration project launched Jun 2011; funded by a 3-year grant from the Health Resources and Services Administration's Office for the Advancement of Telehealth	Check-up appointments onsite at health facilities	Improved access to medical care Reduced health care disparities Decreased hospitalizations Decreased visits to emergency departments Improved health outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Self-service automated kiosks to triage and treatment in the emergency department	Noncritical patients visiting an emergency department (ED)	Nearly half of ED patients experience long wait times because they are classified as low-risk; wait times and overcrowding contribute to poorer health outcomes and patient dissatisfaction. Kiosk-based patient self-service triage and treatment enables a patient to, without direct staff interaction, complete registration and assessment, measure vital signs, and dispense medication based on telemedicine control by a physician and pharmacist. The approach is intended to be implemented as follows: (1) patients register at the 1st kiosk by swiping/scanning their insurance cards; kiosk touch screen guides them through self-assessment where they register, describe symptoms, and outline the reasons for their visit; (2) patients' vital signs are taken at the 2nd kiosk; and (3) patients speak with a doctor via video conferencing for diagnosis and, if medication is prescribed, it is dispensed. NCR Corp., Duluth, GA; StayHealthy, Monrovia, CA Launched in Canada Sept 2010	Standard, non-automated ED triage and treatment	Reduced ED wait times Reduced ED overcrowding Improved health outcomes Improved patient satisfaction Reduced costs of ED visits for minor conditions
Senior-specific emergency departments for treatment of elderly patients	Senior or elderly patients who visit an emergency department ED	Twenty percent 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). Senior-specific EDs have been opened in Colorado, Missouri, New Jersey, New York, and Texas First senior-specific ED launched in 2008	General EDs	Improved health outcomes for seniors Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Wireless monitoring program (Care Beyond Walls and Wires) for rural patients with chronic conditions	Patients with chronic conditions who have been recently discharged from the hospital	Up to half 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, other transportation, running water, or electricity. The Care Beyond Walls and Wires program is intended to overcome these barriers and improve hospital readmission outcomes. 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. For rural residents without electricity, solar-powered batteries are used. Flagstaff Medical Center, Flagstaff, AZ 50-patient trial ongoing; the program is a National Institutes of Health (NIH) Public-Private Partnership	In-person patient-monitoring visits Kiosk monitoring programs Other rural health programs in development (e.g., Project ECHO)	Fewer office visits and hospital readmissions Improved patient monitoring Improved patient outcomes Reduced costs

Section 2. Interventions Added Since Last Update: 34 Interventions

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
MAP kinase inhibitor (ARRY-797) for treatment of osteoarthritis	Patients in whom osteoarthritis (OA) has been diagnosed	Current OA treatments relieve pain only temporarily and do not prevent further joint damage. Long-term pain management with opioids can lead to tolerability issues and substance abuse. Nonsteroidal anti-inflammatory drugs (NSAIDs) are purported to lead to only partial analgesic relief. Effective therapies to better manage pain and inflammation are needed. ARRY-797 is purported to be a p38 MAP kinase inhibitor intended to reduce pain and inflammation in the joint, resulting in pain relief. MAP kinase is involved in activating many cellular functions involved in stress responses including the pain mediator prostaglandin E2 and the inflammatory mediators tumor necrosis factor-alpha and interleukin-1. ARRY-797 is purported to inhibit these mediators by functioning as a p38 antagonist. Administered orally, 400 mg, twice daily. Array BioPharma, Inc., Boulder, CO Phase II trial completed	Joint replacement Lifestyle modification NSAIDs Opioids p38 MAP kinase inhibitors in development Physical therapy Platelet-rich plasma therapy Viscosupplementation	Reduced pain Improved mobility Improved quality of life

Table 17. AHRQ Priority Condition: 02 Cancer: 15 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti-frizzled receptor monoclonal antibody (OMP-18R5) for treatment of various cancers	Patients in whom advanced or metastatic cancer has been diagnosed	Activation of the WNT pathway has been implicated in the development of various tumor types. Activation of the WNT pathway leads to changes in the expression of a number of target genes involved in cellular processes such as cell growth, cell proliferation, cell survival, and metastasis. In particular, a form of familial colorectal cancer depends on the presence of mutations in a key intracellular regulator of the WNT pathway. Therefore, inhibition of the WNT pathway activity may be of therapeutic benefit in cancer. WNT pathway signaling is transduced by a number of frizzled (FZD) proteins that serve as receptors for WNT ligands. OMP-18R5 is a monoclonal antibody that binds to a subset of these FZD receptors (e.g., FZD1, FZD2, FZD5, FZD7, FZD8) and is purported to inhibit WNT pathway activity. Preclinical studies suggest that OMP-18R5 treatment causes differentiation of cancer cells, reducing their tumorigenicity. OncoMed Pharmaceuticals, Inc., Redwood City, CA Phase I trial ongoing	Various combination chemotherapy regimens	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
CD34-positive cell selection system (CliniMACS) for treatment of acute myeloid leukemia	Patients in whom acute myeloid leukemia (AML) has been diagnosed who are undergoing allogeneic 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 donor immune cells attack recipient tissues. 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. Miltenyi Biotec, GmbH, Bergisch Gladbach, Germany Phase II trial complete; company filed for a humanitarian use device exemption with FDA	Noncommercial, manual methods of T-cell depletion	Improved engraftment rate Increased duration of disease-free survival Improved rate of acute GVHD Improved rate of chronic GVHD
CRM1 antagonist (KPT-330) for treatment of various cancers	Patients in whom advanced or metastatic cancer has been diagnosed	Tumor suppressors normally function in cells to inhibit the aberrant cellular activities associated with cancer development. Many tumor suppressors (e.g., p53, pRB, TOXO, APC, NPM1) require nuclear localization to function, and many tumor types have been shown to drive cytoplasmic localization of these tumor suppressors through overexpression of the nuclear export factor CRM1. KPT-330 is an orally administered antagonist of CRM1 activity that is purported to restore nuclear localization of tumor suppressors, potentially inhibiting the growth and/or survival of cancers. Karyopharm Therapeutics, Inc., Natick, MA Phase I trial in hematologic malignancies ongoing; phase I trial in solid tumors ongoing	Various combination chemotherapy regimens	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Dual action EGFR and HER3 specific monoclonal antibody (MEHD7945A) for treatment of colorectal cancer	Patients in whom metastatic, K-RAS wild type, colorectal cancer has been diagnosed who have undergone prior treatment with 1st-line chemotherapy (e.g., FOLFOX)	Monoclonal antibodies targeting epidermal growth factor receptor (EGFR) have demonstrated activity in treating patients with colorectal cancer. However, the efficacy of these antibodies may be limited by crosstalk or redundancy between EGFR family members, which may underlie resistance to EGFR-targeted therapies. In particular, signaling activation of EGFR family member HER3 has been shown to be involved in EGFR-targeted therapy resistance. MEHD7945A is a monoclonal antibody that is specific for both EGFR and HER3. Its dual binding is based on a single antigen binding domain that can bind either EGFR or HER3. Because of this attribute, MEHD7945A has the potential to bind any combination of dimerized EGFR/HER3 receptors (e.g., EGFR-EGFR dimers, HER3-HER3 dimers, EGFR-HER3 heterodimers), potentially improving on the degree of EGFR-family pathway inhibition seen with current EGFR-targeted monoclonal antibodies. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase II trial ongoing	Cetuximab Panitumumab	Increased overall survival Increased progression-free survival Improved quality of life
Dual action EGFR and HER3 specific monoclonal antibody (MEHD7945A) for treatment of head and neck cancer	Patients with recurrent or metastatic squamous cell carcinoma of the head or neck that has progressed during or after platinum-based chemotherapy	Monoclonal antibodies targeting epidermal growth factor receptor (EGFR) have demonstrated activity in treating patients with head and neck cancer. However, the efficacy of these antibodies may be limited by crosstalk or redundancy between EGFR family members, which may underlie resistance to EGFR-targeted therapies. In particular, signaling activation of EGFR family member HER3 has been shown to be involved in EGFR-targeted therapy resistance. MEHD7945A is a monoclonal antibody that is specific for both EGFR and HER3. Its dual binding is based on a single antigen binding domain that can bind either EGFR or HER3. Because of this attribute, MEHD7945A has the potential to bind any combination of dimerized EGFR/HER3 receptors (e.g., EGFR-EGFR dimers, HER3-HER3 dimers, EGFR-HER3 heterodimers), potentially improving on the degree of EGFR-family pathway inhibition seen with current EGFR-targeted monoclonal antibodies. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase II trial ongoing	Cetuximab	Increased overall survival Increased progression-free survival Improved patient quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
High-intensity focused ultrasound (Ablatherm-HIFU 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. EDAP TMS S.A., Lyon, France Phase II/III trial ongoing; system available in Europe since 2000	Brachytherapy External beam radiation Observation Radical prostatectomy Other HIFU systems in development	Increased overall survival Increased progression-free survival Improved patient quality of life
High-intensity focused ultrasound (Sonablate 500 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® 500 system in the U.S. is studying its use in treating patients with localized prostate cancer that has recurred following initial therapy with external beam radiation therapy. USHIFU, LLC, Charlotte, NC Phase III trial ongoing; system available in Europe since 2001	Brachytherapy External beam radiation Observation Radical prostatectomy Other HIFU systems in development	Increased overall survival Increased progression-free survival Improved patient quality of life
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 is purported to indicate the likelihood of prostate cancer. Beckman Coulter, Inc., Brea, CA FDA approved Jul 2012; available in Europe since 2010	PSA testing alone Free PSA testing alone Percent-free-PSA testing Prostate cancer antigen 3 (PCA3) testing	Improved positive and negative predictive values Improved sensitivity Improved specificity Reduced number of unnecessary biopsies

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Indoleamine 2,3-dioxygenase-1 inhibitor (INCB024360) for treatment of metastatic melanoma	Patients in whom metastatic melanoma has been diagnosed	Ipilimumab (Yervoy™) is an immune checkpoint inhibitor that has been shown to improve overall survival of patients with metastatic melanoma. However, only a minority of patients responds to the immune-stimulating effects of ipilimumab; treatments to further enhance the immune response to melanoma are needed. A mechanism of action by which cancers are believed to inhibit an immune response is through the expression of indoleamine 2,3-dioxygenase-1 (IDO1), which converts the essential amino acid tryptophan to kynurenine. Depletion of tryptophan is believed to inhibit T-cell responses by inhibiting T-cell proliferation. INCB024360 is a small-molecule inhibitor of IDO1 with potential to overcome this mechanism of immune tolerance. In clinical trials, it is being administered as an adjunct to therapy with ipilimumab. Incyte Corp., Wilmington, DE Phase I/II trial ongoing	Ipilimumab monotherapy	Increased overall survival Increased progression-free survival Improved patient quality of life
Magnetic resonance imaging and ultrasound image fusion for image-guided prostate biopsy	Patients who are suspected of having prostate cancer based on elevated prostate-specific antigen (PSA) or abnormal digital rectal exam	Transrectal ultrasound (TRUS)-guided biopsy has been the standard of care for many years. However, TRUS does not have the ability to discriminate normal tissue from cancerous tissue; therefore, a random sampling procedure is used and some cancers may be missed. Magnetic resonance imaging (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. Philips Healthcare unit of Royal Philips Electronics, Amsterdam, the Netherlands Philips has initiated a phase III trial. Pilot studies completed by multiple institutions (e.g., Kyoto Prefectural University of Medicine, Kyoto, Japan; University of Regensburg, Regensburg, Germany)	MRI-guided biopsy TRUS-guided biopsy	Improved positive and negative predictive values Improved sensitivity Improved specificity

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
mTor inhibitor (everolimus, Afinitor) for treatment of 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 mTor; therefore, use of an mTor inhibitor such as everolimus may be beneficial in treating these patients. Everolimus is taken once daily, as an oral tablet. Novartis International AG, Basel, Switzerland Phase III trial complete; everolimus is marketed as Afinitor® for multiple cancer indications	Angiomyolipoma embolization	Tumor size reduction Increased progression-free survival Improved quality of life
Phosphoinositide 3-kinase inhibitor (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. BKM120 is a pan-PI3K inhibitor (i.e., inhibits all PI3K isoforms) that is intended to block PI3K/mTOR pathway activity. In clinical trials, BKM120 is being administered orally, in combination with the antiestrogen drug fulvestrant. Novartis International AG, Basel, Switzerland Phase III clinical trials in hormone receptor–positive breast cancer have been registered, but are not yet recruiting. BKM120 is also under study for endometrial cancer, glioblastoma, HER2-positive breast cancer, melanoma, nonsmall cell lung cancer, prostate cancer, and urothelial cancer	Fulvestrant monotherapy Everolimus plus exemestane	Increased overall survival Increased progression-free survival Improved quality of life
Rigosertib (Estybon) for treatment of myelodysplastic syndrome	Patients with azacitidine- or decitabine-refractory myelodysplastic syndrome with excess blasts	Patients with myelodysplastic syndrome with excess blasts that has not responded to azacitidine or decitabine treatment have a poor prognosis and no standard treatment options. Rigosertib (Estybon®) is a small-molecule, multikinase inhibitor with activity against both the alpha and beta isoforms of the phosphoinositide 3 kinase (PI3K) and polo-like kinase 1 (Plk1). Inhibition of PI3K may disrupt cell signaling that promotes cell growth and survival, and inhibition of Plk1 may disrupt mitosis, leading to cell-cycle arrest. In clinical trials, rigosertib is being administered as a monotherapy in a 72-hour continuous intravenous infusion. Onconova Therapeutics®, Inc., Newtown, PA Phase III trial ongoing	Hematopoietic stem cell transplant Immunosuppressive therapy (e.g., anti-thymocyte globulin plus or minus cyclosporine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Smac mimetic (birinapant) for treatment of cancer	Patients in whom solid tumors, lymphomas, or acute myeloid leukemia has been diagnosed	In cell homeostasis, a family of proteins known as inhibitors of apoptosis (IAPs) counteracts the proapoptotic (i.e., pro-cell-death) activity of caspases. In contrast, cellular smac functions to inhibit IAPs, promoting apoptosis. Birinapant is a smac mimetic that is purported to promote cell death by inhibiting IAPs. No other smac mimetic is available. Birinapant may be administered in combination with current treatment options to potentiate the proapoptotic activity of these treatments. TetraLogic® Pharmaceuticals, Malvern, PA Phase I/II trials ongoing	Wide range of chemotherapy and targeted therapy options	Increased overall survival Increased progression-free survival Improved quality of life
Therapeutic peptide vaccine (DPX-0907) for treatment of various cancers	Patients with advanced breast, ovarian, or prostate cancer who are HLA-A2 positive	Patients with late-stage breast, ovarian, or prostate cancer generally have a poor long-term prognosis with current treatment options. DPX-0907 is a novel therapeutic vaccine that is based on 7 peptides expressed by breast, ovarian, prostate cancer cell lines in combination with a nucleotide-based adjuvant and a helper T-cell epitope. The vaccine is delivered in a liposome-in-oil platform that is purported to increase the length of time that antigens and adjuvant are presented to immune cells. The vaccine is administered by multiple subcutaneous injections. Immunovaccine, Inc., Halifax, Nova Scotia, Canada Phase I trial complete	Various biologic and chemotherapy treatment options	Increased overall survival Increased progression-free survival 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

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

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
Selective dopamine receptor antagonist (ecopipam) for treatment of Tourette's syndrome	Patients in whom Tourette's syndrome (TS) has been diagnosed	Approximately 200,000 people in the U.S. have received a diagnosis of TS. In many cases of severely debilitating TS, either the disease does not respond to available pharmacotherapy or patients experience serious adverse events, warranting the need for more effective treatment. Ecopipam is a selective dopamine (D)1 (D1)/D5 antagonist with little affinity for the D2 and 5-HT2 receptors. D1 receptor overactivity is thought to be a primary receptor responsible for TS symptoms. Ecopipam is administered orally in the evening for 8 weeks, 50 mg/day for the 1st 2 weeks and 100 mg/day for 6 weeks. Psyadon Pharmaceuticals, Inc., Germantown, MD Phase I/II trial completed	Pharmacotherapy (e.g., antidepressants, botulinum toxin type A [Botox®] injections, central adrenergic inhibitors, fluphenazine, pimozide, stimulant medications)	Reduced symptom burden Improved quality of life

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

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

Table 22. AHRQ Priority Condition: 07 Diabetes Mellitus: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Small-peptide ghrelin agonist (RM-131) for diabetic gastroparesis treatment	Patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) and gastroparesis	Gastroparesis causes delayed gastric emptying in up to 30% of patients with T1DM or T2DM. Currently available treatments treat symptoms, not the underlying disorder, and work with varying degrees of efficacy. These treatments also are associated with moderate adverse events, warranting the need for new treatment options. RM-131 is a ghrelin agonist purported to stimulate gastrointestinal (GI) motility. This compound is naturally derived from ghrelin, a GI hormone that stimulates GI motility, regulates feeding and absorption, and inhibits GI inflammatory responses. In clinical trials, this drug is administered subcutaneously with dosing regimens ranging from 10 to 100 mcg daily, for 1 month. Rhythm Pharmaceuticals, Boston, MA Phase II trial ongoing	Antiemetics Domperidone Erythromycin Metoclopramide Other antibiotics Dietary modifications Gastric electrostimulation Parenteral nutrition	Decreased GI bacterial overgrowth Decreased bezoar development and intestinal obstruction Improved blood glucose control Improved gastric emptying

Table 23. AHRQ Priority Condition: 08 Functional Limitations and Disability: 8 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Allogeneic mesenchymal stem cells (Stemedyne) for ischemic stroke treatment	Patients in whom ischemic stroke has been diagnosed	Approximately 800,000 people experience ischemic stroke each year in the U.S. and 137,000 die of stroke. Current treatment consists of administering tissue plasminogen activator, which is used in an emergency treatment setting only for patients arriving at the hospital within several hours of symptom onset. Allogeneic mesenchymal stem cells (MSCs; Stemedyne™) are derived from adult bone marrow and processed in a low-oxygen environment. The MSCs are under study for their potential to repair and replace cells damaged or dead from stroke and stimulate new cell growth. The treatment is delivered intravenously and is proposed for administration within 6 months after stroke diagnosis. Stemedica Cell Technologies, Inc., San Diego, CA Clinical trials ongoing	Poststroke rehabilitation therapy	Repaired damaged cells Replaced dead cells Improved patient outcomes
External mechanical stimulation (Kai apnea) for treatment of obstructive sleep apnea	Patients in whom obstructive sleep apnea (OSA) has been diagnosed	OSA affects about 18 million Americans, and fewer than 10% of affected people have the condition diagnosed. OSA is associated with hypertension, diabetes, cardiovascular disease, stroke, depression, and sudden cardiac death. Current treatment efficacy (e.g., lifestyle changes, use of continuous positive airway pressure [CPAP]) depends on patient adherence to therapy, which is known to be low. Kai apnea is an external mechanical stimulator that sends a vibration to the patient in the event of apnea. The device, connected to a patient's neck via a patch, sends an electrical stimulus once the device algorithms detect an apnea event. This stimulation induces patient arousal, limiting the length and number of apnea events. Kai Medical, Inc., Honolulu, HI Phase I trial completed	Behavior and lifestyle therapy (e.g., dietary restrictions, exercise, caffeine restriction) CPAP Oral appliances therapy Positional therapy	Decreased OSA Preventied complications of OSA, including cardiovascular disease and sudden cardiac death
Off-label broad spectrum antibiotic (minocycline) for treatment of Angelman syndrome	Patients in whom Angelman syndrome (AS) has been diagnosed	AS is a neurogenetic disorder, occurring in 1 in 10,000–15,000 live births and characterized by developmental delay, seizures, limited or absent speech, and lack of motor coordination and balance. Investigators have not found treatments for the cognitive, motor, or behavioral deficits associated with AS. Minocycline is a broad-spectrum tetracycline antibiotic traditionally used to treat bacterial infections in several organ systems. Although researchers have not specified the mechanism of action by which minocycline treats symptoms of AS, they have stated that, in preclinical trials, this drug has shown potential to improve condition symptoms. University of South Florida, Tampa Phase I trial planned	Behavior, communication, and speech therapy Antiepileptic medication	Improved communication Improved motor coordination Improved social and cognitive skills Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label naltrexone for treatment of fibromyalgia	Patients in whom fibromyalgia has been diagnosed	Fibromyalgia is poorly understood and effective treatment options are not available 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. Stanford University, Stanford, CA Pilot study completed	Behavior and lifestyle modification Pharmacotherapy (e.g., duloxetine, fluoxetine, gabapentin, lorazepam, milnacipran, pregabalin, tricyclic antidepressants)	Improved ability to perform daily activities Reduced symptoms Improved quality of life
Oral estriol (Trimesta) for treatment of multiple sclerosis	Female patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	Current treatments for RRMS can slow disease progression, but the disease has no cure and more effective treatments are needed. Estriol is an estrogen that is produced in the placenta during pregnancy, and is thought to be involved in maintaining maternal immune tolerance for the fetus. Estriol is purported to induce spontaneous remission of helper T-cell, type-1-mediated autoimmune responses and may have other beneficial immunodulatory effects in women with MS during pregnancy. Oral administration of exogenous estriol (Trimesta™) is postulated by the manufacturer to improve MS symptoms. Administered orally, 8 mg daily. Synthetic Biologics, Inc., Ann Arbor, MI Phase II/III trial ongoing	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Reduced frequency of relapse Slowed disease progression Improved quality of life
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 is purported to differ 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. SPR Therapeutics, LLC, Cleveland, OH Phase III trial ongoing	Anticonvulsants Antidepressants Corticosteroids Nonsteroidal anti-inflammatory drugs	Reduced pain Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Toll-like receptor 7 and 9 antagonist (DV1179) for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	SLE has no cure, and current treatments provide only partial relief of symptoms. DV1179 is a synthetic oligonucleotide purported to be an antagonist of toll-like receptor 7 (TLR7) and 9 (TLR9). TLR7 and TLR9 are receptors responsible for mediating inflammatory innate immune reactions. These reactions are purported by the manufacturer to cause glucocorticoid resistance in SLE patients. DV1179 may be used alone or with other SLE treatments such as corticosteroids to treat SLE. Dynavax Technologies Corp., Berkeley, CA Phase I trial ongoing	Belimumab Corticosteroids Cyclophosphamide Methotrexate Rituximab Tumor necrosis factor-alpha inhibitors	Slowed disease progression Disease remission Improved symptoms
Transthyretin stabilizer (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®) is purported to be 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. Pfizer, Inc., New York, NY 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 TTR stabilization

Table 24. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 4 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
NS5A inhibitor (PPI-668) for treatment of chronic hepatitis C infection	Patients in whom chronic hepatitis C virus infection (HCV) has been diagnosed	Current HCV treatment options are not effective in all patients, even with the newly approved agents 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. PPI-668 is purported to be an inhibitor of the HCV NS5A protein. 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. PPI-668 could exert its function by destabilizing the association of NS5A with the ER membrane, thus inhibiting the formation of functional virions. PPI-668 could be part of an interferon-free treatment regimen. In a clinical trial, it is administered orally, 40–240 mg, once daily. Presidio Pharmaceuticals, Inc., San Francisco, CA Phase I trial completed	Boceprevir NS5A inhibitors in development Nonnucleoside polymerase inhibitors in development Nucleoside polymerase inhibitors in development Pegylated interferon/ribavirin combination Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Sustained virologic response (undetectable virus at week 24) Slowed or halted disease progression (fibrosis and cirrhosis) Decreased need for liver transplant Improved quality of life
Nucleotide analog reverse transcriptase inhibitor tenofovir disoproxil fumarate (Viread) for prevention of HIV infection	People at high risk of 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 infection. Tenofovir disoproxil fumarate (Viread®) is a nucleotide analog reverse transcriptase inhibitor currently used in combination with other antiretroviral agents for treatment of HIV infection. Truvada® (emtricitabine with tenofovir disoproxil fumarate) has been approved as preexposure prophylaxis for people at high risk of HIV infection. Clinical studies have suggested that daily prophylactic use of tenofovir without emtricitabine can also reduce the risk of sexual acquisition of HIV. Administered orally, 300 mg, once daily. Gilead Sciences, Inc., Foster City, CA Phase III trial ongoing	Condoms Harm reduction campaigns Preexposure prophylaxis (tenofovir with or without emtricitabine) Prophylactic vaccines in development Vaginal microbicide gels in development	Reduced HIV transmission Reduced HIV incidence

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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. This 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 a manufacturer's support center 24 hours a day, 7 days a week for counseling on the test results and referral to medical services. OraSure Technologies, Inc., Bethlehem, PA FDA approved Jul 2012	Home-based blood tests (mail-in) Clinic-based rapid test (OraQuick)	Reduced HIV transmission Earlier intervention to control viral load Increased HIV screening rate
Streaming weekly educational soap opera episodes to smartphones for people at high risk for HIV	Patients whom are at high risk of 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 that incorporated HIV risk reduction messages. Delivering risk-reduction messages in this format could lead to better awareness. Rutgers College of Nursing, Newark, NJ Study completed	Standard risk-reduction programs Text messaging risk reduction programs	Reduced HIV incidence in at-risk women Increased knowledge and identification of high-risk behavior

Table 25. AHRQ Priority Condition: 10 Obesity: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Melanocortin type 4 receptor agonist (RM-493) for treatment of obesity	Adults with obesity	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, all approved drugs have significant potential side effects and work in only a proportion of patients taking them. RM-493 is a peptide melanocortin receptor partial agonist that purportedly acts by stimulating the melanocortin type 4 receptor, which has been implicated in hunger suppression and energy homeostasis. Rhythm Therapeutics, Boston, MA Phase I trial ongoing	AZD2820 (melanocortin receptor 3 and 4 agonist) Dietary and lifestyle modifications Variable obesity drugs on the market and under development	Improved weight loss Improved insulin sensitivity Decreased obesity-associated comorbidities (e.g., prediabetes, high blood pressure) Improved quality of life

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: 2 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Inhaled vasoactive intestinal peptide (aviptadil) 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. Vasoactive intestinal peptide (VIP) is purported to be a neuropeptide with anti-inflammatory and immunomodulatory effects. VIP is also purported to have systemic vasodilator and bronchodilator activity while inhibiting the proliferation of vascular and bronchial smooth muscle cells, which could relieve symptoms of PAH. Administered by inhalation, 100 mcg, daily. mondoBIOTECH holding AG, Stans, Switzerland Phase II trials completed	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced rate of hospitalizations for PAH
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-HT2B and 5-HT2A (serotonin) receptors. Serotonin purportedly stimulates proliferation of smooth muscle cells in the pulmonary artery and can induce fibrosis in pulmonary arteries, which can lead to narrowing. By inhibiting this activity on pulmonary arteries, terguride could improve the signs and symptoms of PAH. Administered orally. Pfizer, Inc., New York, NY Phase II trial completed. FDA granted orphan drug status for treating PAH	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalization

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
Fatty acid amide hydrolase inhibitor (PF-04457845) for treatment of cannabis dependence	Patients in whom cannabis dependence has been diagnosed	No medications are FDA approved (or used off label) for treating marijuana (cannabis) dependence, and cessation of cannabis can lead to withdrawal symptoms, prompting relapse. PF-04457845 is a fatty acid amide hydrolase inhibitor (FAAH-I) that is being investigated for treating cannabis dependence. Researchers hypothesize that FAAH-I will block the breakdown of anandamide, a endocannabinoid that is endogenous to the brain. If the level of anandamide, a cannabis-like substance, is increased in the brain, researchers expect that many of the withdrawal symptoms associated with cannabis abstinence will be mitigated. The agent is administered orally, daily. Yale University, New Haven, CT Phase II trial ongoing	Behavioral interventions (e.g. cognitive behavior therapy)	Decreased withdrawal symptoms Decreased cannabis use Fewer relapses Improved quality of life Improved long-term health

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

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

Section 3. Interventions Tracked but Archived Since Last Update: 26 Interventions

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

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

Table 32. AHRQ Priority Condition: 02 Cancer: 7 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Anticarbonic anhydrase IX monoclonal antibody (girentuximab, Rencarex) for treatment of clear cell renal cell carcinoma	Patients with clear cell renal cell carcinoma (ccRCC) who have undergone nephrectomy and have no evidence of residual disease	Although treating localized renal cell carcinoma with partial or radical nephrectomy can be curative, about 20% to 30% of affected patients develop metastatic disease. Girentuximab (Rencarex®) is a monoclonal antibody specific for the enzyme carbonic anhydrase IX, which is expressed by a number of tumor types (including the majority of ccRCCs) but exhibits limited expression in normal tissues. Girentuximab is under study as a passive immunotherapy for ccRCC, and it may exert its effects through antibody-dependent cellular cytotoxicity. In the current clinical trial, girentuximab is administered intravenously once a week for 24 weeks. Wilex AG, Munich, Germany, in collaboration with Prometheus, Inc., San Diego, CA Phase III trial halted Oct 2012; FDA granted fast track status	No currently available adjuvant therapy for ccRCC	Increased overall survival Increased progression-free survival Improved quality of life	Development halted after phase III trial failed to meet primary endpoints

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Anti-CD200 monoclonal antibody (samalizumab) for treatment of chronic lymphocytic leukemia	Patients with recurrent or treatment-refractory chronic lymphocytic leukemia (CLL)	Although available chemotherapy treatments are often able to slow the progression of CLL, these treatments are not curative, and recurrent disease often develops. Samalizumab is a novel, intravenously administered monoclonal antibody being studied for the treatment for CLL. Samalizumab is specific for CD200, and antibody binding to CD200 is purported to block CD200's binding to its cognate receptors. CD200 activation of CD200 receptors on cells of the immune system appears to downregulate the activity of these immune cells. Multiple cancers including CLL have been shown to upregulate CD200, which may lead to immune tolerance of the cancer. Alexion Pharmaceuticals, Inc., Cheshire, CT Phase I/II trial completed	Various combination chemotherapies	Increased overall survival Increased progression-free survival Improved quality of life	Company halted development; no longer listed in pipeline
c-Met kinase inhibitor (tivantinib) for treatment of nonsmall cell lung cancer	Patients in whom advanced nonsmall cell lung cancer (NSCLC) has progressed or recurred after chemotherapy	Patients with advanced NSCLC that has progressed after chemotherapy have a poor prognosis and few treatment options. Tivantinib (ARQ 197) is a c-Met kinase inhibitor; c-Met is a receptor tyrosine kinase that has been implicated in the development of tumor resistance to epidermal growth factor receptor (EGFR) inhibition. No c-Met inhibitor is currently available. Tivantinib is being studied in combination with the EGFR inhibitor erlotinib in treating NSCLC. ArQule, Inc., Woburn, MA (developer) Daiichi Sankyo Co., Ltd., Tokyo, Japan (performing testing) Phase III trials discontinued because of not meeting primary endpoint at interim analysis	2nd-line comparators: Crizotinib Docetaxel Erlotinib Pemetrexed 3rd-line comparator: Erlotinib	Increased overall survival Increased progression-free survival Improved quality of life	Company halted development; trials did not meet primary endpoint

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Denosumab (Xgeva) for prevention of cancer-related bone fractures and pain	Patients in whom bone metastases have been diagnosed	Denosumab (Xgeva®) is a monoclonal antibody that targets the receptor activator of nuclear factor kappa B ligand, which is involved in cancer-related bone destruction. Denosumab is intended to prevent skeletal-related events, including bone fractures and pain from cancer treatment; Xgeva denosumab is a higher dose of Prolia® denosumab used for osteoporosis. Amgen, Inc., Thousand Oaks, CA FDA approved Nov 2010 to help prevent fractures and slow bone disease in patients with solid tumors	Pamidronic acid Zoledronic acid	Delayed skeletal related events Improved quality of life	No longer meets horizon scanning criteria; approved more than 2 years ago
Sotatercept (ACE-011) for treatment of chemotherapy-induced anemia	Patients in whom anemia following chemotherapy has been diagnosed	Anemia is 1 of the most common and debilitating complications of cancer chemotherapy, often significantly reducing the number of red blood cells (RBCs) and preventing RBC production. Anemia is commonly treated with therapies targeting the erythropoietin pathway; however, therapies targeting this pathway have exposed patients to increased risk of tumor stimulation and progression, as well as increased risk of thrombosis. ACE-011 is a soluble form of the activin receptor type IIA (ActRIIA), and it inhibits signaling of several members of the transforming growth factor-beta protein super family, responsible for stimulation of RBC production, cell type differentiation, bone formation, and inhibition of tumor growth and metastasis. ACE-011 is administered via subcutaneous injection, every 42 days, up to 4 doses/cycles at 15, 30, or 45 mg. Celgene Corp., Summit, NJ, in collaboration with Acceleron Pharma, Inc., Cambridge, MA Phase II/III trial terminated because of low enrollment	Erythropoiesis stimulating agents	Decreased risk of thrombosis and tumor stimulation Increased hemoglobin levels Reduced fatigue and inflammation Improved quality of life	Company discontinued trial due to slow enrollment and no longer lists as an actively investigated indication

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Talactoferrin alfa for treatment of nonsmall cell lung cancer	Patients with nonsmall cell lung cancer (NSCLC) who are undergoing 1st-line chemotherapy; patients with treatment-resistant NSCLC	Talactoferrin alfa is a derivative of lactoferrin, a modulator of the immune response and is intended to stimulate the immune system in an effort to destroy the tumor. Talactoferrin alfa is under study in the 1st-line setting in combination with carboplatin and paclitaxel and under study in the 3rd-line setting as a monotherapy. Agennix AG, Heidelberg, Germany Phase III trials ongoing	1st-line comparator: carboplatin and paclitaxel alone 3rd-line comparator: best supportive care	Increased overall survival Increased progression-free survival Improved quality of life	Company discontinued development after phase III trial in the salvage setting failed to meet primary or secondary endpoints; phase III trial in 1st-line setting also discontinued
Ultra-low-molecular-weight heparin (semuloparin) for prevention of venous thromboembolism in patients undergoing chemotherapy	Patients who are at high risk of venous thromboembolism (VTE) who are undergoing chemotherapy treatment for cancer	Up to 20% of patients in whom cancer has been diagnosed experience a VTE, and the risk of VTE is further increased in patients undergoing chemotherapy treatment. However, no treatments are currently approved by FDA for thromboprophylaxis in this setting (i.e., thromboprophylaxis is recommended only for cancer patients undergoing major surgery and/or hospitalized or critically ill). The potential benefits of thromboprophylaxis in this setting have not been firmly established. Semuloparin is an ultra-low-molecular-weight heparin that has exhibited high anti-factor Xa and minimal residual anti-factor IIa (thrombin) activities and is proposed for use in patients receiving chemotherapy at risk of VTE. In a clinical trial, semuloparin given by subcutaneous injection, 20 mg, daily. Sanofi, Paris, France Phase III trial completed; biologics license application submitted to FDA Sept 2011; In Jun 2012, FDA's Oncologic Drugs Advisory Committee voted 14-1 (with 1 abstention) against recommending approval of semuloparin	Low-molecular-weight heparin No treatment	Decreased rate of thromboembolytic events Improved safety profile (e.g., fewer bleeding events)	Company discontinued development after FDA decision recommending against approval

Table 33. AHRQ Priority Condition: 03 Cardiovascular Disease: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Dabigatran (Pradaxa) for prevention of thrombosis associated with atrial fibrillation	Patients in whom nonvalvular atrial fibrillation (AF) has been diagnosed	For this population, warfarin (Coumadin®, a vitamin K antagonist) is the anticoagulant routinely used long-term to prevent blood clots that cause stroke or pulmonary embolism. Warfarin use is associated with high risk of bleeding and appropriate dosing is a challenge; its use requires daily/weekly monitoring of clotting parameters and dose adjustment as needed. Dabigatran (Pradaxa®) represents a new mechanism of action/new drug class for this disease state; recently approved by FDA for prevention of stroke in patients with AF as an oral direct thrombin inhibitor intended to reduce risk of stroke by reducing blood clot formation. According to prescribing information, treatment does not require blood monitoring or related dose adjustments and has no recommended dietary restrictions. Boehringer Ingelheim GmbH, Ingelheim, Germany FDA approved Oct 2010	Available pharmacotherapy (e.g., warfarin)	Reduced blood clotting Reduced need for monitoring clotting parameters Reduced stroke incidence Improved long-term outcomes	No longer meets horizon scanning criteria; approved more than 2 years ago

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

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

Table 35. AHRQ Priority Condition: 05 Depression and Other Mental Health Disorders: 3 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Antipsychotic (pomaglumetad methionil) for treatment of schizophrenia	Patients in whom schizophrenia has been diagnosed	Pomaglumetad methionil (LY-2140023) is an oral agent that acts through a novel pathway (glutamate receptors rather than dopamine receptors) and is intended to relieve schizophrenia symptoms. Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing; development halted Aug 2012	Pharmacotherapy (e.g., atypical antipsychotics)	Reduced symptoms Reduced side effects compared with other drugs Improved quality of life	Company halted development when independent futility analysis found the treatment was unlikely to be effective
Deep brain stimulation (Reclaim system) therapy for severe obsessive-compulsive disorder	Adult patients with chronic, severe, treatment-resistant obsessive compulsive disorder (OCD) that has failed to respond to at least 3 selective serotonin reuptake inhibitors (SSRIs)	Electrode leads (Reclaim™ system) connected from chest to anterior limb of the internal capsule stimulate the patient's brain. Medtronic, Inc., Minneapolis, MN Approved under humanitarian device exemption as adjunct to medications and alternative to anterior capsulotomy in patients whose disease has failed to respond to 3 SSRIs	Anterior capsulotomy Combination therapy Drug therapy alone Psychotherapy alone	Reduced scores on OCD measures Improved quality of life	No longer meets horizon scanning criteria; approved more than 2 years ago
Extended intensive psychotherapy assisted by MDMA (methylenedioxy methamphetamine) for treatment of posttraumatic stress disorder	Patients in whom treatment-refractory posttraumatic stress disorder (PTSD) has been diagnosed	Methylenedioxymethamphetamine (MDMA; ecstasy) has pharmacologic effects that include serotonin release, 5-HT2 receptor stimulation, and increased levels of oxytocin, prolactin, and cortisol. Exact mechanism of action unclear, but lowers inhibitions in a way that some think might make psychotherapy more productive. Patients receive 125 mg of pure methylenedioxymethamphetamine before two 8-hour sessions of intensive psychotherapy followed by overnight stay. MDMA is not given as long-term drug therapy (e.g., selective serotonin reuptake inhibitors [SSRIs]). Its purpose is only to enhance psychotherapy to enable patients to engage in discussion. Funded by Multidisciplinary Association for Psychedelic Studies, Santa Cruz, CA Phase II trial ongoing, with permission from FDA and the U.S. Drug Enforcement Administration	Psychotherapy (without MDMA)	Improved efficacy of intensive psychotherapy sessions Improved rating scales (e.g., Clinician-Administered PTSD Scale) Improved quality of life	Expert comments indicated no potential for high impact at this time because it would not be feasible as a therapeutic model

Table 36. AHRQ Priority Condition: 06 Developmental Delays, Attention-Deficit Hyperactivity Disorder, and Autism: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
ND0801 dermal patch for cognitive improvement in adults with attention-deficit hyperactivity disorder	Adults in whom attention-deficit disorder/attention-deficit hyperactivity disorder (ADD/ADHD) has been diagnosed	ND0801 dermal patch is intended to work by preventing desensitization of neural nicotinic receptors, thereby improving cognition and focus. NeuroDerm, Ltd., Ness Ziona, Israel Phase IIa trial ongoing	Behavioral therapies and psychotherapy Pharmacotherapy (e.g. central nervous system stimulants, selective serotonin reuptake inhibitors, antidepressants, clonidine [Catapres®])	Cognitive improvement Fewer side effects than current ADHD stimulant medications Improved quality of life	Development apparently halted; company has not updated trial status on national clinical trials site in more than 2 years

Table 37. AHRQ Priority Condition: 07 Diabetes Mellitus: 0 Interventions

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

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
Bardoxolone methyl (RTA 402) for treatment of chronic kidney disease	Patients with type 2 diabetes mellitus who have moderate to severe chronic kidney disease (CKD)	Effective treatment options are needed for slowing or preventing progression of severe CKD in patients with diabetes. Bardoxolone methyl is an antioxidant inflammation modulator that activates Nrf2; Nrf2 induces transcription of genes that reduce oxidative stress levels and suppress inflammatory mediators; intended to improve kidney function and delay progression of CKD. Administered as an oral, once-daily pill. Reata Pharmaceuticals, Inc., Irving, TX Phase III trial ongoing	Dialysis Human recombinant erythropoietin to treat anemia Kidney transplantation Management of diabetes or high blood pressure Palliative treatments	Prevention of kidney failure, dialysis or kidney transplantation Improved glomerular filtration rate Improved renal function Improved CKD stage	Company terminated phase III in patients with stage 4 chronic kidney disease and type 2 diabetes because of Independent Data Monitoring Committee recommendation "for safety concerns due to excess serious adverse events and mortality in the bardoxolone methyl arm."
Fingolimod (Gilenya) for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	Fingolimod (Gilenya™) is the 1st approved oral therapy for RMMS. Fingolimod is an agonist to sphingosine-1-phosphate receptors on the surface of thymocytes and lymphocyte. It is intended to reduce the number of circulating lymphocytes available to have an autoimmune reaction to the myelin sheath of axons. Taken once daily. Novartis International AG, Basel, Switzerland FDA approved Sept 2010	Dimethyl fumarate (investigational) Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Reduced frequency of relapse Slowed disease progression Improved quality of life	No longer meets horizon scanning criteria; approved more than 2 years ago

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Gene therapy NLX-P101 (AAV2-GAD) for treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	Current treatments for PD address symptoms rather than the underlying cause, and the patient eventually plateaus or ceases to respond to them; gene therapy is a novel treatment modality for this indication. Glutamic acid decarboxylase (GAD) is an enzyme that catalyzes production of gamma aminobutyric acid (GABA), an inhibitory neurotransmitter); in patients with PD, too little GABA is produced, resulting in overstimulation of the subthalamic nucleus; as a result of this overstimulation, neurons that produce dopamine (major role in movement control) are strained. NLX-P101 is administered in a neurosurgical procedure by injecting virus (which carries gene that codes for GAD) directly into the brain. Neurologix, Inc., Fort Lee, NJ Phase II trial completed	Levodopa/carbidopa MOA-B inhibitors	Improved motor skill functions/movement control Slowed disease progression Improved quality of life	Organization filed Chapter 7 bankruptcy to liquidate in 2012; Website and pipeline no longer available.
Implantable Miniature Telescope (IMT) for treatment of end-stage age-related macular degeneration	Patients with end-stage age-related macular degeneration who have severe vision loss	A small telescope replaces the natural lens and is intended to enable recipients to see an image that is magnified more than 2 times; surgically implanted in 1 eye; other eye is used for peripheral vision. The labeled indication is "for monocular implantation to improve vision in patients greater than or equal to 75 years of age with stable severe to profound vision impairment (best corrected distance visual acuity 20/160 to 20/800) caused by bilateral central scotomas associated with end-stage age-related macular degeneration." VisionCare Ophthalmic Technologies, Inc., Saratoga, CA FDA approved Jul 2010	Anti-vascular endothelial growth factor injections Laser surgery Photodynamic therapy	Improved vision Improved quality of life	No longer meets horizon scanning criteria; approved more than 2 years ago

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
Linking hepatitis C screening to screening colonoscopy to increase hepatitis C virus detection	Patients for whom colorectal screening is recommended (aged 50–65 years)	Patients aged 50–65 years of age represent the population that carries the most risk of undiagnosed hepatitis C virus (HCV) infection, and the population represents 70% of undiagnosed cases. As patients approach 60 years of age, the rate of HCV progression in those infected is faster; more adverse effects from interferon treatment are also experienced in those being treated. Better methods to screen patients for HCV are needed. This patient population is also recommended to undergo a baseline routine colonoscopy, at which time HCV risk assessment questionnaires can be administered and blood samples drawn to screen for HCV. Linking colonoscopy screening to HCV screening is intended to increase screening rates in a population with high rates of undiagnosed HCV infection. Texas A&M College of Medicine Pilot study conducted	Current screening practices at other health care settings	Improved HCV detection rates Earlier treatment Slowed or halted disease progression Prevention of end-stage liver disease and HCV transmission	Program deemed to not meet HS criteria for innovation
Nucleotide polymerase inhibitor (ALS-2158) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Standard of care for HCV infection has a long dosing schedule and poor tolerability. Better-tolerated treatments with more convenient dosing are needed. ALS-2158 is an oral nucleoside analog purported to block the activity of HCV polymerase, which is essential for replicating the viral genome, and ultimately functional virus particles. ALS-2158 purportedly inhibits the activity of all HCV polymerase genotypes, and it can be dosed once daily. Vertex Pharmaceuticals, Inc., Cambridge, MA Phase I trial	Boceprevir NS5A inhibitors in development Nonnucleoside polymerase inhibitors in development Nucleoside polymerase inhibitors in development Pegylated interferon/ribavirin combination Telaprevir	Slowed or halted disease progression Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life	Company halted development because of lack of efficacy in trial

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Polymerase inhibitor (BMS 094; formerly INX-189) 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 cures the infection in less than half of treated patients, and newly approved protease inhibitors are associated with frequent adverse events. Effective and more tolerable treatments are needed. BMS-094 (formerly INX-189) is an orally administered prodrug and 2'-C-methylguanosine analog. It is purported to inhibit the HCV NS5B polymerase activity, which may limit viral replication by inhibiting viral genome replication. INX-189 is intended to be used in combination with standard-of-care pegylated interferon plus ribavirin (IFN/RBV) for this indication. Administered orally at a dose of 100–200 mg. Manufacturer states trial data supports BMS-094's potential for once-daily dosing. Bristol-Myers Squibb, New York, NY Phase I/II trials ongoing; FDA granted fast track status; company halted development Aug 2012	Boceprevir Sofosbuvir (investigational) Pegylated interferon/ribavirin Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Sustained virologic response (HCV RNA undetectable after 24 weeks of followup) Reduced need for liver transplantation Reduced symptoms	Company halted development due to cardiac-related death of patient in a mid-stage trial and hospitalization of 8 other patients related to kidney or heart problems believed to be associated with the drug.
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. McGill University Health Centre, Montreal, Quebec, Canada Early adoption ongoing	Antimicrobial copper touch surfaces Terminal cleaning procedures using bleach and cleaning of visibly soiled surfaces as necessary Ultraviolet light	Reduced health care–acquired infection rates Increased overall survival	No longer meets horizon scanning criteria; diffused past early adoption

Table 40. AHRQ Priority Condition: 10 Obesity: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Neuropeptide Y antagonist (velneperit, S-2367) for treatment of obesity	Adults with body mass index (BMI) ≥30 kg/m^2	Pharmacotherapy options for weight loss are limited and associated with side effects and risks. Velneperit is an oral neuropeptide Y (NPY) Y5 receptor antagonist, which appears to be the main mediator of the orexigenic effect of NPY; the NPY system is a crucial component of the central hypothalamic mechanisms implicated in the control of food intake and energy metabolism; in preclinical studies, it has reduced hyperphagia and visceral adipose tissue. Velneperit is administered orally, 1,600 mg (4 x 400 mg) per day, once daily. Shionogi & Co., Ltd., Osaka, Japan Phase IIb trial completed; trial investigating use with orlistat halted after endpoints not reached	Antiobesity pharmacotherapies Behavioral and lifestyle modifications Surgical therapy (e.g. bariatric surgery)	Total weight loss Excess weight loss Decline in obesity-associated comorbidities (e.g., prediabetes, high blood pressure)	Company no longer lists drug in company's research and development pipeline; rights to the drug development do not appear in any other company pipeline

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

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

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Cell phone bi-directional communication educational program (Text4Baby) for pregnant women and new mothers	Pregnant women, new mothers, and perinatal case managers and providers	A public-private partnership to support free mobile cell phone texting educational service (Text4Baby) to deliver timely health education and information about prenatal care during pregnancy and neonatal/infant care through baby's 1st year. National Healthy Babies, Healthy Mothers Coalition, Alexandria, VA Nov 2011 University of California, San Diego, presented Text4Baby data at American Public Health Association Conference in Washington, DC	No intervention Standard case management (face - to-face) Telephone contact Health education services Home visits	Increased awareness of and adherence to appropriate prenatal and infant care Reduced missed appointments Reduced preterm births Reduced infant morbidity and mortality (e.g., low birth weight due to smoking)	No longer meets horizon scanning criteria; has diffused widely after 2 years of tracking
In utero fetal surgery to repair myelomeningocele (spina bifida)	Pregnant women with a fetus at 19–25 weeks gestation in whom myelomeningocele lesion has been diagnosed that starts no higher than T1 and no lower than S1 with lowest parts of the cerebellum (hindbrain) herniation present	Surgery in a newborn with spina bifida to repair the defect does not restore function to nerve damage that occurred during gestation; thus, neurologic outcomes are not optimal. Researchers hypothesized that earlier repair of the defect in utero might lead to better neurologic outcomes in affected neonates; the surgery involves intrauterine repair of fetal myelomeningocele at 19–25 weeks of gestation (before 26 weeks) with delivery by cesarean section scheduled for 37 weeks' gestation. Eunice Kennedy Shriver National Institute of Child Health and Human Development, part of the National Institutes of Health, Bethesda, MD; Children's Hospital of Philadelphia, Philadelphia, PA Late-phase trial halted early due to high efficacy of procedure	Postnatal surgery to repair myelomeningocele	Increased neonatal survival Improved Bayley Scales of Infant Development (Mental Development Index) Improved functional-anatomical level of lesion at 30 months of age Reduced need for ventricular shunt by 1 year of life	No longer meets horizon scanning criteria because procedure has diffused to various medical institutions performing complex in utero surgery

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Roflumilast (Daliresp) for treatment of chronic obstructive pulmonary disease	Patients in whom severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis and a history of exacerbations have been diagnosed	About 20% of patients with COPD have chronic bronchitis and pulmonary exacerbations; overall only about 10% of COPD patients respond to inhaled corticosteroids, so more effective treatments are needed. Roflumilast (Daliresp™) is the 1st and only orally formulated selective phosphodiesterase type 4 (PDE-4) inhibitor; as a PDE-4, the drug is intended to inhibit COPD-related inflammation. Administered as a once-daily, 500 mcg tablet (in contrast to multiple inhalations per day), to reduce the risk of COPD exacerbations. Forest Laboratories, Inc., New York, NY FDA approved Jan 2011	Glucocorticoids Long-acting anticholinergic agents Long-acting beta2-agonists Roflumilast	Increased forced expiratory volume in 1 second Reduced exacerbation rate	Expert comments designated this as having little potential for high impact because it is an incremental add-on to other treatments

Table 44. 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	Reason
Naltrexone extended-release (Vivitrol) for treatment of opioid dependence	Patients in whom opioid dependence has been diagnosed	Treatment adherence is an issue with opioid dependence. Extended-release naltrexone (Vivitrol®) is a monthly injectable opioid receptor antagonist intended to reduce pleasure from taking opioids. An oral formulation is approved for alcoholism and opioid dependence and an injectable form is approved for alcoholism only; this formulation would offer a once-monthly injectable option instead of daily dosing, and it would be the 1st injectable therapy for this indication. Alkermes, Waltham, MA FDA approved in Oct 2010 for prevention of relapse to opioid dependence following opioid detoxification	Oral or sublingual pharmacotherapies (e.g., buprenorphine, methadone, naltrexone)	Decreased pleasure derived from opioid use Lower relapse rates Improved long-term health outcomes Improved quality of life	No longer meets horizon scanning criteria; approved more than 2 years ago

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Self-service automated pharmacy kiosk (MedCentre) to dispense medications	Patients in need of commonly prescribed pharmaco-therapies	Retail pharmacies may not be available in remote locations; high patient volume for routine medication pick-up makes it difficult for pharmacists to spend time with individual patients; patient medication adherence rates are suboptimal. PharmaTrust MedCentre™ is a free-standing, automated medication dispensing and management system with the 4 following main components: remote access point for complete, personal, private pharmacist counseling; a point-of-care dispensary of patient medications; home delivery service; and a pharmaceutical distribution system designed to ensure the correct drugs are dispensed to patients. The machine stores 340 common (many generic) medications and is linked to a "tele-pharmacist"; tele-pharmacist verifies the patient's prescription, and the machine fills the prescription. Intended to be deployed in hospitals, medical clinics, and pharmacies, as well as retail, employer, and other public locations. PharmaTrust Corp., subsidiary of PCAS Patient Care Automation Services, Inc., Oakville, Ontario, Canada Released in Canada and UK; opening marketing to U.S.	Retail pharmacy Mail-order pharmacy	Improved access to prescription medication Increased patient adherence with medications Increased patient volume in retail pharmacies	PharmaTrust Corp. went bankrupt

Section 4. Interventions Identified and Not Tracked: 1 Intervention

Table 46. AHRQ Priority Condition: 01 Arthritis and Nontraumatic Joint Disease: 0 Interventions

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

Table 47. AHRQ Priority Condition: 02 Cancer: 0 Interventions

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

Table 48. 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

Table 49. 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

Table 50. AHRQ Priority Condition: 05 Depression and Other Mental Health Disorders: 0 Interventions

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

Table 50. AHRQ Priority Condition: 06 Developmental Delays, Attention-Deficit Hyperactivity Disorder, and Autism: 0 Interventions

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

Table 51. AHRQ Priority Condition: 07 Diabetes Mellitus: 0 Interventions

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

Table 52. AHRQ Priority Condition: 08 Functional Limitations and Disability: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
OptiNose sumatriptan device for treatment of migraine headaches	Patients in whom migraine headaches have been diagnosed	Nearly 28 million people in the U.S. are affected by migraine headaches each year. Currently, migraine headaches are treated with a variety of pharmacotherapies but many patients either do not achieve sufficient pain relief or do not achieve it quickly enough. The OptiNose bi-directional device is intended to deliver sumatriptan powder intranasally to purportedly achieve more rapid pain relief than other medications and delivery methods. OptiNose US Inc., Yardley, PA Phase II trials completed; phase III ongoing	NSAIDS Triptans Ergotamines Anti-nauseates Opiates	Improved relief times Improved quality of life

Table 53. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 0 Interventions

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

Table 54. AHRQ Priority Condition: 10 Obesity: 0 Interventions

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

Table 55. 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 56. 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 57. 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 58. AHRQ Priority Condition: 14 Substance Abuse: 0 Interventions

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

Table 60. 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