

# ***AHRQ Healthcare Horizon Scanning System – Status Updates***

## **Horizon Scanning Status Update: May 2012**

Prepared for:

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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. HHS A290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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## Preface

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

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

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

This edition of the Status Update lists interventions that have been identified and are being monitored. The next edition will be published in 2 - 3 months. We welcome comments on the list, which may be sent by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to [effectivehealthcare@ahrq.hhs.gov](mailto: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 every 2 months, with each new report superseding the prior version. This Status Update report builds on pilot reports prepared during the first 8 months of horizon scanning. It 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" (during the 2-month interval since the prior report), followed by "Interventions Tracked but Archived Since Last Update," and finally, "Interventions Identified and Not Tracked" during the prior 2-month tracking period. 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 the topic nomination meeting 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 target for profile development must be far enough along in development (typically phase III for drugs and phase II 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 to target with less 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, it sometimes becomes apparent 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 of the horizon scanning system has been ongoing since December 2010 (18 months). During that time, more than 11,000 leads have been uploaded into the system and reviewed by analysts, from which about 1,400 topics have been initially identified and moved through the system. This Status Update report contains a total of 930 identified interventions. While we continued to identify and collect leads, we identified no new interventions for entry into the system during the previous 60 days (the period since the last update was prepared) because of an intense focus on updating the development and diffusion status of all topics in the system, updating topic profiles, and determining which topics met criteria for archiving. That effort led to archiving of 68 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 comments 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 had widely diffused since tracking started or were 2 years post-approval by the U.S. Food and Drug Administration. The leads collected during this period will be processed along with additional leads collected for the next reporting period.

In this update, five priority areas comprise 76% (707/930) of the interventions (including programs) being tracked. Interventions related to cancer account for about 31% (285/930) of identified and currently monitored 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%, 168/930), infectious diseases (11.5%, 107/930), cardiovascular diseases (10%, 94/930), and diabetes (6%, 54/930).

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 designated as cross-cutting, account for 4% or less each, or a combined total of 24% (223/930) of the topics being tracked in the system. These proportions in each priority area have changed by only one or two percentage points compared with the proportions for each of the priority areas in previous Status Update reports.

In terms of overall types of interventions, 84% fall into one of four general categories. About 62% of topics in the system are a pharmaceutical/biotechnology (i.e., drugs, vaccines, biologics); about 14% are devices—either implanted or used to deliver treatments externally; about 5% are technologies intended to screen, diagnose, and/or monitor a disease state; and about 3% are programs/services/care-delivery innovations. 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: 930 Interventions**

**Table 1. AHRQ Priority Condition: 01 Arthritis and Nontraumatic Joint Disease: 31 Interventions**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Atacept for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	<p>There is no permanent cure for SLE, and current treatments provide only partial relief of symptoms. Atacept 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. Atacept 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, atacept is also called TACI-Ig. Atacept is purported to be an antagonist for the TACI receptor. Atacept is hypothesized to selectively impair mature B cells and plasma cells more than memory B cells or progenitor cells. Atacept is administered subcutaneously, 75 or 150 mg, once weekly.</p> <p>EMD Serono, Inc., Rockland, MA</p> <p>Phase II/III trial ongoing</p>	AGS-009 Belimumab Rituximab Rontalizumab	Delayed disease progression Reduced symptoms Fewer flares Improved quality of life
Autologous conditioned serum for treatment of osteoarthritis (knee and back)	Patients in whom osteoarthritis (OA) has been diagnosed	<p>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.</p> <p>NY Spine Medicine, Schottenstein Pain &amp; Neurology, New York, NY</p> <p>Pilot studies completed; procedure currently offered in the U.S.</p>	Mesenchymal stem-cell therapy Nonsteroidal anti-inflammatory drugs Physical therapy Platelet-rich plasma	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
BAFF-targeting peptibody blisibimod (A-623) for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	<p>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 via weekly subcutaneous injection.</p> <p>Anthera Pharmaceuticals, Inc., Hayward, CA</p> <p>Phase III trial planned</p>	Belimumab Disease-modifying antirheumatic drugs LY2127399	Delayed disease progression Symptom relief Improved quality of life
Belimumab (Benlysta) for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	<p>Current SLE treatments provide partial symptomatic relief; treatments with improved efficacy are needed. Belimumab (Benlysta®) is a fully human monoclonal antibody that specifically recognizes and inhibits the biologic activity of B-lymphocyte stimulator, which plays a key role in B-lymphocyte differentiation, survival, and activation.</p> <p>Human Genome Sciences, Inc., Rockville, MD GlaxoSmithKline, Middlesex, UK</p> <p>FDA approved Mar 9, 2011</p>	Corticosteroids Antimalarial drugs Cyclophosphamide and mycophenolate Methotrexate and azathioprine Intravenous immunoglobulin	Slowed disease progression Disease remission Symptom improvement
Canakinumab (Ilaris) for treatment of gouty arthritis	Patients in whom gouty arthritis has been diagnosed	<p>Canakinumab (Ilaris®) is a human monoclonal antibody targeted at interleukin-1 beta.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Phase III trials ongoing; FDA advisory committee in Jun 2011 voted 11-1 against approving canakinumab for treatment of acute gout because of safety concerns, despite unanimous agreement by committee that the drug was effective; committee hoped the company would present more data in future to address safety concerns. Company received complete response letter in Aug 2011 requesting additional clinical data; indication sought could change from acute gout to gouty arthritis</p>	Nonsteroidal anti-inflammatory drugs Pegloticase Steroids Prophylaxis: Febuxostat and allopurinol Probenecid	Reduced inflammation Reduced pain Faster return to 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
C-reactive protein inhibitor (ISIS-CRPRx) 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	<p>Elevated CRP levels have been associated with various inflammatory disorders including RA, cardiovascular disease, and diabetes. ISIS-CRPRx is intended to directly test whether lowering CRP might benefit patient outcomes in patients with these disorders; ISIS-CRPRx 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.</p> <p>ISIS Pharmaceuticals, Inc., a unit of Johnson &amp; Johnson, New Brunswick, NJ</p> <p>Phase II trial ongoing</p>	No other CRP reducing agent available	<p>Reduced CRP levels</p> <p>Reduced symptoms</p> <p>Slowed disease progression</p>
Denosumab (Xgeva) for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	<p>Current RA treatments attempt to reduce inflammation, but do not directly address or prevent structural bone damage observed in RA patients. Denosumab (Xgeva®) is a monoclonal antibody that targets the receptor activator of nuclear factor kappa B ligand (RANKL). RANKL is required for osteoclast development, activation, and survival (leading to bone mineral loss); may be used with methotrexate.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase II trial completed; drug is approved and indicated for prevention of skeletal-related events in patients with bone metastases from solid tumors</p>	<p>Bisphosphonates</p> <p>Disease-modifying antirheumatic drugs: methotrexate, hydroxychloroquine, sulfasalazine</p> <p>Nonsteroidal anti-inflammatory drugs</p> <p>Tocilizumab (interleukin-6 antagonist)</p> <p>Anti-tumor necrosis factor alpha</p>	<p>Improved RA-MRI erosion score from baseline</p> <p>Improved radiographic joint space narrowing score</p> <p>Improved bone (CTX I and PINP) and cartilage (CTX II) markers</p> <p>Improved bone mineral density</p>
Epratuzumab for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	<p>There is no 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.</p> <p>UCB S.A., Brussels, Belgium</p> <p>Phase III trials ongoing</p>	<p>Belimumab</p> <p>Rituximab</p> <p>Rontalizumab</p>	<p>Delayed progression of disease</p> <p>Reduced symptoms</p> <p>Fewer flares</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fostamatinib disodium for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	<p>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. Intended for treatment of early stage RA to reduce swelling and tissue destruction. The drug is taken orally.</p> <p>Rigel Pharmaceuticals, Inc., South San Francisco, CA</p> <p>Phase III trials ongoing</p>	<p>Analgesics Anti-inflammatory agents: glucocorticoids, nonsteroidal anti-inflammatory drugs Biologic monoclonal antibodies and inhibitors Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine</p>	<p>Decreased inflammation Slowed disease progression Reduced pain Improved function and activities of daily living Improved quality of life</p>
Interleukin-1-beta antagonist canakinumab (Ilaris) for treatment of systemic juvenile idiopathic arthritis	Patients in whom systemic juvenile idiopathic arthritis (SJIA) has been diagnosed	<p>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, in a clinical trial.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Phase III trials ongoing; approved for cryopyrin-associated periodic syndromes</p>	<p>Anakinra Corticosteroids Hydroxychloroquine Methotrexate Nonsteroidal anti-inflammatory drugs</p>	<p>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</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interleukin-6 receptor antagonist tocilizumab (Actemra) for treatment of systemic juvenile idiopathic arthritis	Patients in whom systemic juvenile idiopathic arthritis (SJIA) has been diagnosed	<p>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.</p> <p>F. Hoffmann-La Roche, Ltd., Basel, Switzerland</p> <p>FDA approved for treatment of SJIA Apr 2011</p>	Anakinra Canakinumab Corticosteroids Hydroxychloroquine 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
JAK 1 inhibitor (GLPG0634) for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	<p>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.</p> <p>Galápagos NV, Mechelen, Belgium GlaxoSmithKline, Middlesex, UK</p> <p>Phase II trial complete</p>	Anti-inflammatory agents Disease-modifying antirheumatic drugs Fostamatinib Monoclonal antibodies Tofacitinib	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	<p>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.</p> <p>Incyte Corp., Wilmington, DE Eli Lilly and Co. Indianapolis, IN</p> <p>Phase II trials ongoing</p>	<p>Adalimumab DMARDs Etanercept Fostamatinib Infliximab Tocilizumab Tofacitinib</p>	<p>Improved symptom scores as measured by the American College of Rheumatology 20/50/70 instruments</p>
JAK 3 inhibitor (tofacitinib) for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	<p>Tofacitinib (CP-690,550) is a selective and potent oral tyrosine kinase inhibitor that is being investigated as a targeted disease-modifying antirheumatic drugs (DMARDs) for treatment of 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.</p> <p>Pfizer, Inc., New York, NY</p> <p>Phase III trial completed; May 9, 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 first new oral DMARD for RA in more than 10 years and the first JAK inhibitor to be approved; FDA decision date is Aug 2012.</p>	<p>Anti-inflammatory agents DMARDs Monoclonal antibodies</p>	<p>Reduced inflammation Improved symptoms Improved activities of daily living Improved quality of life</p>

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	<p>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.</p> <p>Vertex Pharmaceuticals, Inc., Cambridge, MA</p> <p>Phase II trial completed</p>	<p>Adalimumab DMARDs Etanercept Fostamatinib Infliximab Tocilizumab Tofacitinib</p>	<p>Improved symptoms scores as measured by American College of Rheumatology 20/50/70 instruments</p>
KB003 for treatment of rheumatoid arthritis	Patients is whom rheumatoid arthritis (RA) has been diagnosed	<p>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. KB003 is a monoclonal antibody against granulocyte macrophage colony-stimulating factor, a proinflammatory cytokine believed to be elevated in RA patients. KB003 is purported to be “humaneered” to reduce the likelihood of immune reactions that may occur after long-term use of the drug.</p> <p>KaloBios Pharmaceuticals, Inc., South San Francisco, CA</p> <p>Phase II trial completed</p>	<p>Adalimumab DMARDs Etanercept Fostamatinib Infliximab Tocilizumab Tofacitinib VX-509</p>	<p>Improved symptom scores as measured by American College of Rheumatology 20/50/70 instruments Improved quality of life</p>

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 rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	<p>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.</p> <p>AB Science S.A., Paris, France</p> <p>Phase II/III trial ongoing</p>	<p>Analgesics Anti-inflammatory agents: glucocorticoids, nonsteroidal anti-inflammatory drugs Disease-modifying antirheumatic drugs: methotrexate, hydroxychloroquine, sulfasalazine Biologic monoclonal antibodies and inhibitors</p>	<p>Improved symptom scores as measured by American College of Rheumatology 20/50/70 instruments Improved quality of life</p>
LX2931 for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	<p>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. LX2931 inhibits 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 inflammation in joints. Administered orally.</p> <p>Lexicon Pharmaceuticals, Inc., The Woodlands, TX</p> <p>Phase II trial completed</p>	<p>Hydroxychloroquine Methotrexate Monoclonal antibodies Nonsteroidal anti-inflammatory drugs Sulfasalazine</p>	<p>Improved RA symptoms Reduced number of lymphocytes in circulation Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mesenchymal precursor cells (NeoFuse) for treatment of degenerative disc disease	Patients in whom degenerative disc disease (DDD) of the lower back has been diagnosed	<p>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.</p> <p>Mesoblast, Ltd., New York, NY</p> <p>Phase II trials ongoing</p>	Spinal fusion Total disc replacement	Increased activities of daily living Reduced chronic lumbar back pain Reduced use of pain medications
Mesenchymal stem cells for treatment of osteoarthritis	Patients in whom osteoarthritis (OA) has been diagnosed	<p>Other than joint replacement and symptom management, effective treatment for OA to restore function long-term is not available. Viscosupplementation provides temporary relief and improves function short-term for some patients, but long-term nonsurgical treatments are needed. Adult stem cells, platelet-rich plasma (PRP), and fat are injected into the affected site; PRP stimulates stem cell growth and the fat provides a framework and bulk for the stem cells to adhere to.</p> <p>Arthritis Treatment Center, Frederick, MD</p> <p>Phase II/III trial ongoing; procedure currently available to patients</p>	Viscosupplementation Joint replacement surgery Lifestyle modification (weight loss, exercise) Pharmacologic pain management Physical therapy Alternative medicine	Reduced pain Increased range of motion Increased tissue regeneration

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Monoclonal antibody (LY2127399) for treatment of rheumatoid arthritis</p>	<p>Patients in whom rheumatoid arthritis (RA) has been diagnosed</p>	<p>RA is a chronic inflammatory disease causing polyarthritis with frequent progression to permanent joint damage, deformity, and functional disability. LY2127399 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, LY2127399 inhibits the stimulation, proliferation, and differentiation of B cells. Intravenous and injectable formulations are under development for RA.</p> <p>Eli Lilly and Co., Indianapolis, IN</p> <p>Phase III trials ongoing</p>	<p>Anti-inflammatory agents Biologics Disease-modifying antirheumatic drugs</p>	<p>Reduced symptoms Delayed progression of disease Improved quality of life</p>
<p>Monoclonal antibody (LY2127399) for treatment of systemic lupus erythematosus</p>	<p>Patients in whom systemic lupus erythematosus (SLE) has been diagnosed</p>	<p>There is no permanent cure for SLE, and current treatments provide only partial relief of symptoms. LY2127399 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.</p> <p>Eli Lilly and Co., Indianapolis, IN</p> <p>Phase III trials ongoing</p>	<p>Standard care Nonsteroidal anti-inflammatory drugs Rituximab (off label)</p>	<p>Improved SLE Responder Index Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nitronaproxen (Naproxinod) for treatment of osteoarthritis	Patients in whom osteoarthritis (OA) has been diagnosed	<p>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 donors (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.</p> <p>NicOx, Sophia Antipolis, France</p> <p>Phase III trials completed; manufacturer received FDA response letter to new drug application requesting long-term safety data on cardiovascular effects; April 2012, manufacturer met with FDA to discuss additional data required for NDA resubmission</p>	Celecoxib Ibuprofen Naproxen	Increased mobility Decreased pain Improved cardiovascular effects (i.e., blood pressure)
Off-label bisphosphonates for prevention of revision surgery after knee or hip arthroplasty	Patients who have undergone knee or hip arthroplasty	<p>Knee or hip replacement revision surgery adds to the cost and risk of complications of the original 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. Patients taking bisphosphonates are purported to be less likely to need arthroplasty revision surgery.</p> <p>Lund University Hospital, Lund, Sweden Phase II trial ongoing in hip surgery patients</p>	Other bone resorption inhibitors such as: Denosumab Zoledronic acid	Reduced need for revision surgery Improved quality of life
Pegloticase (Krystexxa) for treatment of chronic gout	Patients in whom chronic gout has been diagnosed	<p>Pegloticase (Krystexxa®) is a recombinant, porcine-like uricase, which metabolizes uric acid to allantoin, which reduces risk of precipitates because allantoin is 5–10 times more soluble than uric acid. In contrast to rasburicase, pegloticase is pegylated to increase its elimination half-life from about 8 hours to 10–12 days and to decrease the immunogenicity of the foreign uricase protein. The drug is intended to treat severe, treatment-refractory, chronic gout.</p> <p>Savient Pharmaceuticals, Inc., East Brunswick, NJ FDA approved Sept 15, 2010</p>	<p>Treatments: Nonsteroidal anti-inflammatory drugs Steroids</p> <p>Prophylaxis: Febuxostat and allopurinol Probenecid</p>	Reduced inflammation Reduced pain Faster return to 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
Platelet-rich plasma therapy for treatment of knee osteoarthritis	Patients in whom knee osteoarthritis has been diagnosed	<p>Other than joint replacement and symptom management, effective treatment for OA to restore function long-term is not available. 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.</p> <p>Orthohealing Center, Los Angeles, CA</p> <p>Phase III trials ongoing</p>	<p>Analgesics Artificial knee replacement Lifestyle modification Physical therapy Viscosupplementation</p>	<p>Decreased pain Increased mobility Improved quality of life</p>
Purine nucleoside phosphorylase inhibitor BCX4208 to prevent acute gout flares	Patients in whom chronic gout has been diagnosed	<p>Despite new treatment options, some patients do not respond adequately to current gout therapies; thus, treatments with new mechanisms of action are needed. 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. BCX4208 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.</p> <p>BioCryst Pharmaceuticals, Inc., Research Triangle, NC</p> <p>Phase II trials ongoing</p>	<p>Allopurinol Febuxostat Probenecid Rilonacept</p>	<p>Reduced frequency of gout flares Reduced serum uric acid levels Improved quality of life</p>
Rilonacept (Arcalyst) for treatment of acute gout	Patients in whom acute gout has been diagnosed	<p>Despite new treatment options, some patients do not respond adequately to current gout therapies; thus, treatments with new mechanisms of action are needed. Rilonacept (Arcalyst®) is a dimeric fusion protein consisting of the extracellular domain of human interleukin-1 (IL-1) receptor and the FC domain of human immunoglobulin G1 that binds and neutralizes IL-1. The drug is intended to decrease inflammation. Administered by subcutaneous injection.</p> <p>Regeneron Pharmaceuticals, Inc., Tarrytown, NY</p> <p>Phase III trial ongoing; FDA advisory panel voted 11-0 against approval May 8, 2012; final FDA decision date July 30, 2012; approved in 2008 for children with autoinflammatory cryopyrin-associated periodic syndromes in which IL-1 has a pathogenic role</p>	<p>Treatment: Nonsteroidal anti-inflammatory drugs Pegloticase Steroids</p> <p>Prophylaxis: Febuxostat and allopurinol Probenecid</p>	<p>Reduced inflammation Reduced pain Faster return to activities of daily living Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
TissueGene-C allogeneic chondrocyte implantation for treatment of knee osteoarthritis	Patients in whom grade 3 degenerative chronic osteoarthritis of the knee has been diagnosed	<p>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.</p> <p>TissueGene, Inc., Rockville, MD</p> <p>Phase II trial ongoing</p>	Autologous chondrocyte implantation (Carticel) Knee replacement Microfracture surgery Osteochondral autograft transfer	Decreased knee pain Improved knee function Delayed or avoided knee replacement surgery
Tissue-specific COX-2 inhibitor CG100649 for treatment of osteoarthritis	Patients in whom osteoarthritis (OA) has been diagnosed	<p>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 cyclooxygenase-2 (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 mg, once daily.</p> <p>CrystalGenomics, Seoul, South Korea</p> <p>Phase II trials ongoing</p>	Celecoxib NSAIDs	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 for acute gout	<p>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.</p> <p>Ardea Biosciences, Inc., San Diego, CA</p> <p>Phase III trials ongoing</p>	Allopurinol (gout, hyperuricemia) Febuxostat (hyperuricemia) Uricosurics (probenecid, benzbromarone and sulfapyrazone, for hyperuricemia)	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
Abiraterone (Zytiga) for treatment of castration-resistant prostate cancer	Patients with metastatic prostate cancer that is nonresponsive to androgen deprivation or antiandrogen drugs	<p>Median overall survival for patients with castration-resistant prostate cancer (CRPC) is only about 18 months. Administered in combination with prednisone, abiraterone (Zytiga™) inhibits a cytochrome P-450 subunit (CYP17) 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.</p> <p>Janssen Biotech unit of Johnson &amp; Johnson, New Brunswick, NJ</p> <p>FDA approved Apr 2011</p>	Cabazitaxel Docetaxel Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
ADXS11-001 for treatment of advanced cervical cancer	Patients in whom advanced cervical cancer has been diagnosed	<p>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 <i>Listeria monocytogenes</i> bacteria that have been engineered to express the human papillomavirus 16 E7 protein, which is believed to be crucial for cervical oncogenesis; the recombinant <i>Listeria</i> 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<sup>9</sup>, 3.3x10<sup>9</sup> or 1x10<sup>10</sup> CFUs (colony-forming units).</p> <p>Advaxis, Inc., New Brunswick, NJ</p> <p>Phase II trials ongoing</p>	Cisplatin Radiotherapy	Increased overall survival Increased progression-free 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 breast cancer	Patients in whom HER2-positive breast cancer has been diagnosed	<p>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 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.</p> <p>Boehringer Ingelheim GmbH, Ingelheim, Germany</p> <p>Phase III trials ongoing</p>	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	<p>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.</p> <p>Boehringer Ingelheim GmbH, Ingelheim, Germany</p> <p>Phase III trials ongoing</p>	Cetuximab (Erbix®)	Increased overall survival Increased progression-free survival Improved quality of life
Afatinib (BIBW 2992, Tomtovok) for treatment of non-small cell lung cancer	Patients in whom non-small cell lung cancer (NSCLC) has been diagnosed	<p>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.</p> <p>Boehringer Ingelheim, GmbH, Ingelheim, Germany</p> <p>One phase III trial complete; additional phase III trials ongoing</p>	First-line NSCLC: platinum based chemotherapy Second- and 3rd-line NSCLC: docetaxel, pemetrexed, 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
Aflibercept (Zaltrap) for treatment of metastatic colorectal cancer	Patients with metastatic colorectal cancer (CRC) that has recurred after oxaliplatin-based chemotherapy	<p>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).</p> <p>Collaboration between Regeneron, Tarrytown, NY, and Sanofi, Paris, France</p> <p>Phase III trial complete; biologics license application (BLA) submitted to FDA Nov 2011; BLA withdrawn in Dec 2011 after comments by FDA on the Chemistry, Manufacturing, and Controls section of the BLA; BLA resubmitted and has been granted priority review with an FDA decision date of August 4, 2012</p>	5-FU-based therapy plus bevacizumab FOLFIRI (folinic acid [leucovorin], 5-FU, and irinotecan) FOLFIRI plus cetuximab or panitumumab 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	<p>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.</p> <p>CytRx Corp., Los Angeles, CA</p> <p>Phase IIb initiated in Dec 2011; FDA granted orphan drug status</p>	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 stage II) adenocarcinoma of the pancreas has been diagnosed	<p>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.</p> <p>NewLink Genetics Corp., Ames, IA</p> <p>Phase III trial ongoing under special protocol assessment with FDA; FDA granted fast track and orphan drug status</p>	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 recurrent metastatic melanoma has been diagnosed	<p>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 infusion on outpatient basis.</p> <p>Vical, Inc., San Diego, CA</p> <p>Phase III trials ongoing; FDA granted orphan drug and fast track status for invasive and metastatic melanoma</p>	Dacarbazine or Interferon Ipilimumab Personalized vaccination (in clinical development) Proleukin (interleukin-2) Temozolomide Therapeutic vaccines (in clinical development) 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 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	<p>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 treatment with 1st-line 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.</p> <p>NovaRx, San Diego, CA</p> <p>Phase III trial ongoing under a special protocol assessment with FDA; FDA granted fast track status</p>	<p>Watchful waiting after successful 1st-line therapy</p> <p>Maintenance therapy (various chemotherapy regimens determined according to NSCLC subtype)</p>	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
ALN-VSP/RNAi for treatment of secondary liver metastases	Patients with liver metastases from advanced solid tumors	<p>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.</p> <p>Alnylam Pharmaceuticals, Cambridge, MA</p> <p>Phase I trial completed</p>	<p>Chemotherapy</p> <p>Immunotherapy</p> <p>Intrahepatic microspheres/drug-eluting beads</p> <p>Radiation therapy</p>	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
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)	<p>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.</p> <p>Pfizer, Inc., New York, NY</p> <p>FDA approved Aug 2011 for treatment of locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test</p>	<p>First-line chemotherapy: Pemetrexed plus cisplatin</p> <p>Second-line chemotherapy: Docetaxel plus pemetrexed</p> <p>Erlotinib (Tarceva)</p>	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Androgen receptor antagonist (enzalutamide) for treatment of castration-resistant prostate cancer</p>	<p>Patients in whom castration-resistant prostate cancer (CRPC) has been diagnosed</p>	<p>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 prostate cancers do not respond to these therapies or develop resistance. Enzalutamide (formerly known as MDV3100) 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 daily at a dose of 160 mg.</p> <p>Medivation, Inc., San Francisco, CA</p> <p>Phase III trial in patients previously treated with docetaxel was stopped early due to clear benefit in Enzalutamide arm; new drug application submission expected to be filed in 2012; phase III trial in pre-docetaxel setting ongoing</p>	<p>Chemotherapy-naive CRPC: Abiraterone plus prednisone Docetaxel Sipuleucel-T</p> <p>Pretreated CRPC: Abiraterone plus prednisone Cabazitaxel</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
<p>Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of advanced hepatocellular carcinoma</p>	<p>Patients with advanced hepatocellular carcinoma (HCC) who have had no prior systemic chemotherapy</p>	<p>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.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase II trial ongoing</p>	<p>Sorafenib Sunitinib</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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	<p>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.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase II trial ongoing</p>	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	<p>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).</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase II trials ongoing</p>	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
<p>Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of metastatic gastrointestinal cancer</p>	<p>Patients with metastatic gastric, gastroesophageal junction, or distal esophageal adenocarcinoma who have had no prior chemotherapy</p>	<p>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.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase II trial results reported mid-2011 for this indication were negative; development status uncertain</p>	<p>Cisplatin plus capecitabine</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
<p>Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of ovarian, peritoneal, and fallopian tube cancers</p>	<p>Patients with epithelial ovarian, primary peritoneal, or fallopian tube cancer that is partially platinum sensitive or resistant</p>	<p>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.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase III trials ongoing</p>	<p>Docetaxel Etoposide Gemcitabine Liposomal doxorubicin Paclitaxel Topotecan</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of persistent or recurrent endometrial cancer</p>	<p>Patients with persistent or recurrent endometrial cancer that has not responded to prior chemotherapy</p>	<p>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 will repeat every 28 days if disease has not progressed and side effects are tolerable.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase II trial ongoing</p>	<p>Cisplatin/doxorubicin Cisplatin/doxorubicin/paclitaxel Ifosfamide/paclitaxel Carboplatin/paclitaxel Cisplatin Carboplatin Doxorubicin or liposomal doxorubicin Paclitaxel Hormonal therapy</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
<p>Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of recurrent glioblastoma multiforme</p>	<p>Patients in whom recurrent glioblastoma multiforme has been diagnosed</p>	<p>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.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase II trial ongoing</p>	<p>Bevacizumab monotherapy Cyclophosphamide Nitrosurea Platinum-based cytotoxic chemotherapy Temozolomide</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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; no prior systemic chemotherapy.	<p>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.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase II trial results reported mid-2011 were negative; further development uncertain</p>	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	<p>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.</p> <p>GlaxoSmithKline, Middlesex, UK</p> <p>Phase III trial complete; new drug application submitted to FDA; FDA Oncologic Drugs Advisory Committee voted Mar 2012 to approve; FDA target decision date is May 6, 2012; FDA approved pazopanib for treatment of renal cell carcinoma in 2009, and it is marketed as Votrient</p>	<p>No consensus 2nd-line treatment for soft tissue sarcoma</p> <p>Placebo Ridaforolimus (submitted to FDA) Sorafenib (off label) Sunitinib (off label)</p>	Increased overall survival Increased progression-free 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 advanced pancreatic cancer	Patients in whom advanced pancreatic cancer has been diagnosed	<p>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.</p> <p>Agensys, an affiliate of Astellas Pharma, Deerfield, IL Seattle Genetics, Inc., Bothell, WA</p> <p>Phase I trial ongoing</p>	Chemotherapy with gemcitabine or gemcitabine and erlotinib	Increased overall survival Increased progression-free survival Improved quality of life
Antibody-drug conjugate (ASG-5ME) for treatment of castration-resistant prostate cancer	Patients in whom castration-resistant prostate cancer (CRPC) has been diagnosed	<p>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.</p> <p>Agensys, an affiliate of Astellas Pharma, Deerfield, IL Seattle Genetics, Inc., Bothell, WA</p> <p>Phase I trial ongoing</p>	Abiraterone Cabazitaxel Docetaxel	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Antibody-drug conjugate (gemtuzumab ozogamicin) for treatment of acute myeloid leukemia</p>	<p>Patients in whom acute myeloid leukemia (AML) has been diagnosed</p>	<p>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.</p> <p>Pfizer, Inc., New York, NY</p> <p>FDA approved under accelerated approval in 2000 for treatment of 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.</p>	<p>Standard chemotherapy with daunorubicin and cytarabine</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
<p>Antibody-drug conjugate (inotuzumab ozogamicin) for treatment-resistant or recurrent non-Hodgkin's lymphoma</p>	<p>Patients with treatment-resistant or recurrent CD20- and CD22-positive non-Hodgkin's lymphoma (NHL) who are not candidates for high-dose chemotherapy</p>	<p>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<sup>2</sup> by intravenous infusion once every 4 weeks) is being administered as an adjunct to treatment with rituximab.</p> <p>Pfizer, Inc., New York, NY</p> <p>Phase III trial ongoing</p>	<p>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</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anticarbonyc 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	<p>While treatment of localized renal cell carcinoma by 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.</p> <p>Wilex AG, Munich, Germany, in collaboration with Prometheus, Inc., San Diego, CA</p> <p>Phase III trial ongoing; FDA granted fast track status</p>	No currently available adjuvant therapy for ccRCC	Increased overall survival Increased progression-free survival Improved quality of life
Anti-CD200 monoclonal antibody (samalizumab) for treatment of chronic lymphocytic leukemia	Patients with recurrent or treatment-refractory chronic lymphocytic leukemia (CLL)	<p>While 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.</p> <p>Alexion Pharmaceuticals, Inc., Cheshire, CT</p> <p>Phase I/II trial completed</p>	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

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	<p>While 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.</p> <p>Bristol-Myers Squibb, New York, NY</p> <p>Phase III trials ongoing</p>	<p>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</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
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	<p>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 activation 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.</p> <p>Bristol Myers Squibb, New York, NY</p> <p>Phase III trial ongoing</p>	<p>Bevacizumab Carboplatin/ paclitaxel Carboplatin/ pemetrexed Cisplatin/pemetrexed Erlotinib Crizotinib</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
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	<p>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 activation of cytotoxic T-lymphocyte antigen 4, which could lead to increased antitumor cytotoxic activity (reduce immune tolerance to tumor cells).</p> <p>Bristol Myers Squibb, New York, NY</p> <p>Phase III trials ongoing</p>	<p>Abiraterone Cabazitaxel Docetaxel Sipuleucel-T</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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	<p>Few effective treatments exist for metastatic melanoma, particularly for patients in whom <i>BRAF</i> 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 activation of cytotoxic T-lymphocyte antigen 4, which could lead to increased antitumor cytotoxic activity (reduce immune tolerance to tumor cells).</p> <p>Bristol Myers Squibb, New York, NY</p> <p>FDA approved Mar 2011</p>	Dacarbazine High-dose interleukin-2 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	<p>While 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.</p> <p>OncoMed Pharmaceuticals, Inc., Redwood City, CA</p> <p>Phase I trials ongoing</p>	Large variety of anti-cancer chemotherapies	Increased overall survival Increased progression-free survival Improved quality of life
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	<p>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.</p> <p>Merrimack Pharmaceuticals, Inc., Cambridge, MA</p> <p>Phase II trials ongoing</p>	Second-line setting: Exemestane Non-steroidal aromatase inhibitors: anastrozole, letrozole Fulvestrant Tamoxifen Toremifene Neoadjuvant setting: paclitaxel	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Anti-ErbB3 monoclonal antibody (MM-121) for treatment of lung cancer</p>	<p>Patients in whom metastatic nonsmall cell lung cancer (NSCLC) has been diagnosed</p>	<p>While 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.</p> <p>Merrimack Pharmaceuticals, Inc., Cambridge, MA, in collaboration with Sanofi, Paris, France</p> <p>Phase II trial ongoing</p>	<p>Erlotinib monotherapy</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
<p>Antifolate receptor monoclonal antibody (farletuzumab) for treatment of ovarian cancer</p>	<p>Patients with recurrent ovarian cancer that is platinum-sensitive, platinum-resistant, or platinum-refractory</p>	<p>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.</p> <p>Morphotek, Exton, PA, a subsidiary of Eisai Co., Ltd., Tokyo, Japan</p> <p>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</p>	<p>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</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti-GD2 monoclonal antibody (ch14.18) for treatment of neuroblastoma	Patients with high-risk neuroblastoma who have undergone induction therapy and autologous stem cell transplantation	<p>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.</p> <p>United Therapeutics Corp., Silver Spring, MD, in collaboration with the National Cancer Institute, Bethesda, MD</p> <p>Phase III trial complete; phase III trials ongoing; orphan drug designation in U.S. and EU</p>	Isotretinoin	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
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	<p>Patients in whom stage III melanoma has been diagnosed 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 treatment of melanoma. In a late-phase clinical trial, GSK2132231A is being administered as a course of 13 injections.</p> <p>GlaxoSmithKline, London, UK</p> <p>Phase III trial ongoing</p>	<p>Granulocyte-macrophage colony stimulating factor Interferon-alpha Radiation therapy</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
Anti-insulin-like growth factor receptor monoclonal antibody (ganitumab) for treatment of metastatic pancreatic cancer	Patients in whom metastatic pancreatic cancer has been diagnosed	<p>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. Insulin-like growth factor receptor type I (IGF-1R) has been implicated in cell growth and cell survival; therefore, targeted inhibition of IGF-1R is a potential therapeutic cancer intervention; ganitumab (AMG 479) is a humanized monoclonal antibody specific for IGF-1R. In current clinical trials for pancreatic cancer it is being administered intravenously in combination with the cytotoxic agent gemcitabine.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase III trial ongoing</p>	<p>Gemcitabine Gemcitabine plus cisplatin or oxaliplatin Gemcitabine plus erlotinib Gemcitabine plus a fluoropyrimidine</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>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 treatment of NSCLC.</p> <p>F. Hoffmann-La Roche, Ltd., Basel, Switzerland</p> <p>Phase III trial ongoing</p>	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	<p>While 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.</p> <p>CureTech, Ltd., Yavne, Israel Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, is investing in the research</p> <p>Phase II trial complete; CT-011 is also being studied for treatment of colorectal cancer and melanoma</p>	No consensus treatment option for patients post-autologous stem cell transplantation	Increased overall survival Increased progression-free survival Improved quality of life
Anti-placental growth factor monoclonal antibody (TB-403) for treatment of glioblastoma	Patients with recurrent glioblastoma multiforme	<p>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.</p> <p>F. Hoffmann-La Roche, Ltd., Basel, Switzerland, licensed from BioInvent International AB, Lund, Sweden</p> <p>Phase Ib/II trial ongoing</p>	Bevacizumab monotherapy 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
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	<p>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.</p> <p>Progenics Pharmaceuticals, Inc., Tarrytown, NY</p> <p>Phase I trials ongoing</p>	Abiraterone Cabazitaxel	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life (e.g., palliation of pain associated with metastases)</p>
Anti-RANKL monoclonal antibody (denosumab, Xgeva) for prevention of prostate cancer bone metastases	Patients in whom nonmetastatic castration-resistant prostate cancer (CRPC) has been diagnosed	<p>Bone is a frequent site of prostate cancer metastases, and bone metastases have a significant impact on prostate cancer patient morbidity and mortality. No treatments are currently approved for the prevention of prostate cancer metastases to bone. Denosumab functions by binding to the receptor activator of nuclear factor kappa B ligand (RANKL), which is involved in the activation of a type of bone-modifying cells known as osteoclasts. Modification of the bone microenvironment by RANKL expression and osteoclast activity may promote establishment of tumor cells in bone. Denosumab is administered by subcutaneous injection (120 mg) once every 4 weeks.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Denosumab is FDA approved for prevention of skeletal related events in patients with established bone metastases from solid tumors. Denosumab is also FDA approved for treating osteoporosis and bone loss in certain cancer patients. In Feb 2012, FDA's Oncologic Drugs Advisory Committee voted 12-1 against expansion of the denosumab label to include prevention of CRPC-related bone metastasis; Apr 26, 2012, FDA issued a complete response letter for the supplemental biologics license application stating it cannot approve the application in its present form. FDA concluded that the potential risks (including osteonecrosis of the jaw) outweighed the benefits and requested data from an adequate and well-controlled trial to support a favorable risk-benefit profile that can be generalized to the U.S. population.</p>	No FDA approved therapies available for bone metastasis prevention	<p>Increased overall survival</p> <p>Decreased rates of bone metastases and skeletal complications</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti-telomerase therapeutic cancer vaccine (TeloB-Vax) for treatment of prostate cancer	Patients in whom advanced prostate cancer has been diagnosed	<p>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 (hTERT), an enzyme expressed at high levels by many cancers and responsible for allowing cancer cells to continually divide without undergoing senescence. An hTERT-encoding plasmid is transduced into patient-derived B cells, which express the antigen for up to 5 days, potentially eliciting an immune response.</p> <p>Adamis Pharmaceuticals Corp., San Diego, CA</p> <p>Phase I trial completed</p>	Abiraterone Docetaxel Sipuleucel-T	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	<p>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.</p> <p>ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN</p> <p>Phase III trials ongoing</p>	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	<p>These patients have a poor prognosis with current treatment options. Ramucirumab is a novel monoclonal antibody that binds to the extracellular domain of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2), which is a receptor tyrosine kinase that acts as a central mediator of tumor angiogenesis. Available inhibitors of the VEGF pathway include a monoclonal antibody specific for VEGF and small-molecule inhibitors of the kinase activity of VEGFR2 (and other receptor tyrosine kinases). Therefore, ramucirumab represents a novel mechanism of action for 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.</p> <p>ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN</p> <p>Phase III trial ongoing</p>	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	<p>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.</p> <p>ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN</p> <p>Phase III trial ongoing</p>	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	<p>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.</p> <p>ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN</p> <p>Phase III trials ongoing</p>	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	<p>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.</p> <p>ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN</p> <p>Phase III trials ongoing</p>	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) for detection of prostate cancer	Patients undergoing digital rectal examinations for prostate cancer screening	<p>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 PROGENSA PCA3 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.”</p> <p>Gen-Probe, Inc., San Diego, CA</p> <p>FDA approved Feb 2012; Conformité Européene (CE) marked in 2006</p>	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	<p>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 treatment of 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.</p> <p>Millennium Pharmaceuticals, Inc., subsidiary of Takeda Pharmaceutical Co., Ltd., Osaka, Japan</p> <p>Phase II and phase III trials ongoing</p>	<p>Alemtuzumab Brentuximab vedotin (ALCL subtype only) Bortezomib Cyclosporine (angioimmunoblastic T-cell lymphoma subtype only) Denileukin diftitox Gemcitabine Pralatrexate Radiation therapy Romidepsin</p>	Increased overall survival Increased progression-free 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	<p>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.</p> <p>Bellicum Pharmaceuticals, Inc., Houston, TX</p> <p>Phase I/II trial completed</p>	Abiraterone Cabazitaxel Docetaxel 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	<p>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.</p> <p>Service de Chirurgie Thoracique, Hôpital Européen Georges Pompidou, Paris, France</p> <p>Procedure rarely done in U.S.; a randomized trial is beginning</p>	Physical therapy Compression garments	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	<p>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.</p> <p>U-Systems, Inc., Sunnyvale, CA</p> <p>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</p>	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)	<p>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).</p> <p>Pfizer, Inc., New York, NY</p> <p>Phase III trials ongoing; FDA approved Jan 27, 2012, for RCC that has not responded to prior treatment</p>	Sorafenib 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	<p>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.</p> <p>Peregrine Pharmaceuticals Inc., Tustin, CA</p> <p>Phase II trials completed; investigator-sponsored phase I trial ongoing</p>	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	<p>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.</p> <p>Peregrine Pharmaceuticals Inc., Tustin, CA</p> <p>Phase II trials ongoing</p>	<p>Carboplatin Docetaxel Erlotinib Paclitaxel Pemetrexed</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
Bavituximab for treatment of advanced pancreatic cancer	Patients in whom advanced pancreatic cancer has been diagnosed	<p>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.</p> <p>Peregrine Pharmaceuticals, Inc., Tustin, CA</p> <p>Phase II trials ongoing</p>	<p>Gemcitabine</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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	<p>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.</p> <p>Peregrine Pharmaceuticals, Inc., Tustin, CA</p> <p>Phase I/II trials ongoing</p>	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	<p>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.</p> <p>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland, in collaboration with Abbott Laboratories, Abbott Park, IL</p> <p>Phase II trial ongoing</p>	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
<p>Bevacizumab (Avastin) for treatment of ovarian cancer</p>	<p>Patients in whom advanced or recurrent ovarian cancer has been diagnosed</p>	<p>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 (Fit-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. Administered 15 mg/kg of body weight, intravenously, every 3 weeks and intended to be used with platinum-based chemotherapy.</p> <p>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland</p> <p>Phase III trials ongoing; preliminary data from 2 phase III trials on ovarian cancer in Dec 2011 did not meet endpoints; but some trials are continuing</p>	<p>Paclitaxel plus carboplatin</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
<p>Biophotonic cervical screening system (Luviva Advanced Cervical Scan) for detection of cervical disease in adolescent females</p>	<p>Females aged 16–21 years who are sexually active</p>	<p>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.</p> <p>Guided Therapeutics, Inc., Norcross, GA</p> <p>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 PMA; company continues to pursue approval and will seek an independent panel review</p>	<p>Biopsy Colposcopy Human papillomavirus DNA test Pap test</p>	<p>Earlier detection of cervical disease Improved screening and followup adherence Reduced unnecessary referrals to biopsy and colposcopy</p>

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	<p>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.</p> <p>Micromet, Inc., Rockville, MD, acquired in Jan 2012 by Amgen, Thousand Oaks, CA</p> <p>Phase II trials ongoing; FDA granted orphan drug status</p>	<p>Relapsed/refractory ALL:            Anthracyclines (doxorubicin, daunorubicin),            Asparaginase            Cyclophosphamide            cytarabine (ara-C)            Etoposide, teniposide)            Vincristine            Minimal residual disease–positive ALL:            No current standard of care</p>	<p>Increased overall survival            Increased progression-free survival            Improved quality of life</p>
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	<p>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.</p> <p>Mayo Clinic, Rochester, MN</p> <p>Unphased small trial ongoing</p>	Standard external beam radiation therapy	<p>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</p>

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 advanced nonsmall cell lung cancer (NSCLC) has been diagnosed	<p>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<sup>2</sup> 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 antitumor responses are observed.</p> <p>Merck KGaA, Darmstadt, Germany Oncothyreon, Seattle, WA</p> <p>Phase III trials restarted in 2011 after being halted for about a year</p>	<p>Bevacizumab Cetuximab Cisplatin Docetaxel Erlotinib Gefitinib Gemcitabine Irinotecan Paclitaxel Pemetrexed Vinorelbine</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
BRAF kinase inhibitor (dabrafenib) for treatment of metastatic melanoma	Patients in whom metastatic melanoma characterized as having activated <i>BRAF</i> mutations has been diagnosed	<p>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.”</p> <p>GlaxoSmithKline, Middlesex, UK</p> <p>Phase III trials ongoing for melanoma; phase I and II trials ongoing for other solid tumors</p>	<p>High dose interleukin-2 Dacarbazine (DTIC-Dome) Ipilimumab Vemurafenib</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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 <i>BRAF</i> mutations has been diagnosed	<p>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<sup>V600E</sup> mutation. It has no effect on tumor cells that lack the V600E mutation.</p> <p>F. Hoffmann-La Roche Ltd., Basel, Switzerland Roche Molecular Systems, Inc., Pleasanton, CA</p> <p>First BRAF inhibitor to be FDA approved; approved Aug 2011 for treatment of unresectable or metastatic melanoma with BRAF<sup>V600E</sup> mutation as detected by the test approved at the same time: cobas® 4800 BRAF<sup>V600</sup> mutation automated molecular assay</p>	High dose interleukin-2 Dacarbazine (DTIC-Dome) Ipilimumab	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	<p>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) the treatment of 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) the treatment of patients with systemic ALCL after failure of at least 1 prior multi-agent chemotherapy regimen.</p> <p>Seattle Genetics, Inc., Bothell, WA</p> <p>FDA approved Aug 19, 2011, for treatment of systemic ALCL after failure of at least 1 prior multi-agent chemotherapy regimen.</p>	Allogeneic stem cell transplantation 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
Brentuximab vedotin (Adcetris) for treatment of recurrent/refractory Hodgkin's lymphoma	Patients in whom recurrent and or radiation/chemotherapy-refractory Hodgkin's lymphoma has been diagnosed	<p>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.</p> <p>Seattle Genetics, Inc., Bothell, WA</p> <p>FDA approved Aug 19, 2011, for treatment of 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</p>	Standard of care	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
Brussels sprout extract (sulforaphane) for treatment of prostate cancer	Patients with recurrent prostate cancer after radical prostatectomy or definitive radiation therapy	<p>While 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.</p> <p>Oregon Health Sciences University, Portland</p> <p>Phase II trial ongoing</p>	<p>Androgen deprivation therapy</p> <p>Salvage radiation therapy</p> <p>Salvage surgery</p> <p>Watchful waiting</p>	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
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	<p>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.</p> <p>Pharmacyclics, Inc., Sunnyvale, CA</p> <p>Phase II trials ongoing</p>	Various cytotoxic chemotherapy regimens combined with various immunotherapeutic drugs	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>

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	<p>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.</p> <p>Exelixis, San Francisco, CA</p> <p>Phase III trial reported as meeting primary endpoint in Oct 2011; new drug application submission to FDA expected in 2012; FDA granted orphan drug status for follicular, medullary, and anaplastic thyroid carcinoma</p>	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	<p>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.</p> <p>Exelixis, San Francisco, CA</p> <p>Phase II trials ongoing</p>	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	<p>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.</p> <p>Exelixis, San Francisco, CA</p> <p>Phase II trial ongoing</p>	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	<p>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.</p> <p>Exelixis, San Francisco, CA</p> <p>Phase II trial ongoing</p>	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	<p>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.</p> <p>Exelixis, San Francisco, CA</p> <p>Phase II trial ongoing</p>	<p>Bevacizumab Cetuximab Cisplatin Docetaxel Erlotinib Gemcitabine Paclitaxel Pemetrexed Radiotherapy Surgery Vinorelbine</p>	<p>Reduced bone metastasis Increased overall survival Increased progression-free survival Improved quality of life</p>
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	<p>Few treatment options exist for advanced or recurrent primary ovarian peritoneal or fallopian tube 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 trials.</p> <p>Exelixis, San Francisco, CA</p> <p>Phase II trial ongoing</p>	<p>Bevacizumab Chemotherapy Radiation Sorafenib Sunitinib Surgery (debulking)</p>	<p>Reduced bone metastasis Increased overall survival Increased progression-free survival Improved quality of life</p>

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	<p>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.</p> <p>Exelixis, San Francisco, CA</p> <p>Phase II and phase III trials ongoing</p>	Abiraterone Cabazitaxel Denosumab Docetaxel Radium-223 (in development)	Reduced bone metastasis Reduced bone pain Increased overall survival Increased progression-free survival Improved quality of life
Cabozantinib (XL 184) for treatment of recurrent or progressive glioblastoma multiforme	Patients in whom recurrent or progressive glioblastoma multiforme has been diagnosed	<p>No treatments for glioblastoma multiforme target MET, which may be responsible for drug resistance in patients treated with current receptor tyrosine kinase (RTK) inhibitors. Cabozantinib is an oral, small-molecule, RTK 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.</p> <p>Exelixis, San Francisco, CA</p> <p>Phase II trials ongoing</p>	Antiangiogenic therapy Chemotherapy Corticosteroids Personalized vaccination (in clinical development) Radiation Radiosurgery 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
Carbon ion beam radiation therapy for cancer	Patients with cancer amenable to treatment with radiation	<p>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.</p> <p>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</p> <p>Two carbon ion beam facilities are currently operating—1 in Japan for 10 years, and 1 that went online at University Hospital Heidelberg, Germany, in 2009. Another, planned to open in Germany in 2012, is NRoCK, the North European Radiooncological Center Kiel, Schleswig-Holstein, Germany. Ten trials are ongoing or planned in Germany. In the U.S., Colorado State University announced in 2010 a partnership with the Japanese center to perform carbon ion therapy research; collaborations among several hospitals in Michigan and Ohio to explore developing carbon ion centers were announced in 2008, but further development is unclear at this time.</p>	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 for treatment of multiple myeloma	Patients in whom recurrent or treatment-refractory multiple myeloma has been diagnosed	<p>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 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.</p> <p>Onyx Pharmaceuticals, Emeryville, CA</p> <p>Phase III trials ongoing; FDA granted fast track status; Onyx submitted new drug application (NDA) in Sept 2011 based on phase IIb data; NDA formally accepted by FDA for standard review in Nov 2011 with a decision date set for Jul 2012</p>	<p>Combination therapies Cytotoxic chemotherapies (bendamustine, cyclophosphamide, doxorubicin, melphalan, vincristine) Immunomodulatory drugs (lenalidomide, thalidomide) Proteasome inhibitors (bortezomib) Steroids (dexamethasone, prednisone)</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
CD40 agonist (CP-870,893) for treatment of pancreatic cancer	Patients in whom unresectable pancreatic cancer has been diagnosed	<p>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. While 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.</p> <p>Pfizer, Inc., New York, NY, in collaboration with University of Pennsylvania, Philadelphia</p> <p>Phase I trial complete; 2nd phase I trial registered, not yet recruiting</p>	<p>Gemcitabine monotherapy Gemcitabine plus erlotinib</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
CD56-specific antibody-drug conjugate (IMGN901) for treatment of multiple myeloma	Patients in whom CD56-positive relapsed or relapsed/refractory multiple myeloma has been diagnosed	<p>Patients in whom relapsed multiple myeloma has been diagnosed have few treatment options and median survival of less than 1 year. 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, IMGN901 is being administered as an adjunct to a conventional cytotoxic chemotherapy regimen of lenalidomide and dexamethasone.</p> <p>ImmunoGen, Inc., Waltham, MA</p> <p>Phase I trial ongoing; FDA granted orphan drug status</p>	Lenalidomide plus dexamethasone	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
CD56-specific antibody-drug conjugate (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	<p>The 5-year survival rate for patients in whom SCLC is diagnosed is only about 15%. 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, IMGN901 is being administered as an adjunct to a conventional cytotoxic chemotherapy regimen (carboplatin plus etoposide).</p> <p>ImmunoGen, Inc., Waltham, MA</p> <p>Phase I/II trial ongoing; FDA granted orphan drug status</p>	Carboplatin plus etoposide	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>

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	<p>While 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.</p> <p>University of Pennsylvania, Philadelphia</p> <p>Case studies reported</p>	Allogeneic stem cell transplant	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
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	<p>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.</p> <p>ArQule, Inc., Woburn, MA</p> <p>Phase II trial ongoing</p>	Placebo	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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 locally advanced or metastatic gastric cancer	Patients with locally advanced or metastatic gastric cancer that has progressed after prior 1st-line chemotherapy	<p>No effective treatment is available for this patient population whose prognosis is poor. 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.</p> <p>ArQule, Inc., Woburn, MA, in collaboration with Kyowa Hakko Kirin Co., Tokyo, Japan</p> <p>Phase II trial ongoing</p>	Capecitabine Irinotecan Oxaliplatin	Increased overall survival Increased progression-free survival Improved quality of life
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	<p>While 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.</p> <p>ArQule, Inc., Woburn, MA in collaboration with Daiichi Sankyo, Tokyo, Japan</p> <p>Phase I/II trial ongoing</p>	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
C-Met kinase inhibitor (tivantinib) for treatment of non-small cell lung cancer	Patients in whom advanced non-small cell lung cancer (NSCLC) has progressed or recurred after chemotherapy	<p>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 treatment of NSCLC.</p> <p>ArQule, Inc., Woburn, MA (developer) Daiichi Sankyo, Tokyo, Japan (performing testing)</p> <p>Phase III trials ongoing</p>	<p>Second line comparators: Erlotinib monotherapy Docetaxel Pemetrexed</p> <p>Third-line comparator: Erlotinib monotherapy</p>	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>COLD-PCR amplification for detection of small quantities of mutated DNA</p>	<p>Populations undergoing screening for cancer</p>	<p>Co-amplification at lower denaturing temperature polymerase chain reaction (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.</p> <p>Dana-Farber Cancer Institute, Boston, MA Transgenomic, Omaha, NE</p> <p>Firm has completed “development studies”; study in collaboration with University of Texas MD Anderson Cancer Center, Houston, initiated</p>	<p>Various methods including: Sequencing Restriction fragment length polymorphism analysis Matrix assisted laser desorption/ionization time-of-flight analysis Denaturing HPLC/Surveyor Ligation-mediated PCR Peptide nucleic acid-3-locked nucleic acids Antiprimer quenching real-time PCR</p>	<p>Earlier detection of cancer presence</p>
<p>Combined digital breast tomography and diffuse optical tomography for diagnosing breast cancer</p>	<p>Patients who are undergoing followup diagnostic imaging for breast cancer after a suspicious result on mammography screening</p>	<p>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.</p> <p>Multiple manufacturers</p> <p>Early phase trials</p>	<p>Computed tomography Digital breast tomography alone Diffuse optical tomography alone MRI Standard mammography Ultrasound</p>	<p>Increased sensitivity, leading to earlier detection and improved outcomes Increased specificity, leading to a reduced number of biopsy procedures and their attendant stress</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>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.</p> <p>Ethicon Endo-Surgery unit of Johnson &amp; Johnson, New Brunswick, NJ</p> <p>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</p>	Propofol sedation administered and monitored by anesthesiologist	Successful and safe propofol sedation without need for an anesthesiologist
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	<p>While 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.</p> <p>University of California, San Francisco</p> <p>Large randomized control trials completed</p>	Primary care physician recommended CRC screening	<p>Increased rate of adherence with CRC screening guidelines</p> <p>Reduced morbidity from CRC</p> <p>Reduced mortality from CRC</p> <p>Reduced costs of care through earlier intervention</p> <p>Reduced health disparities</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cordycepin (OVI-123) for treatment of refractory acute lymphoblastic leukemia	Patients in whom refractory negative acute lymphoblastic leukemia (ALL) has been diagnosed	<p>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 one of the hallmarks 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.</p> <p>OncoVista Innovative Therapies, Inc., San Antonio, TX</p> <p>Phase I/II trial initiated, but on hold due to limited capital resources; firm intends to reinstate trial in 2012; FDA granted orphan drug status for ALL</p>	<p>Allogeneic bone marrow transplant Asparaginase Chemotherapy Dasatinib Imatinib Nilotinib Nelarabine Radiation Steroids</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
Cotara (131 iodine-chTNT-1/B-linked monoclonal antibody) for treatment of glioblastoma multiforme	Patients in whom glioblastoma multiforme has been diagnosed	<p>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.</p> <p>Peregrine Pharmaceuticals, Inc., Tustin, CA</p> <p>Phase II trials completed</p>	<p>Personalized therapeutic vaccines (investigational) Radiotherapy Temozolomide</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
CP-4126 (CO-101) for treatment of advanced pancreatic cancer	Patients in whom advanced pancreatic cancer has been diagnosed	<p>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.</p> <p>Clavis Pharma ASA, Oslo, Norway Clovis Oncology, Boulder, CO</p> <p>Phase II trials ongoing</p>	<p>Gemcitabine</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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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 treatment of advanced, unresectable NSCLC as an adjunct to chemotherapy. Given by injection.  OncoGenex Pharmaceuticals, Inc., Bothell, WA Teva Pharmaceutical Industries Ltd., Jerusalem, Israel  Phase II trials completed; phase III trials being planned	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., Jerusalem, Israel  Phase III trials (SATURN and SYNERGY) ongoing under FDA special protocol assessment; FDA granted fast track status	Standard chemotherapy Abiraterone Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
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 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	Surgical resection Radiation therapy with adjuvant chemotherapy (cisplatin)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Denosumab (Xgeva) for prevention of cancer-related bone fractures and pain	Patients in whom bone metastases have been diagnosed	<p>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.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>FDA approved Nov 2010 to help prevent fractures and slow bone disease in patients with solid tumors</p>	Pamidronic acid Zoledronic acid	Delayed skeletal related events Improved quality of life
Depot antiandrogen formulation (Liproca) for treatment of localized prostate cancer	Patients in whom localized prostate cancer has been diagnosed	<p>Prostate cancer often responds to treatment with antiandrogens; however, these treatments have significant side effects due to systemic exposure to the antiandrogen. Liproca® is a depot formulation of 2-hydroxyflutamide, which is prepared in a calcium sulfate paste that cures upon local injection to the prostate. Local administration of flutamide could provide higher local doses of antiandrogen as well as avoid systemic exposure to the drug.</p> <p>LIDDS AB, Helsingborg, Sweden</p> <p>Phase I/II trial complete</p>	Bicalutamide Flutamide	Equivalent progression-free survival to systemic antiandrogens Equivalent overall survival to systemic antiandrogens Reduced systemic side effects relative to systemic antiandrogens Improved quality of life

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Digital breast tomosynthesis for mammography screening	Women undergoing routine mammography to screen for breast cancer	<p>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 one 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.</p> <p>Hologic, Inc., Bedford, MA</p> <p>FDA approved for marketing Mar 3, 2011</p>	Standard 2-D digital mammography	<p>Increased sensitivity and specificity Increased predictive values Reduced unnecessary followup procedures</p>
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	<p>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.</p> <p>BioCancell Therapeutics, Inc., Jerusalem, Israel</p> <p>Phase IIb trial ongoing; FDA granted fast track status</p>	5-Fluorouracil/ leucovorin monotherapy Gemcitabine monotherapy	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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Dual ALK and EGFR kinase inhibitor (AP26113) for treatment of nonsmall cell lung cancer	Patients with translocation-positive nonsmall cell lung cancer (NSCLC)	<p>While 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.</p> <p>ARIAD Pharmaceuticals, Inc., Cambridge, MA</p> <p>Phase I/II trial ongoing</p>	Bevacizumab Cisplatin Crizotinib 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)	<p>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.</p> <p>Roche mtm laboratories AG, Heidelberg, Germany</p> <p>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</p>	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	<p>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).</p> <p>Celldex Therapeutics, Inc., Needham, MA</p> <p>Phase III trial ongoing</p>	Temozolomide alone	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
Electrical impedance scanner (SciBase III Electrical Impedance Spectrometer) for melanoma diagnosis	Patients in whom a suspicious skin lesion that may be melanoma has been identified	<p>Distinguishing melanoma from nonmelanotic skin lesions is difficult and requires a significant amount of training. The SciBase III Electrical Impedance Spectrometer 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.</p> <p>SciBase AB, Stockholm, Sweden</p> <p>Pivotal trial ongoing (1,200 lesions); FDA premarket approval submission planned for 2012</p>	Dermatologist diagnosis MelaFind multispectral dermatoscope (in development)	<p>Increased sensitivity and specificity for melanoma</p> <p>Improved positive and negative predictive values</p> <p>Reduction in unnecessary biopsies</p>
Electro-immunotherapy (OncoSec Medical System) for treatment of metastatic melanoma	Patients in whom metastatic melanoma has been diagnosed	<p>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.</p> <p>OncoSec Medical, Inc., San Diego, CA</p> <p>Phase II trial ongoing</p>	Dacarbazine Ipilimumab Vemurafenib	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Endocervicospscopy (office-based) for diagnosis of high-grade cervical lesions	Patients with abnormal high grade cervical cytology who have undergone unsatisfactory colposcopy and who wish to preserve their fertility	<p>Procedures to minimize the invasiveness and complications associated with treating high grade cervical lesions with unsatisfactory or negative colposcopy are needed, especially for women desiring to preserve fertility. Endocervicospscopy is the endoscopic evaluation of the endocervical mucosa, after application of acetic acid 5%, performed with an office continuous-flow hysteroscope; endocervicospscopy may be used to obtain a more precise localization of lesions and minimize the depth of cone excisions, which may result in more conservative treatment and preservation of fertility in patients.</p> <p>University of Naples Federico II, Naples, Italy</p> <p>Trial completed (95 patients; phase unstated)</p>	Blind curettage of the endocervix	<p>Reduced adverse events/complications</p> <p>Reduced pain</p> <p>Reduced recovery time</p> <p>Sparing of fertility</p>
EndoVe electrical field generator to improve chemotherapy uptake	Patients undergoing chemotherapy for solid localized tumors	<p>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.</p> <p>Mercy Hospital, Cork, Ireland</p> <p>Phase I trial ongoing for rectal cancer</p>	Conventional chemotherapy administration	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Reduced chemotherapy dose, potentially reducing side effects</p> <p>Lower costs associated with lower doses of chemotherapy</p> <p>Improved quality of life</p>

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Enkephalin (NTDDS NP2) gene therapy for chronic cancer pain	Patients experiencing intractable pain stemming from metastatic disease	<p>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.</p> <p>Diamyd Medical AB, Stockholm, Sweden</p> <p>Phase II trial ongoing</p>	Oral and intravenous opioid pain medications	<p>Reduced cancer-related pain</p> <p>Reduced side effects from pain medication</p> <p>Improved quality of life</p>
Ex vivo expanded cord blood as allogeneic bone marrow transplant for treatment of hematologic malignancies	Patients with hematologic malignancy who need a bone marrow transplant and for whom no suitable matched donor is available	<p>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. While 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.</p> <p>Mesoblast, Ltd., New York, NY</p> <p>Pilot studies completed by University of Texas MD Anderson Cancer Center, Houston; phase III trial protocol approved by FDA to begin</p>	Pooled unexpanded cord blood transplant Unexpanded cord blood transplant	<p>Improved bone marrow engraftment rate</p> <p>Improved rate of neutrophil recovery</p> <p>Improved rate of platelet recovery</p>

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)	<p>No FLT3 inhibitors are available for treatment of 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.</p> <p>Ambit Biosciences, San Diego, CA</p> <p>Phase II trial ongoing; received fast track status from FDA</p>	Cladribine, cytarabine, and granulocyte colony-stimulating factor plus or minus mitoxantrone or idarubicin Fludarabine, cytarabine, and granulocyte colony stimulating factor plus or minus idarubicin High-dose cytarabine and anthracycline Mitoxantrone, etoposide, and cytarabine	Increased overall survival Increased progression-free survival Improved quality of life
Gene-mediated cytotoxic immunotherapy for malignant glioma	Patients in whom malignant glioma has been diagnosed	<p>Median survival of patients diagnosed with malignant glioma is only about 15 months and current treatments are often unsuccessful. Gene-mediated cytotoxic immunotherapy (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 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 treatment of malignant glioma GMCI is being administered in combination with radiation therapy and surgical resection.</p> <p>Advantagene, Inc., Auburndale, MA</p> <p>Phase II trial ongoing</p>	Chemotherapy Radiation therapy Surgical resection 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
Gene-mediated cytotoxic immunotherapy for pancreatic adenocarcinoma	Patients in whom pancreatic adenocarcinoma has been diagnosed	<p>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 treatment of pancreatic cancer GMCI is being administered in combination with radiation therapy in locally advanced disease and in combination with surgical resection in surgically resectable disease.</p> <p>Advantagene, Inc., Auburndale, MA</p> <p>Phase I trial ongoing</p>	Chemotherapy Chemoradiation therapy Gemcitabine Radiation therapy Surgical resection	Increased overall survival Increased progression-free survival Improved quality of life
Gene-mediated cytotoxic immunotherapy (ProstAtak) for prostate cancer	Patients in whom intermediate to high-risk localized prostate cancer has been diagnosed	<p>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 treatment of prostate cancer GMCI is being administered in combination with radiation therapy.</p> <p>Advantagene, Inc., Auburndale, MA</p> <p>Phase III trial ongoing</p>	Androgen deprivation therapy Radiation therapy Surgical resection	Increased overall survival Increased disease-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Genetic test (Insight) for identifying ALK-activating gene fusions/mutations in patients with cancer	Patients with cancer types driven by underlying activated anaplastic lymphoma kinase (ALK) mutations	<p>Genetic test to identify mutations in the <i>ALK</i> gene. Test would allow identification of patients for whom ALK inhibitory pharmaceuticals in development might be appropriate.</p> <p>Insight Genetics, Nashville, TN</p> <p>Early phase development; available as research-use-only product; partnered with QIAGEN to produce a companion diagnostic test</p>	<p>Fluorescence in situ hybridization to identify chromosomal translocations/deletions leading to ALK fusions</p> <p>Immunohistochemistry</p> <p>Variant-specific polymerase chain reaction</p>	<p>Informed targeted therapy for cancer patients</p> <p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
Genetic test (Methylated Septin 9 Plasma DNA Test) for colorectal cancer screening	All patients undergoing routine colorectal cancer (CRC) screening	<p>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.</p> <p>Epigenomics AG, Berlin, Germany (developer) Abbott Laboratories, Abbott Park, IL (licensee)</p> <p>First-generation test kit (Epi proColon) available in Europe; 2nd-generation test kit (Epi proColon 2.0) anticipated to be available in Europe in 2011; Epigenomics submitted the 1st module of a premarket approval (PMA) application to FDA in Dec 2011; PMA is expected to be completed by the 2nd half of 2012.</p>	<p>Colonoscopy</p> <p>Computed tomographic colonography</p> <p>Fecal DNA test</p>	<p>Increased sensitivity and specificity</p> <p>Increased predictive values</p> <p>Avoided unnecessary followup procedures</p> <p>Improved adherence with colorectal screening</p> <p>Earlier intervention for identified cancer</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ghrelin receptor agonist (anamorelin) for treatment of cancer-related cachexia/anorexia	Patients in whom cancer-related cachexia/anorexia (CRCA) has been diagnosed	<p>While 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/or 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.</p> <p>Helsinn Healthcare S.A., Lugano/Pazzallo, Switzerland</p> <p>Phase III trials ongoing</p>	<p>Appetite stimulants: Cannabinoids Corticosteroids Cyproheptadine Progesterone derivatives Dietary counseling Melanocortin antagonists Metabolic disturbance modulators: Anti-cytokine antibodies Pentoxifylline Thalidomide</p>	<p>Improved lean body mass Improved muscle strength Increased body weight Increased overall survival Improved quality of life</p>
Gonadotropin-releasing hormone analogs for prevention of chemotherapy-induced menopause	Women undergoing systemic chemotherapy for cancer	<p>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.</p> <p>SWOG, Ann Arbor, MI, and International Breast Cancer Study Group IBCSG, Bern, Switzerland</p> <p>Phase III trial complete</p>	No standard therapies available	<p>Decreased rate of amenorrhea at 12 months post-chemotherapy Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
GSK1572932A vaccine for treatment of 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	<p>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.</p> <p>GlaxoSmithKline, Middlesex, UK</p> <p>Phase III trial ongoing</p>	Surgery Chemotherapy Radiation therapy	Increased overall survival Increased progression-free survival Improved quality of life
HER2-dimerization inhibitor (pertuzumab) for treatment of metastatic breast cancer	Patients with metastatic HER2-positive breast cancer who are receiving 1st-line trastuzumab and docetaxel	<p>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 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 diagnosed with metastatic breast cancer.</p> <p>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland</p> <p>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 decision date is Jun 8, 2012</p>	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 human leukocyte antigen (HLA)-A2 and/or HLA-A3 positive early stage breast cancer	<p>While many patients in whom early-stage breast cancer has been diagnosed achieve remission after 1st-line chemotherapy, a significant proportion eventually have disease recurrence. While 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.</p> <p>RXi Pharmaceuticals Corp., Worcester, MA</p> <p>Phase III ongoing under FDA special protocol assessment</p>	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	<p>While 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; Ceplene 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.</p> <p>EpiCept Corp., Tarrytown, NY</p> <p>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</p>	No consensus treatment exists for postremission patients.	Decrease in 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	<p>While 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. While multiple HDAC inhibitors have come to market, none are approved for the treatment of 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.</p> <p>Acetylon Pharmaceuticals, Inc., Boston, MA</p> <p>Phase I/II trial ongoing</p>	<p>Various chemotherapies, singly and/or in various combinations at standard or high doses:</p> <p>Bendamustine Bortezomib Cisplatin Cyclophosphamide Dexamethasone Doxorubicin Etoposide Lenalidomide Thalidomide</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
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	<p>While treatments for multiple myeloma have improved, the median life expectancy for patients in whom multiple myeloma is diagnosed is only 5 to 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. While 2 HDAC inhibitors (vorinostat and romidepsin) have been approved for treatment of cutaneous T-cell lymphoma, no HDAC inhibitor is currently approved for treatment of multiple myeloma. In an ongoing registration-phase clinical trial, panobinostat is being tested in combination with the proteasome inhibitor bortezomib and the glucocorticosteroid dexamethasone.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Phase III trial ongoing</p>	<p>Various chemotherapies, singly and/or in various combinations at standard or high doses:</p> <p>Bendamustine Bortezomib Cisplatin Cyclophosphamide Dexamethasone Doxorubicin Etoposide Lenalidomide Thalidomide</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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	<p>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.</p> <p>S*BIO Pte, Ltd., Singapore</p> <p>Phase II trial ongoing</p>	Abiraterone Docetaxel 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	<p>While 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. While 2 HDAC inhibitors (vorinostat and romidepsin) have been approved for treatment of cutaneous T-cell lymphoma, no HDAC inhibitor is currently approved for treatment of 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.</p> <p>Merck &amp; Co. Inc., Whitehouse Station, NJ</p> <p>Phase III trial ongoing; preliminary results released in Dec 2011 indicated that vorinostat met its primary endpoint of extending progression-free survival (PFS was extended by 25 days)</p>	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 (ganetespi) for treatment of advanced nonsmall cell lung cancer	Patients with treatment-resistant, advanced or metastatic nonsmall cell lung cancer (NSCLC)	<p>Patients with advanced NSCLC that has progressed after prior chemotherapy have a poor prognosis and few treatment options. Ganetespi 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, ganetespi is being tested as an adjunct to the cytotoxic agent docetaxel.</p> <p>Synta Pharmaceuticals Corp., Lexington, MA</p> <p>Phase II/III trial ongoing</p>	Docetaxel monotherapy	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
Huachansu for treatment of pancreatic cancer	Patients in whom pancreatic cancer has been diagnosed	<p>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.</p> <p>University of Texas MD Anderson Cancer Center, Houston</p> <p>Phase II trial ongoing</p>	5-Fluorouracil/ leucovorin Gemcitabine alone	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
Human papillomavirus vaccination (Gardasil) for prevention of anal cancer	Males and females 9–26 years of age	<p>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.</p> <p>Merck &amp; Co., Inc., Whitehouse Station, NJ</p> <p>FDA granted supplemental approval Dec 2010 for prevention of anal cancer</p>	<p>Abstinence from anal intercourse Abstinence from sexual activity Safer sex practices</p>	<p>Decreased rate of anal intraepithelial neoplasia Decreased rate of anal cancer</p>

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	<p>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.</p> <p>Threshold Pharmaceuticals, South San Francisco, CA</p> <p>Phase III trial ongoing in soft tissue sarcoma; also under study in other cancer types including pancreatic cancer</p>	Doxorubicin monotherapy	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
Immunomodulator (Imprime PGG) for treatment of advanced colorectal cancer	Patients in whom advanced colorectal cancer (CRC) has been diagnosed	<p>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.</p> <p>Biothera, Eagan, MN</p> <p>Phase III trial ongoing</p>	Cetuximab monotherapy	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
Immunotherapy (Arcelis) for treatment of renal cell carcinoma	Patients in whom renal cell carcinoma has been diagnosed	<p>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.</p> <p>Argos Therapeutics, Inc., Durham, NC</p> <p>Phase III trial planned</p>	Interferon alpha Interleukin-2 Monoclonal antibodies Surgery	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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; 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
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	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)	<p>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.</p> <p>Stemline Therapeutics, Inc., New York, NY</p> <p>Phase I/II trial complete; FDA granted orphan drug status</p>	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 (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	<p>Patients in whom advanced ovarian cancer has been diagnosed often have recurrent disease and a poor prognosis. EGEN-001 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.</p> <p>EGEN, Inc., Huntsville, AL</p> <p>Phase II trial ongoing; FDA granted orphan drug status</p>	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
<p>Irreversible electroporation (NanoKnife) for treatment of hepatocellular carcinoma</p>	<p>Patients in whom early-stage hepatocellular carcinoma (HCC) that is not surgically resectable has been diagnosed</p>	<p>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 treatment of HCC, irreversible electroporation is performed in a minimally invasive laparoscopic procedure.</p> <p>AngioDynamics, Latham, NY</p> <p>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</p>	<p>Cryotherapy RF ablation</p>	<p>Increased overall survival Increased clinical downstaging to surgically resectable tumor Improved adverse event profile Improved quality of life</p>

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	<p>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 treatment of pancreatic cancer, irreversible electroporation is performed in a minimally invasive laparoscopic procedure.</p> <p>AngioDynamics, Latham, NY</p> <p>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</p>	Cryotherapy RF ablation	<p>Increased overall survival Increased rate of clinical downstaging to surgically tumor Improved adverse event profile Improved quality of life</p>
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	<p>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.</p> <p>Incyte Corp., Wilmington, DE in collaboration with Novartis AG, Basel, Switzerland</p> <p>FDA approved Nov 2011; 1<sup>st</sup> quarter 2012 sales from product launch suggest rapid acceptance by physicians and patients</p>	None Off-label treatments are only palliative	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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	<p>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.</p> <p>S*Bio Pte, Ltd., Singapore</p> <p>Phase II trial complete</p>	Ruxolitinib	<p>Increased overall survival Increased progression-free survival Reduced spleen size Improved quality of life</p>
Kinase inhibitor (ENMD-2076) for platinum-based treatment-resistant ovarian cancer	Patients in whom ovarian cancer has been diagnosed	<p>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).</p> <p>EntreMed, Inc., Rockville, MD</p> <p>Phase II trial ongoing; FDA granted orphan drug status</p>	<p>Carboplatin Carboplatin/docetaxel Carboplatin/gemcitabine Carboplatin/liposomal doxorubicin Carboplatin/paclitaxel Cisplatin Cisplatin/gemcitabine Docetaxel Etoposide Gemcitabine Liposomal doxorubicin Paclitaxel Topotecan</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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	<p>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. While 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.</p> <p>DARA BioSciences, Inc., Raleigh, NC</p> <p>Phase II trial completed; FDA granted fast-track status</p>	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	<p>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. Has shown strong anticancer activity in mice bearing human liver tumors; taken orally.</p> <p>Apricus Biosciences, Inc., San Diego, CA</p> <p>Phase III trial special protocol assessment under discussion with FDA; FDA granted orphan drug status</p>	Doxorubicin Nexavar	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	<p>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.</p> <p>Bayer AG, Leverkusen, Germany</p> <p>Multiple trials ongoing</p>	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 for treatment of cancer	Patients in whom advanced solid malignancies have been diagnosed	<p>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 tumor growth and/or angiogenesis. Atu027 is administered by intravenous infusion.</p> <p>Silence Therapeutics, plc, London, UK</p> <p>Phase I trial ongoing</p>	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	<p>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.</p> <p>Merrimack Pharmaceuticals, Inc., Cambridge, MA</p> <p>Phase III trial ongoing; FDA granted orphan drug status for 2nd-line treatment of pancreatic cancer</p>	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 Philadelphia-chromosome-negative acute lymphoblastic leukemia (ALL) who are experiencing their 2nd or 3rd relapse	<p>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.</p> <p>Talon Therapeutics, Inc., San Mateo, CA</p> <p>Phase III trial complete in salvage setting; phase III trial ongoing in frontline setting; new drug application submitted to FDA; FDA's Oncology Drugs Advisory Committee recommended approval in Mar 2012; FDA granted Marqibo orphan drug status for treatment of ALL in the salvage setting</p>	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	<p>Liver cancer is largely refractory to standard systemic chemotherapy; while targeted chemotherapy delivery options are available for treatment of 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.</p> <p>Delcath Systems, New York, NY</p> <p>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 intends to refile NDA in 2nd quarter 2012; Conformité Européene (CE) marked for liver cancer</p>	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
<p>MarginProbe System for intraoperative identification of positive margins during breast cancer lumpectomy</p>	<p>Patients undergoing breast lumpectomy</p>	<p>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.</p> <p>Dune Medical Devices, Inc., Framingham, MA</p> <p>Pivotal trial completed; premarket approval application submitted May 2011; FDA granted expedited review; FDA's General &amp; Plastic Surgery Devices advisory panel scheduled to meet on the application June 21, 2012; system is available in Europe</p>	<p>No currently marketed comparator in the U.S.</p>	<p>Reduced number of re-excision surgeries performed Improved rate of complete surgical resection (e.g., no positive margin)</p>
<p>Marine depsipeptide (plitidepsin) for treatment of relapsed/refractory multiple myeloma</p>	<p>Patients with multiple myeloma who have undergone at least 3 treatments, including bortezomib- and lenalidomide-based regimens</p>	<p>While 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 <i>Aplidium albicans</i>. 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 treatment of multiple myeloma, plitidepsin is being administered by infusion at a dose of 5 mg/m<sup>2</sup> in combination with orally administered dexamethasone.</p> <p>PharmaMar subsidiary of Grupo Zeltia, Madrid, Spain</p> <p>Phase III trial ongoing</p>	<p>Various chemotherapy regimens such as: Bendamustine/ bortezomib Bortezomib/ dexamethasone Cyclophosphamide/ lenalidomide/ dexamethasone Dexamethasone/ cyclophosphamide/ etoposide/cisplatin High-dose cyclophosphamide Lenalidomide/ dexamethasone Thalidomide/ dexamethasone</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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	<p>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 the treatment of various cancers, including ovarian cancer, colorectal cancer, melanoma, nonsmall cell lung cancer, and hepatocellular carcinoma.</p> <p>AstraZeneca, London, UK</p> <p>Phase II trials ongoing</p>	Standard chemotherapy regimens	Increased overall survival Increased progression-free survival Improved quality of life
MEK inhibitor (trametinib) for treatment of advanced melanoma with activating <i>BRAF</i> mutation	Patients with stage IIIc or IV malignant cutaneous melanoma that harbors an activating <i>BRAF</i> mutation	<p>Patients with metastatic melanoma have a poor prognosis with current treatments yielding a 5-year survival rate of less than 10%. Melanomas harboring activating <i>BRAF</i> 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.</p> <p>GlaxoSmithKline, Middlesex, UK</p> <p>Phase III trial as a monotherapy versus standard chemotherapy was reported to have met its primary endpoint in early 2012; phase II trial ongoing in patients previously treated with a <i>BRAF</i> inhibitor; phase II trial ongoing in combination with the <i>BRAF</i> inhibitor dabrafenib</p>	High dose interleukin-2 Dacarbazine (DTIC-Dome) Ipilimumab 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	<p>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.</p> <p>GlaxoSmithKline, Middlesex, UK</p> <p>Phase II trial ongoing</p>	Gemcitabine alone	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
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	<p>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. While 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.</p> <p>Sanofi, Paris, France</p> <p>Phase III trial ongoing</p>	<p>No consensus 2nd-line treatment for soft tissue sarcoma Placebo Pazopanib (in development) Sorafenib (off label) Sunitinib (off label)</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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	<p>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).</p> <p>Cornerstone Pharmaceuticals, Inc., Cranbury, NJ</p> <p>Phase I trial ongoing in hematologic malignancies; phase I/II trial ongoing in pancreatic cancer; FDA granted orphan drug status for AML and pancreatic cancer</p>	Various chemotherapy regimens	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
Mobile telemedicine for cervical screening	Patients in rural areas in need of routine cervical screening	<p>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.</p> <p>Department of Dermatology, University of Pennsylvania, Philadelphia</p> <p>Pilot study conducted in Gaborone, Botswana</p>	Pap (Papanicolaou) screening VIA	<p>Reduced cost of care</p> <p>Increased rate of cervical cancer screening</p> <p>Reduced rates of cervical disease</p> <p>Increased screening adherence</p>

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	<p>Despite numerous 1st-line treatment options for breast cancer, many women experience disease recurrence; therefore, there is a need 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.</p> <p>Antigen Express, Inc., Worcester, MA</p> <p>Phase IIb trial ongoing</p>	Trastuzumab	<p>Increased overall survival                      Increased progression-free survival                      Reduced breast cancer recurrence                      Improved quality of life</p>
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	<p>For patients whose breast cancer progresses following treatment with 1st-line 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 the treatment of 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.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Phase III trial ongoing; preliminary results released in Sept 2011 indicated that everolimus met its primary endpoint of increasing progression-free survival; a supplemental new drug application for everolimus is expected to be filed in 2012</p>	Exemestane monotherapy	<p>Increased overall survival                      Increased progression-free survival                      Improved quality of life</p>

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	<p>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 treatment of renal cell carcinoma and subependymal giant cell astrocytomas. It is proposed for treatment of PNETs. In clinical trials of patients with PNETs, everolimus was administered in a daily, oral dose of 10 mg.</p> <p>Novartis AG, Basel, Switzerland</p> <p>FDA approved May 2011 for treatment of PNETs</p>	5-Fluorouracil Capecitabine Dacarbazine Doxorubicin Streptozocin Sunitinib Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life
mTOR inhibitor (ridaforolimus, Taltorvic) for treatment of soft tissue and bone sarcomas	Patients with metastatic soft tissue and bone sarcomas who have previously had a positive response to systemic chemotherapy	<p>While many soft tissue and bone sarcomas initially respond to chemotherapy, most cancers develop resistance and recur. Ridaforolimus is a small-molecule inhibitor of the protein mammalian target of rapamycin (mTOR), which plays a central role in the regulation of cell growth; while various mTOR inhibitors have been approved for cancer indications in the U.S., no mTOR inhibitor has been approved for treatment of soft tissue and bone sarcomas.</p> <p>ARIAD Pharmaceuticals, Inc., Cambridge, MA, in collaboration with Merck &amp; Co., Inc., Whitehouse Station, NJ</p> <p>Phase III trial ongoing; new drug application submitted to FDA and accepted for standard review in Oct 2011; FDA's Oncologic Drugs Advisory Panel advised against approval in Mar 2012; a final decision is scheduled for June 5, 2012</p>	No currently approved therapy in the maintenance therapy setting	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	<p>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.</p> <p>Prima BioMed, Ltd., Melbourne, Australia</p> <p>Phase II/III trial ongoing</p>	Bevacizumab Paclitaxel	Increased of overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
MUC1 therapeutic vaccine (TG4010) for nonsmall cell lung cancer	Patients with chemotherapy-naïve nonsmall cell lung cancer (NSCLC) who are mucin-1 (MUC-1)-positive	<p>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.</p> <p>Transgene SA, Cedex, France</p> <p>Phase IIb/III trial ongoing; FDA granted fast track status</p>	Melanoma antigenic epitope-A3 therapeutic vaccine (in development) Paclitaxel/carboplatin	Increased overall survival Increased progression-free survival Improved quality of life
Multikinase inhibitor (brivanib) for treatment of hepatocellular carcinoma	Patients in whom hepatocellular carcinoma (HCC) has been diagnosed	<p>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 treatment of 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).</p> <p>Bristol-Myers Squibb, New York, NY</p> <p>Phase III trials ongoing; phase III trial in the 2nd-line setting failed to meet its primary endpoint; however, additional phase III trials continue</p>	Sorafenib alone TACE 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
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)	<p>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 treatment of 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.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Phase III trial ongoing</p>	Sorafenib	<p>Increased overall survival                      Increased progression-free survival                      Improved quality of life</p>
Multikinase inhibitor (lenvatinib) for treatment of differentiated thyroid cancer	Patients with differentiated thyroid cancer that is resistant to radioiodine therapy	<p>Differentiated thyroid cancer (e.g., papillary, follicular) comprises the majority of diagnosed thyroid cancers. While 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.</p> <p>Eisai Co., Ltd., Tokyo, Japan</p> <p>Phase III trial ongoing</p>	Pazopanib (off label) Sorafenib (off label) Sunitinib (off label)	<p>Increased overall survival                      Increased progression-free survival                      Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multikinase inhibitor (masitinib) for treatment of activating <i>c-KIT</i> mutation-positive, metastatic melanoma	Patients with non-resectable or metastatic melanoma that harbors an activating mutation in the <i>c-KIT</i> gene	<p>A subset of melanomas harbor an activating mutation in the <i>c-KIT</i> 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 <i>c-KIT</i> mutations. While KIT kinase inhibitors have been developed for other cancers dependent on KIT activity (e.g., imatinib for treatment of gastrointestinal stromal tumors), currently no KIT kinase inhibitor is approved for treatment of <i>c-KIT</i> 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 treatment of melanoma.</p> <p>AB Science S.A., Paris, France</p> <p>Phase III trial ongoing</p>	Dacarbazine Interleukin-2 Ipilimumab Nilotinib (in development)	Increased overall survival Increased progression-free survival Improved quality of life
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 <i>FLT3</i> gene (ITD- <i>FLT3</i> )	<p>The presence of activating <i>FLT3</i> 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.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Phase III trial ongoing</p>	Cytarabine/ daunorubicin	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multikinase inhibitor (nilotinib, Tassigna) for treatment of activating <i>c-KIT</i> mutation-positive, metastatic melanoma	Patients with non-resectable or metastatic melanoma who harbor an activating <i>c-KIT</i> mutation	<p>A subset of melanomas harbor an activating mutation in the <i>c-KIT</i> 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 <i>c-KIT</i> mutations. While KIT kinase inhibitors have been developed for other cancers dependent on KIT activity (e.g., imatinib for treatment of gastrointestinal stromal tumor), currently no KIT kinase inhibitor is approved for treatment of <i>c-KIT</i> mutation-positive melanoma. Nilotinib (Tassigna®) is an orally administered, tyrosine kinase inhibitor approved for the treatment of 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 treatment of melanoma.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Phase II trials ongoing</p>	Dacarbazine Interleukin-2 Ipilimumab Masitinib (in development)	Increased overall survival Increased progression-free survival Improved quality of life
Multikinase inhibitor (nintedanib, Vargatef) for chemotherapy-resistant ovarian cancer	Patients in whom chemotherapy-naive treatment-resistant ovarian cancer has been diagnosed	<p>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.</p> <p>Boehringer Ingelheim GmbH, Ingelheim, Germany</p> <p>Phase III trial ongoing</p>	Intraperitoneal carboplatin/paclitaxel Intravenous carboplatin/paclitaxel	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>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.</p> <p>Boehringer Ingelheim GmbH, Ingelheim, Germany</p> <p>Phase III trials ongoing</p>	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 to IV ovarian cancer, fallopian tube, or primary peritoneal carcinoma who have undergone surgical debulking and successful treatment with platinum agent/taxane combination therapy	<p>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.</p> <p>GlaxoSmithKline, London, UK</p> <p>Phase III trial ongoing; FDA approved for renal cell carcinoma</p>	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	<p>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).</p> <p>Bayer AG, Leverkusen, Germany</p> <p>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 phase III trial</p>	Nilotinib 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	<p>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., imatinib, sunitinib).</p> <p>Bayer AG, Leverkusen, Germany</p> <p>Phase II trial ongoing</p>	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	<p>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., imatinib, sunitinib).</p> <p>Bayer AG, Leverkusen, Germany</p> <p>Phase III trial for salvage therapy was reported as having met its primary endpoint in Oct 2011; FDA has granted regorafenib fast-track status for this indication; phase II trial for 1st-line therapy ongoing</p>	<p>First-line therapy comparators include: FOLFOX (folinic acid [leucovorin], 5-fluorouracil [5-FU], oxaliplatin) alone FOLFOX plus targeted therapy (e.g., bevacizumab, cetuximab, panitumumab)</p> <p>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])</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
Multikinase inhibitor (regorafenib) for treatment of renal cell carcinoma	Patients in whom metastatic or unresectable renal cell carcinoma (RCC) has been diagnosed	<p>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., imatinib, sunitinib).</p> <p>Bayer AG, Leverkusen, Germany</p> <p>Phase II trial ongoing</p>	<p>Bevacizumab plus or minus interferon High-dose interleukin-2 Pazopanib Sorafenib Sunitinib Temsirrolimus</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Multikinase inhibitor (sunitinib, Sutent) for treatment of pancreatic neuroendocrine tumors</p>	<p>Patients with surgically unresectable pancreatic neuroendocrine tumors (PNETs) that have progressed within the past year</p>	<p>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.</p> <p>Pfizer, Inc., New York, NY</p> <p>FDA approved May 2011 for treatment of PNETs</p>	<p>5-Fluorouracil Capecitabine Dacarbazine Doxorubicin Everolimus Streptozocin Temozolomide</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
<p>Multispectral dermoscope (MelaFind) to identify melanoma in suspect lesions</p>	<p>Patients in whom pigmented skin lesions are present requiring diagnosis</p>	<p>Computer-controlled multispectral dermoscope (MelaFind®) 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.</p> <p>MELA Sciences, Inc., Irvington, NY</p> <p>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.</p>	<p>Biopsy Physician observation of skin lesions (dermoscope)</p>	<p>Increased sensitivity and specificity Reduced number of biopsies performed on suspect lesions Earlier detection of suspect lesions Increased overall survival Improved quality of life</p>

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	<p>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 treatment of many cancers but is not labeled for treatment of NSCLC.</p> <p>Eli Lilly &amp; Co., Indianapolis, IN Bristol-Myers Squibb Co., Princeton, NJ</p> <p>Phase III trials ongoing</p>	Cetuximab (off label; not indicated for NSCLC) 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	<p>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.</p> <p>Gardasil, Merck &amp; Co., Inc., Whitehouse Station, NJ; Cervarix, GlaxoSmithKline, plc, Middlesex, UK</p> <p>Both vaccines FDA approved for prevention of cervical cancer</p>	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.	<p>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.</p> <p>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</p>	<p>Various chemotherapy regimens Various hormone therapies</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
Off-label rosuvastatin to prevent colon cancer recurrence	Patients who have had a stage I or II colon cancer surgically resected	<p>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.</p> <p>Under study by National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA, and the National Cancer Institute, Bethesda, MD</p> <p>Phase III trial ongoing</p>	<p>There is no commonly used chemopreventive agent for colorectal cancer Compounds under investigation include: Aspirin Calcium supplements Curcumin Nonsteroidal anti-inflammatory drugs Omega-3 fatty acids</p>	<p>Reduced recurrence rate of adenomatous polyps Increased overall survival</p>
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	<p>Zoledronic acid (Zometa®) is a bisphosphonate used to prevent skeletal fractures in cancer patients at risk for 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., postmenopausal patients). Given that the drug is commercially available, its off-label use for this may be an option exercised by oncologists.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Two phase III trials completed; 1 trial (ABCSSG-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</p>	<p>Chemotherapy Hormone therapy</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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 multiple myeloma	Patients in whom 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.  Novartis AG, Basel, Switzerland  Postmarket trial (NCT00432458) under way independently (of manufacturer)	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) therapy for advanced <i>KRAS</i> mutant colorectal cancer	Patients in whom advanced or metastatic <i>KRAS</i> mutant colorectal cancer (CRC) has been diagnosed	Oncolytic reovirus (Reolysin®) 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	Chemotherapy Radiation Surgery	Increased overall survival Increased progression-free survival Improved quality of life
Oncolytic reovirus (Reolysin) therapy for advanced pancreatic cancer	Patients in whom advanced pancreatic cancer has been diagnosed	Oncolytic reovirus (Reolysin®) 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	Chemotherapy Surgery	Increased overall survival Increased progression-free survival Improved quality of life
Oncolytic reovirus (Reolysin) therapy for platinum-resistant head and neck cancer	Patients in whom platinum-resistant head and neck cancer has been diagnosed	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	Chemotherapy Radiation Surgery Targeted 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
Oncolytic reovirus (Reolysin) therapy for recurrent malignant gliomas	Patients in whom recurrent malignant gliomas (brain or spinal cord tumors) have been diagnosed	<p>Oncolytic reovirus (Reolysin®) intended to treat various cancers and cell proliferative disorders, including brain cancer; replicates specifically in cells that have activated RAS. Activating mutations of RAS are believed to play a role in more than half of brain tumors. Administered in combination with folinic acid (leucovorin), 5-fluorouracil, and irinotecan combination.</p> <p>Oncolytics Biotech, Inc., Calgary, Alberta, Canada</p> <p>Phase I/II trial complete</p>	Chemotherapy Radiation Surgery	Increased overall survival Increased progression-free survival Improved quality of life
Oncolytic reovirus (Reolysin) therapy for recurrent or persistent ovarian cancer	Patients in whom recurrent or persistent ovarian, fallopian tube, or primary peritoneal cancer has been diagnosed	<p>Reolysin® is a formulation of oncolytic reovirus being developed for the treatment of 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.</p> <p>Oncolytics Biotech, Inc., Calgary, Alberta, Canada</p> <p>Phase II trial ongoing</p>	Chemotherapy Radiation	Increased overall survival Increased progression-free survival Improved quality of life
Oncolytic reovirus (Reolysin) therapy for refractory solid tumors in children	Pediatric patients in whom relapsed or refractory solid tumor has been diagnosed	<p>Reolysin® is a formulation of oncolytic reovirus being developed for treatment of 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.</p> <p>Oncolytics Biotech Inc., Calgary, Alberta, Canada</p> <p>Phase I trial ongoing</p>	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	<p>While the availability of treatments such as B-RAF 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.</p> <p>Viralitics, Ltd., Pymble, New South Wales, Australia</p> <p>Phase II trial ongoing</p>	Dacarbazine Ipilimumab 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	<p>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; (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.</p> <p>Jennerex, Inc., San Francisco, CA</p> <p>Phase II trials ongoing</p>	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	<p>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<sup>8</sup> pfu/mL/per intratumoral injection in trials.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase III trial ongoing</p>	Dacarbazine or interferon Personalized vaccination (in clinical development) Proleukin (interleukin-2) Temozolomide Therapeutic vaccines (in clinical 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
Orteronel (TAK 700) for treatment of castration-resistant prostate cancer	Patients in whom castration-resistant prostate cancer (CRPC) has been diagnosed	<p>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.</p> <p>Millennium Pharmaceuticals, Inc., Cambridge, MA</p> <p>Phase III trials ongoing</p>	Abiraterone Cabazitaxel Docetaxel Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
Ovarian scanning (HistoScanning) for diagnosis of ovarian masses	Patients with a suspicious ovarian mass	<p>HistoScanning™ captures transvaginal sonographic images and analyzes them to try to determine whether the mass is benign or malignant.</p> <p>Advanced Medical Diagnostics S.A./NV, Waterloo, Belgium</p> <p>Early phase trials ongoing</p>	Doppler transvaginal sonography Exploratory surgery Visual analysis of mass morphology	Increased sensitivity and specificity More accurate referral for followup Avoid unnecessary diagnostic followup and unnecessary treatment
<i>P53</i> activator (APR-246) for treatment of hematologic malignancies or prostate cancer	Patients with a hematologic malignancy or prostate cancer	<p><i>P53</i> is a tumor-suppressor gene that plays a prominent role in promoting apoptosis. The loss of <i>p53</i> function is associated with many cancer types; however, no therapy attempting to restore <i>p53</i> function is currently available. APR-246 is a small, peptide molecule that has been shown to promote restoration of the transcriptional activity of mutated <i>p53</i>, potentially restoring <i>p53</i> function and apoptosis of cancer cells.</p> <p>Aprea AB, Solna, Sweden</p> <p>Phase I/II trial completed</p>	Various 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
Pan-RAF inhibitor (MLN-2480) for treatment of metastatic melanoma	Patients in whom metastatic melanoma has been diagnosed	<p>The identification of activating <i>BRAF</i> 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. While targeting <i>BRAF</i> has demonstrated significant anticancer activity, its activity is limited to the subset of melanomas with activating <i>BRAF</i> mutations, and the majority of these cancers develop resistance to <i>BRAF</i> inhibition. Pan-RAF inhibition might allow targeting of a wider range of melanomas and/or overcome some of the resistance mechanisms associated with <i>BRAF</i> inhibition.</p> <p>Millennium Pharmaceuticals, Inc., subsidiary of Takeda Pharmaceutical Co., Ltd., Osaka, Japan, in collaboration with Sunesis Pharmaceuticals, South San Francisco, CA</p> <p>Phase I trial ongoing</p>	Dacarbazine Ipilimumab Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life
Partial wave spectroscopy for lung cancer screening	Patients at high risk of developing lung cancer (e.g., smokers, ex-smokers)	<p>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”).</p> <p>Northwestern University, Chicago, IL</p> <p>Preliminary validation study completed on 135 smokers</p>	No screening equivalent currently available Other tests for lung cancer screening: Chest radiograph Sputum cytology Computed tomography	Increased sensitivity and specificity Increased predictive value Avoid 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	<p>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.</p> <p>Polaris Pharma, San Diego, CA</p> <p>Phase III trial initiated under FDA special protocol assessment; FDA granted orphan drug status</p>	Placebo Regorafenib (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
Pegylated human recombinant hyaluronidase (PEG-PH20) for treatment of pancreatic cancer	Patients with metastatic pancreatic cancer and no prior treatment	<p>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 treatment of pancreatic cancer, PEG-PH20 is being administered in combination with the standard chemotherapy drug gemcitabine.</p> <p>Halozyme Therapeutics, San Diego, CA</p> <p>Phase I/II trial ongoing</p>	5-Fluorouracil/ leucovorin Gemcitabine	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	<p>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.</p> <p>MolMed, S.p.A., Milan, Italy</p> <p>Phase II trial ongoing</p>	Standard chemotherapy regimens: Cisplatin/gemcitabine Cisplatin/pemetrexed	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	<p>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.</p> <p>MolMed, S.p.A., Milan, Italy</p> <p>Phase II trial completed</p>	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	<p>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.</p> <p>MolMed, S.p.A., Milan, Italy</p> <p>Phase III trial ongoing in 2nd-line setting; phase II trial ongoing in 1st-line setting</p>	<p>Pemetrexed plus cisplatin as 1st-line treatment</p> <p>Single-agent chemotherapy as a 2nd-line treatment (e.g., doxorubicin, gemcitabine, vinorelbine)</p>	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
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	<p>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.</p> <p>MolMed, S.p.A., Milan, Italy</p> <p>Phase II trials completed</p>	<p>Standard chemotherapy: Oxaliplatin/ capecitabine</p>	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
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	<p>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.</p> <p>MolMed, S.p.A., Milan, Italy</p> <p>Phase II trial ongoing</p>	<p>Standard 2nd-line chemotherapies: Docetaxel Doxorubicin Etoposide Gemcitabine Tamoxifen Topotecan</p>	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
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	<p>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.</p> <p>MolMed, S.p.A., Milan, Italy</p> <p>Phase II trial completed</p>	<p>Doxorubicin monotherapy</p>	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>

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	<p>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.</p> <p>MolMed, S.p.A., Milan, Italy</p> <p>Phase II trial ongoing</p>	Doxorubicin monotherapy	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
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	<p>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).</p> <p>Stemline Therapeutics, Inc., New York, NY</p> <p>Phase I/II trial completed</p>	Temozolomide chemotherapy	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
Perifosine (KRX-0401) for treatment of chronic lymphocytic leukemia	Patients in whom chronic lymphocytic leukemia (CLL) has been diagnosed	<p>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.</p> <p>Keryx Biopharmaceuticals, Inc., New York, NY</p> <p>Phase II trial ongoing</p>	Chemotherapy Prednisolone Rituximab	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>

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	<p>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 treatment of several tumor types. Administered as a single oral agent and in combination with novel therapies.</p> <p>Keryx Biopharmaceuticals, Inc., New York, NY</p> <p>Phase III trials ongoing for multiple myeloma under FDA special protocol assessment</p>	Chemotherapy Stem cell transplants Steroids Newer drugs, such as lenalidomide and bortezomib	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	<p>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.</p> <p>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland</p> <p>Phase II trial ongoing</p>	Fulvestrant	Increased overall survival Increased progression-free survival Improved quality of life
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	<p>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 on treatment of symptomatic CRPC.</p> <p>Oncothyreon, Inc., Seattle, WA</p> <p>Phase II trial ongoing</p>	Docetaxel plus prednisone Docetaxel/prednisone/dasatinib (under development) Docetaxel/prednisone/lenalidomide (under 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
Photodynamic therapy (Cevira System) with hexaminolevulinate ointment for treatment of cervical intraepithelial neoplasia	Patients in whom low-grade cervical intraepithelial neoplasia has been diagnosed	<p>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.</p> <p>Photocure ASA, Oslo, Norway, in collaboration with Sagentia, Ltd., Cambridge, UK</p> <p>Phase IIb trial ongoing</p>	Cryotherapy Laser therapy Loop electrosurgical excision Surgical conization	Complete lesion eradication
Photodynamic therapy with Tookad photosensitive agent for treatment of localized prostate cancer	Patients in whom localized low-risk prostate cancer has been diagnosed	<p>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.</p> <p>Steba Biotech S.A., Cedex, France</p> <p>Phase III trial ongoing</p>	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	<p>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.</p> <p>Gilead, San Dimas, CA</p> <p>Phase III trial ongoing</p>	Cyclophosphamide, doxorubicin, vincristine and prednisolone Fludarabine with cyclophosphamide Fludarabine, cyclophosphamide, and rituximab Fludarabine with 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
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	<p>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) activity in a DNA repair pathway. No PARP inhibitors are currently on the market. It has been observed that cancers are often deficient in a 2nd arm of the DNA repair pathway, and loss of both types of DNA repair is hypothesized to result in cancer cell lethality in response to DNA damage. Iniparib is being administered in combination with a DNA damage inducing chemotherapy regimen (gemcitabine, carboplatin).</p> <p>BiPar Sciences, San Francisco, CA Sanofi, Paris, France</p> <p>Phase III trial ongoing</p>	Cytotoxic chemotherapy (e.g., gemcitabine, carboplatin) alone PARP Inhibitors in development: AG014699 CEP9722 MK 4827 Olaparib Veliparib	Increased overall survival Increased progression-free survival Improved quality of life
Polydisperse oligonucleotide (defibrotide) for treatment of chemotherapy-induced severe veno-occlusive disease	Patients receiving chemotherapy in whom severe veno-occlusive disease has been diagnosed	<p>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.</p> <p>Gentium S.p.A., Villa Guardia, Italy</p> <p>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.</p>	Analgesia Diuresis Renal replacement therapy Transfusion	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
<p>Ponatinib for treatment of chronic myelogenous leukemia or Philadelphia-chromosome-positive acute lymphoblastic leukemia</p>	<p>Patients in whom chronic myelogenous leukemia (CML) or Philadelphia chromosome–positive negative acute lymphoblastic leukemia (ALL) has been diagnosed</p>	<p>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.</p> <p>Ariad Pharmaceuticals, Inc., Cambridge, MA</p> <p>Phase II trials ongoing; regulatory filing for accelerated approval based on phase II trial data anticipated in 2012; FDA granted orphan drug status for CML and Philadelphia chromosome–positive ALL</p>	<p>Dasatinib Imatinib Nilotinib</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
<p>Positron emission tomography-based tumor hypoxia imaging to inform personalization of cancer treatment</p>	<p>Patients in whom a solid tumor has been diagnosed</p>	<p>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.</p> <p>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)</p> <p>Phase II trials ongoing</p>	<p>No currently available in vivo hypoxia imaging technology</p>	<p>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</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Positron emission tomography imaging agent (F18-ML10, EarliTest) for assessing tumor response to treatment	Patients undergoing treatment for solid tumors	<p>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.</p> <p>Aposense, Ltd., Petach Tikva, Israel</p> <p>Phase II trials ongoing</p>	<p>Circulating Tumor Cell detection Fluorodeoxyglucose computed tomography imaging MRI PET imaging</p>	<p>Correlation between EarliTest result and tumor response Correlation between EarliTest result and improved patient outcomes (e.g., overall survival, progression-free survival)</p>
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	<p>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 (adrenocorticotropic hormone) typically by pituitary, adrenal, or ectopic endocrine tumors. While 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 have no FDA-approved medical options for treatment. Mifepristone (Korlym™) acts to block the cortisol receptor, potentially ameliorating the effects of elevated cortisol levels. Mifepristone is an oral medication that was taken once daily in clinical trials.</p> <p>Corcept Therapeutics, Menlo Park, CA</p> <p>FDA approved Feb 2012 to control hyperglycemia in adults with endogenous Cushing's syndrome</p>	<p>Ketoconazole (off label) Metyrapone (off label) Mitotane (off label)</p>	<p>Improved symptoms of Cushing's syndrome (e.g., diabetes, glucose intolerance, hypertension)</p>
Prophage series G-200 therapeutic vaccine for gliomas	Patients diagnosed with primary or recurrent brain and central nervous system cancers (gliomas)	<p>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.</p> <p>Agenus, Inc., Lexington, MA</p> <p>Phase II trials ongoing in adults; phase I trial planned for pediatric brain cancers; FDA granted orphan drug status</p>	<p>Current surgery (radiation)/ chemotherapy treatments for glioblastoma multiforme</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

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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 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  Trials ongoing	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	<p>ThermoDox™ is a heat-labile liposomal encapsulation of the chemotherapeutic agent doxorubicin to induce local hyperthermia (39.5 ° to 42° C) when radiofrequency (RF) energy is applied to release the agent.</p> <p>Celsion Corp., New York, NY</p> <p>Phase III trial ongoing; National Cancer Institute recommended phase III trial as priority for HCC; granted orphan drug status by FDA Mar 2009</p>	RF tumor ablation alone Surgical resection Transcatheter arterial chemoembolization (directed chemotherapy delivery)	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	<p>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.</p> <p>Wilex AG, Munich, Germany</p> <p>Phase III trial complete</p>	CT imaging alone	Increased sensitivity and specificity for ccRCC
Radiopharmaceutical (tilmanocept) for sentinel lymph node detection	Selected patients undergoing surgical resection of primary breast, melanoma, or head and neck tumors	<p>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.</p> <p>Navidea Biopharmaceuticals (formerly NeoProbe), Dublin, OH</p> <p>Phase III trials complete. In Oct 2011, FDA accepted new drug application for review; FDA decision date set for Jun 10, 2012</p>	Technetium sulfur colloid Vital blue dye (e.g., isosulfan blue)	Increased sentinel node detection sensitivity and specificity Improved patient outcomes Optimized treatment selection

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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	<p>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.</p> <p>Algeta ASA, Oslo, Norway, in collaboration with Bayer HealthCare Pharmaceuticals, Wayne, NJ</p> <p>Phase III trial complete; new drug application submission to FDA expected in 2012; granted fast track status by FDA</p>	Standard therapy plus denosumab or cabozantinib (in development) Standard therapy with and without alpharadin	<p>Increased overall survival Increased progression-free survival Increased rate of alkaline phosphatase normalization Reduced pain from bone metastases Improved quality of life</p>
Raman spectroscopy device (Verisante Aura) for melanoma screening	Patients in whom a suspicious skin lesion has been identified	<p>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.</p> <p>Verisante Technology, Inc., Vancouver, British Columbia, Canada</p> <p>1,000 lesion clinical trial completed; approved for marketing approval in Canada and EU; company stated plans to pursue FDA approval in 2012</p>	Dermatologist visual screening MelaFind multispectral dermoscope	<p>Increased sensitivity and specificity for lesion detection Increased positive and negative predictive values Reduced unnecessary biopsies Improved quality of life</p>

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	<p>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.</p> <p>Tocagen, Inc., San Diego, CA</p> <p>Phase I/II trial ongoing</p>	BCNU Bevacizumab with or without BCNU, irinotecan, or temozolomide Nitrosurea Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life
Rexin-G for treatment of chemotherapy-resistant metastatic pancreatic cancer	Patients with gemcitabine-resistant, metastatic pancreatic cancer	<p>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.</p> <p>Epeius Biotechnologies, San Marino, CA</p> <p>Phase III trial planned; FDA granted fast-track status</p>	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 treatment of chemotherapy-resistant sarcoma	Patients with chemotherapy-resistant, recurrent or metastatic soft tissue sarcoma	<p>Patients with chemotherapy-resistant, recurrent or metastatic soft tissue sarcoma have no effective 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.</p> <p>Epeius Biotechnologies, San Marino, CA</p> <p>Phase I/II trial complete; phase III trial planned</p>	Placebo (patients' cancers have progressed after multiple rounds of conventional 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
Selective estrogen receptor alpha agonist (Capesaris) for treatment of advanced prostate cancer	Patients in whom advanced prostate cancer has been diagnosed	<p>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.</p> <p>GTx, Inc., Memphis, TN</p> <p>Phase II trial completed; additional phase II trials ongoing; trials were put on hold by FDA in Feb 2012 due to reports of increased rates of venous thromboembolic events or blood clots; GTx issued a response to FDA in Apr 2012.</p>	Bilateral orchiectomy Luteinizing-hormone-releasing hormone agonists	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	<p>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.</p> <p>Endocyte, Inc., West Lafayette, IN, in collaboration with Merck &amp; Co., Inc., Whitehouse Station, NJ</p> <p>Phase III trial ongoing</p>	Docetaxel Etoposide Gemcitabine Paclitaxel Pegylated liposomal doxorubicin Topotecan	Increased overall survival Increased progression-free survival Improved quality of life
SNS01-T for treatment-refractory multiple myeloma	Patients in whom treatment-refractory multiple myeloma has been diagnosed	<p>SNS01-T is a novel therapeutic intended to sensitize cancer cells to apoptotic signals via targeting eukaryotic translation initiation Factor 5A1; 5A1 functions as a shuttle protein, selectively translocating mRNA from the nucleus to cytosolic ribosomes for translation. Preclinical studies have shown that Factor 5A1 kills cancer cells through the expression of p53, caspases, tumor necrosis factor receptor 1 and the interferon gamma receptor and the negative regulation of bcl-2 and telomerase.</p> <p>Senesco Technologies, Inc., New Brunswick, NJ</p> <p>Phase I/II trial ongoing; FDA granted orphan drug status</p>	Autologous stem cell transplant Bisphosphonates Bortezomib 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
Sotatercept (ACE-011) for treatment of chemotherapy-induced anemia	Patients in whom anemia following chemotherapy has been diagnosed	<p>Anemia is one 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.</p> <p>Celgene Corp., Summit, NJ, in collaboration with Acceleron Pharma, Inc., Cambridge, MA</p> <p>Phase II/III trial ongoing</p>	Erythropoiesis stimulating agents	<p>Decreased risk of thrombosis and tumor stimulation</p> <p>Increased hemoglobin levels</p> <p>Reduced fatigue and inflammation</p> <p>Improved quality of life</p>
Stool DNA molecular test for colorectal cancer screening	All patients undergoing routine colorectal cancer (CRC) screening	<p>Genetic test (Cologuard™) screens DNA for gene mutations 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 at only 1 gene.</p> <p>Exact Sciences Corp., Madison, WI</p> <p>Clinical trial ongoing (phase unstated)</p>	Colonoscopy Computed tomographic colonography Fecal occult blood testing	<p>Increased sensitivity and specificity for precancerous lesions and CRC</p> <p>Improved positive and negative predictive values</p> <p>Reduced unnecessary followup for screening</p>

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 castration-resistant prostate cancer	Patients in whom castration-resistant prostate cancer (CRPC) has been diagnosed	<p>Patients in whom CRPC has been diagnosed who undergo treatment with docetaxel have a median survival of only about 2 years. 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 chemotherapy agent docetaxel.</p> <p>Eli Lilly and Co., Indianapolis, IN (licensed from ISIS Pharmaceuticals, Inc., a unit of Johnson &amp; Johnson, New Brunswick, NJ)</p> <p>Phase II trial ongoing</p>	Abiraterone Docetaxel	Increased overall survival Increased progression-free survival Improved quality of life
Survivin antisense inhibitor (LY2181308) for treatment of metastatic nonsmall cell lung cancer	Patients with treatment-resistant, metastatic nonsmall cell lung cancer (NSCLC)	<p>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.</p> <p>Eli Lilly and Co., Indianapolis, IN (licensed from ISIS Pharmaceuticals, a unit of Johnson &amp; Johnson, New Brunswick, NJ)</p> <p>Phase II trial ongoing</p>	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 to IV ovarian cancer who have undergone successful debulking surgery and treatment with carboplatin/paclitaxel	<p>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).</p> <p>Immunovaccine, Inc., Halifax, Nova Scotia, Canada</p> <p>Phase I/II trial ongoing</p>	Bevacizumab Paclitaxel	Increased overall survival Increased recurrence-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>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.</p> <p>Agennix AG, Heidelberg, Germany</p> <p>Phase III trials ongoing</p>	<p>First-line comparator: carboplatin and paclitaxel alone</p> <p>Third-line comparator: standard of care</p>	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
Targeted cytotoxic (AEZS-108) for treatment of luteinizing-hormone-releasing hormone-receptor-positive cancers	Patients in whom LHRH receptor-expressing cancer has been diagnosed, including ovarian, endometrial, prostate, or bladder cancer	<p>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 an luteinizing hormone-releasing hormone (LHRH) analog and doxorubicin. The LHRH analog targets cells that express the LHRH receptor, which includes the cells of many cancer types. Compared with naked doxorubicin, 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<sup>2</sup>, every 3 weeks, up to 6 treatment cycles.</p> <p>AEterna Zentaris, Inc., Quebec, Quebec, Canada</p> <p>Phase II trials ongoing; pivotal trial in endometrial cancer anticipated to be initiated in 2012</p>	Doxorubicin	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
Tasquinimod for treatment of castration-resistant prostate cancer	Patients in whom castration-resistant prostate cancer (CRPC) has been diagnosed	<p>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 0.25, 0.5, or 1.0 mg/day.</p> <p>Active Biotech, AB, Lund, Sweden</p> <p>Phase III trial ongoing</p>	<p>Abiraterone</p> <p>MDV-3100 (in development)</p> <p>Orteronel (in development)</p> <p>Sipuleucel-T</p> <p>Thalidomide (in development)</p>	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>Patients in whom advanced/metastatic NSCLC has been diagnosed 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. One 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.</p> <p>Geron Corp., Menlo Park, CA</p> <p>Phase II trial ongoing</p>	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	<p>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.</p> <p>Tengion, Inc., East Norriton, PA</p> <p>Phase I trial ongoing</p>	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
Teseaxel (oral taxane) for treatment of advanced cancers	Patients in whom advanced gastric cancer, melanoma, prostate cancer, breast cancer, or bladder cancer has been diagnosed	<p>Current microtubule stabilizing taxanes (e.g., docetaxel, paclitaxel) are administered by intravenous infusion and have been associated with infusion site reactions. Teseaxel would be the 1st orally administered taxane; other oral taxanes are in development but not as far along. Additionally, preclinical studies suggested that teseaxel could evade a common mechanism by which cancer cells develop taxane resistance and, therefore, could potentially be used to treat taxane-resistant cancers.</p> <p>Genta, Inc., Berkeley Heights, NJ</p> <p>Phase II trials ongoing</p>	Conventional (injected) taxanes: Docetaxel Paclitaxel	Reduced taxane-administration-related adverse events Increased overall survival Increased progression-free 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 dendritic cell vaccine (ICT-107) for glioblastoma multiforme	Patients in whom glioblastoma multiforme has been diagnosed	<p>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.</p> <p>ImmunoCellular Therapeutics Ltd., Los Angeles, CA</p> <p>Phase II trial ongoing; FDA granted orphan drug status in 2010</p>	<p>Antiangiogenic therapy Chemotherapy Corticosteroids Radiation therapy Radiosurgery Surgery</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
Therapeutic peptide vaccine (FPI-01) to prevent or delay acute myeloid leukemia relapse	Patients with acute myeloid leukemia (AML) who have achieved complete remission after standard 1st-line therapy	<p>While 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 (<i>WT-1</i>) gene, which is overexpressed in many cancer types including AML. Vaccine is delivered subcutaneously.</p> <p>Formula Pharmaceuticals, Inc., Berwyn, PA</p> <p>Phase I trial complete; phase II trial ongoing at Memorial Sloan-Kettering Cancer Center</p>	No AML maintenance comparator available	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
Therapeutic vaccine (BiovaxID) for treatment of indolent follicular non-Hodgkin's lymphoma	Patients in whom indolent follicular non-Hodgkin's lymphoma has been diagnosed	<p>Personalized cancer vaccine (BiovaxID<sup>®</sup>) 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.</p> <p>Biovest International, Inc., Tampa, FL</p> <p>Phase III trial complete; FDA granted orphan drug status</p>	<p>Combination therapy Hematopoietic stem cell transplantation Immunotherapy Other chemotherapy Other monoclonal antibodies Radiation therapy</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Therapeutic vaccine (BiovaxID) for treatment of mantle cell lymphoma	Patients in whom mantle cell lymphoma has been diagnosed	<p>Personalized cancer vaccine (BiovaxID<sup>®</sup>) 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.</p> <p>Biovest International, Inc., Tampa, FL</p> <p>Phase II trial complete; FDA granted orphan drug status</p>	<p>Chemotherapy Lymphocyte transplantation Monoclonal antibodies Radioimmunotherapy (ibritumomab and tositumomab) Radiation</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
Therapeutic vaccine (GI-4000) for pancreatic cancer harboring activating RAS mutations	Patients with surgically resectable pancreatic cancer that expresses an activated form of RAS	<p>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 <i>RAS</i> 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.</p> <p>GlobelImmune, Inc., Louisville, CO</p> <p>Phase II trial ongoing</p>	<p>5-Fluorouracil/ leucovorin Gemcitabine</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
Therapeutic vaccine (IMA901) for renal cell carcinoma	Patients in whom renal metastatic and/or locally advanced renal cell carcinoma (RCC) has been diagnosed	<p>RCC is typically highly resistant to conventional chemotherapy/radiation therapy; therefore, there are few treatment options 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.</p> <p>Immatics Biotechnologies GmbH, Tübingen, Germany</p> <p>Phase III trial ongoing</p>	<p>Sunitinib</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Therapeutic vaccine (tertomotide, GV-1001) for pancreatic cancer	Patients in whom pancreatic cancer has been diagnosed	<p>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.</p> <p>KAEL-GemVax Co., Ltd., Seoul, South Korea</p> <p>Phase III trial ongoing (data expected 2nd half of 2012)</p>	Gemcitabine Oncolytic virus therapy	Increased overall survival Increased progression-free survival Improved quality of life
Therapeutic vaccine (TVI-Brain-1) for recurrent glioma	Patients in whom recurrent stage IV glioma has been diagnosed	<p>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.</p> <p>TVAX Biomedical, LLC, Lenexa, KS</p> <p>Phase II trial ongoing</p>	Chemotherapy Radiation Surgery	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	<p>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 the treatment of 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.</p> <p>AVEO Pharmaceuticals, Inc., Cambridge, MA</p> <p>Phase I/II trial complete</p>	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	<p>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 the treatment of 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.</p> <p>AVEO Pharmaceuticals, Inc., Cambridge, MA</p> <p>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 filing anticipated in 2012</p>	<p>Avastin Interleukin-2 Sorafenib Sunitinib Temozolomide Cryoablation</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
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	<p>Tivozanib is a quinoline-urea–derived vascular endothelial growth factor (VEGF) receptor (VEGFR) inhibitor that inhibits several tyrosine kinases. It is being investigated for the treatment of NSCLC. The theoretical basis for VEGFR inhibitors in the treatment of 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.</p> <p>AVEO Pharmaceuticals, Inc., Cambridge, MA</p> <p>Phase I/II trial complete</p>	<p>Palliative care</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>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. While approved for treatment of colorectal cancer, irinotecan is not currently indicated for treatment of 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.</p> <p>Nektar Therapeutics, San Francisco, CA</p> <p>Phase III trial ongoing</p>	Eribulin Gemcitabine Ixabepilone Pemetrexed Vinorelbine	Increased overall survival Increased progression-free survival Improved quality of life
Transferrin targeted anticancer agent (NKP-1339) for treatment of metastatic cancer	Patients in whom metastatic cancer has been diagnosed	<p>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 (programmed cell death).</p> <p>Niiki Pharma, Inc., Hoboken, NJ</p> <p>Phase I portion of phase I/II trial complete</p>	Various anticancer 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
Trastuzumab emtansine for treatment of breast cancer	Patients in whom metastatic HER2-positive breast cancer has been diagnosed	<p>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.</p> <p>F. Hoffmann-La Roche Ltd., Basel, Switzerland</p> <p>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 are anticipated later in 2012</p>	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	<p>Novel cancer therapies for hormone-refractory prostate cancer that may increase treatment efficacy and survival are needed. TroVax® is a modified vaccinia virus Ankara virus vector encoding the oncofetal antigen 5T4 intended to induce cellular immune responses to tumors; oncofetal antigen 5T4 is expressed in many solid tumors. In current trial, TroVax is given in combination with the chemotherapy drug docetaxel.</p> <p>Oxford BioMedica, Oxford, UK</p> <p>Phase II trial ongoing (was halted in development for renal cell carcinoma in 2009)</p>	Docetaxel alone	Increased overall survival Increased progression-free survival Improved quality of life
TRU-016 for treatment of chronic lymphocytic leukemia	Patients in whom chronic lymphocytic leukemia (CLL) has been diagnosed	<p>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 CD20-directed therapies and may be used alone or in combination with chemotherapy (bendamustine) and/or other CD20-directed therapeutics.</p> <p>Emergent BioSolutions, Inc., Rockville, MD</p> <p>Phase I/II trials ongoing</p>	Bone marrow transplantation Chemotherapy (including bendamustine) Monoclonal antibodies (alemtuzumab [anti-CD52]), rituximab and ofatumumab [anti-CD20]) Radiation therapy Splenectomy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>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.</p> <p>Lexicon Pharmaceuticals, Inc., The Woodlands, TX</p> <p>Phase II trials completed; FDA granted fast track status</p>	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 non-small cell lung cancer	Patients in whom stage IIIb–IV non-small cell lung cancer has been diagnosed	<p>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 in the cell's mitotic processes. The therapy is delivered in conjunction with chemotherapy.</p> <p>NovoCure Ltd., Haifa, Israel</p> <p>Phase I/II trial complete</p>	Chemotherapy alone Radiation therapy/ chemotherapy Surgical resection/ chemotherapy	Increased overall survival Increased progression-free survival Improved quality of life
Tumor-treating fields therapy (NovoTTF-100L device) for recurrent glioblastoma	Patients in whom recurrent glioblastoma has been diagnosed	<p>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 in the cell's mitotic processes. The therapy is delivered in conjunction with chemotherapy.</p> <p>NovoCure Ltd., Haifa, Israel</p> <p>FDA approved for recurrent glioblastoma Apr 2011; phase III trial in newly diagnosed glioblastoma ongoing</p>	Brain brachytherapy Combination therapies Cyberknife radiation therapy Proton beam radiation therapy Stereotactic beam 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
Ultra-low-molecular-weight heparin (semuloparin) for prevention of venous thromboembolism in patients undergoing chemotherapy	Patients who are at high risk for venous thromboembolism (VTE) who are undergoing chemotherapy treatment for cancer	<p>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.</p> <p>Sanofi, Paris, France</p> <p>Phase III trial completed; biologics license application submitted to FDA Sept 2011</p>	Low-molecular-weight heparin No treatment	Decreased rate of thromboembolytic events Improved safety profile (e.g., fewer bleeding events)
Urine test (PSP94) for prostate cancer screening	Men undergoing routine prostate cancer screening (generally men older than 50 years of age)	<p>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</p> <p>Miraculins, Inc., Winnipeg, Manitoba, Canada</p> <p>Kit was made available as a research-use-only reagent in Aug 2010; company plans to develop a commercially available diagnostic test kit</p>	Digital rectal examination Prostate-specific antigen screening Other blood marker tests in development	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	<p>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.</p> <p>Bioniche Life Sciences, Inc., Belleville, Ontario Endo Pharmaceuticals, Chadds Ford, PA (licensee in U.S.)</p> <p>Phase II/III trial ongoing</p>	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
Vandetanib (Caprelsa) for treatment of metastatic medullary thyroid cancer	Patients in whom metastatic medullary thyroid cancer has been diagnosed	<p>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 recombinant in transfection (RET); about 25% of medullary thyroid cancer is caused by a mutation in the RET proto-oncogene. Taken orally, once daily.</p> <p>AstraZeneca Pharmaceuticals, LP, Wilmington, DE</p> <p>FDA approved Apr 2011</p>	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	<p>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.</p> <p>Inovio Pharmaceuticals, Inc., Blue Bell, PA</p> <p>Phase II trial ongoing</p>	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	<p>No systemic treatment is currently approved for treatment of basal cell carcinoma, 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 Smoothed, which is essential for transducing hedgehog signaling.</p> <p>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland</p> <p>Phase II trials ongoing; FDA approved Jan 31, 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</p>	No 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	<p>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 Smoothed, 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.</p> <p>National Cancer Institute, Bethesda, MD, and Institute Bergonié, Bordeaux Cédex, France</p> <p>Phase II trial ongoing</p>	Doxorubicin	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
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	<p>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 Smoothed, 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.</p> <p>National Cancer Institute, Bethesda, MD, and New York Cancer Consortium</p> <p>Phase II trial ongoing</p>	FOLFOX chemotherapy alone	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>
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	<p>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 Smoothed, 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.</p> <p>National Cancer Institute, Bethesda, MD</p> <p>Phase II trial ongoing</p>	Neoadjuvant hormone therapy alone	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>

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	<p>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 Smoothed, 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.</p> <p>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland                      Curis Pharmaceuticals, Lexington, MA                      National Cancer Institute, Bethesda, MD</p> <p>Phase II trials ongoing</p>	<p>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</p>	<p>Increased overall survival                      Increased progression-free survival                      Improved quality of life</p>
Vismodegib (GDC-0449) for treatment of multiple myeloma	Patients with multiple myeloma who have previously been treated by autologous stem cell transplant	<p>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 Smoothed, 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.</p> <p>National Cancer Institute, Bethesda, MD, and Johns Hopkins Medicine's Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD</p> <p>Phase Ib trial ongoing</p>	<p>Bortezomib                      Lenalidomide/                      thalidomide</p>	<p>Increased overall survival                      Increased progression-free survival                      Improved quality of life</p>

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	<p>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 Smoothed, 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.</p> <p>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</p> <p>Phase II trials ongoing</p>	<p>Gemcitabine                      Gemcitabine plus cisplatin or oxaliplatin                      Gemcitabine plus erlotinib                      Gemcitabine plus a fluoropyrimidine</p>	<p>Increased overall survival                      Increased progression-free survival                      Improved quality of life</p>
Vismodegib (GDC-0449) for treatment of recurrent glioblastoma multiforme	Patients with recurrent glioblastoma multiforme who have undergone surgical resection of the recurrent tumor	<p>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 Smoothed, 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.</p> <p>National Cancer Institute, Bethesda, MD</p> <p>Phase II trial ongoing</p>	<p>Radiation therapy                      Temozolomide</p>	<p>Increased overall survival                      Increased progression-free survival                      Improved quality of life</p>

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 (AML) cancer has been diagnosed	<p>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<sup>2</sup> for days 1 and 4 for induction and 70 mg/m<sup>2</sup> for all other cycles.</p> <p>Sunesis Pharmaceuticals, Inc., South San Francisco, CA</p> <p>Phase III trial ongoing</p>	<p>Clofarabine (off label) Cytarabine Gemtuzumab ozogamicin Hematopoietic stem cell transplant</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>
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	<p>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 and 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.</p> <p>Emergent BioSolutions, Rockville, MD (acquired from TenX BioPharma, Philadelphia, PA)</p> <p>Phase II trials complete</p>	<p>Denileukin diftitox Photopheresis Vorinostat</p>	<p>Increased overall survival Increased progression-free survival Improved quality of life</p>

**Table 3. AHRQ Priority Condition: 03 Cardiovascular Disease: 93 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	<p>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). First 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.</p> <p>AstraZeneca, London, UK</p> <p>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</p>	Clopidogrel Prasugrel Ticlopidine	Reduced incidence of heart attacks and strokes Increased overall survival Reduced side effects compared with other antiplatelet drugs
Allogeneic mesenchymal stem cell therapy (Revascor) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	<p>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 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.</p> <p>Cephalon, Inc., acquired by Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, in Oct 2011 Mesoblast Ltd., Melbourne, Australia</p> <p>Phase II trial ongoing</p>	Pharmaceutical therapy 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	<p>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.</p> <p>Osiris Therapeutics, Inc., Baltimore, MD</p> <p>Phase II trial ongoing</p>	Biodegradable scaffold (BL-1040, in development) Pharmaceutical therapy (e.g., beta blockers)	<p>Increased ejection fraction</p> <p>Increased left ventricular volume</p> <p>Improved cardiac function</p> <p>Decreased cardiovascular events</p> <p>Improved quality of life</p>
Altitude training using a portable altitude simulation chamber for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	<p>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.</p> <p>Montefiore Medical Center, Bronx, NY</p> <p>Pilot trial completed</p>	High altitude environment Medical intervention	<p>Improved oxygen-delivery efficiency</p> <p>Improved exercise performance</p> <p>Improved morbidity and mortality</p> <p>Improved quality of life</p>
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	<p>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.</p> <p>Merck &amp; Co., Inc., Whitehouse Station, NJ</p> <p>Phase III trials ongoing; company anticipates filing new drug application with FDA after 2015</p>	Lifestyle changes Omega-3 fatty acids Other drug therapies Statins (anacetrapib can be used alone or in conjunction with statins)	<p>Reduced risk of heart attack</p> <p>Improved cardiovascular outcomes</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Apo-B synthesis inhibitor (mipomersen, Kynamro) for treatment of familial hypercholesterolemia</p>	<p>Patients in whom heterozygous or homozygous familial hypercholesterolemia (FH) has been diagnosed</p>	<p>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.</p> <p>Genzyme Corp., Cambridge, MA, a subsidiary of Sanofi ISIS Pharmaceuticals, Inc., a unit of Johnson &amp; Johnson, New Brunswick, NJ</p> <p>Phase III trials completed; new drug application (NDA) filed with FDA in March 2011 for homozygous FH; FDA requested additional 12-month data before NDA filing for heterozygous FH; this trial is ongoing</p>	<p>Bile acid-sequestering resins Extracorporeal apheresis Ezetimibe Fibrates (such as gemfibrozil) Nicotinic acid Statins</p>	<p>Reduced LDL levels Improved cardiovascular outcomes Improved long-term health outcomes Improved quality of life</p>
<p>APOCIII Rx for treatment of hypertriglyceridemia</p>	<p>Patients in whom hypertriglyceridemia has been diagnosed</p>	<p>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-C levels, increased high-density lipoprotein levels and lower risk of cardiovascular disease. The new drug is intended to avoid side effects of current triglyceride-lowering medications.</p> <p>ISIS Pharmaceuticals, Inc., a unit of Johnson &amp; Johnson, New Brunswick, NJ</p> <p>Phase II trial ongoing</p>	<p>Diet and exercise Fenofibric acid (Trilipix®) with a statin (for mixed dyslipidemia) Fibric acid derivatives Gemfibrozil (Lopid®) Lovaza® (for triglycerides ≥500 mg/dL) Niacin Omega-3 fatty acids</p>	<p>Reduction in triglycerides Reduced cardiovascular risk Improved metabolic syndrome</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous bone marrow–derived cells (Ixmyelocel-T) for treatment of critical limb ischemia	Patients in whom critical limb ischemia (CLI) has been diagnosed	<p>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).</p> <p>Aastrom Biosciences, Inc., Ann Arbor, MI</p> <p>Phase III trial ongoing</p>	<p>Cilostazol and pentoxifylline Cholesterol-lowering agents Percutaneous angioplasty and stenting Surgery</p>	<p>Tissue regeneration Improved circulation Reduced need for amputation Reduced morbidity and mortality</p>
Autologous bone marrow–derived mesenchymal stem cells for myocardial repair after infarction	Patients who need cardiac repair after myocardial infarction (MI)	<p>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.</p> <p>Under development by several entities including University of Miami, FL; Amorcyte, Allendale, NJ; and National Heart Lung and Blood Institute, Bethesda, MD</p> <p>Phase I/II trials ongoing</p>	<p>Biodegradable scaffold (BL-1040, in development) Pharmaceutical management (e.g., beta blockers)</p>	<p>Myocardial tissue regeneration Improved cardiac function Reduced cardiovascular events Improved quality of life</p>
Autologous heart stem cell transplantation for postmyocardial infarction revascularization	Patients who have experienced a heart attack within the past month	<p>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.</p> <p>Cedars-Sinai Heart Institute, Los Angeles, CA</p> <p>Phase I trial completed</p>	<p>Coronary artery bypass surgery Percutaneous coronary interventions Medical management Gene therapy</p>	<p>Reduced mortality and morbidity (major adverse cardiac events) Improved activities of daily living Reduced need for coronary reintervention Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 Drug therapy 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 ongoing	Diuretics Inotropic agents Vasodilators	Improved symptoms Improved hemodynamics Improved clinical status Improved long-term outcomes Increased survival Improved quality of life
Biodegradable scaffold (IK-5001) for support postmyocardial infarction	Patients at risk of heart failure (HF) or ventricular remodeling after acute myocardial infarction	IK-5001 (formerly BL-1040) is a partially cross-linked, alginate-based, liquid polymer designed to provide physical support to the heart; it acts like a 3-dimensional scaffold intended to prevent the left ventricular wall from thinning to prevent additional HF. Reabsorbed and 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 trial ongoing	Drug therapy to prevent HF Emerging stem cell scaffolding therapies	Improved left ejection fraction Slowed progression of HF Improved activities of daily living Improved survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bioresorbable stent (Absorb) for treatment of critical limb ischemia	Patients in whom below-the-knee critical limb ischemia (CLI) has been diagnosed	<p>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 a drug-eluting stent made of polylactide polymer that elutes everolimus. It is intended to provide support to the vessel, then dissolve over the course of 2 years. The company claims that because the device is not permanent, natural vessel function may be restored.</p> <p>Abbott Laboratories, Abbott Park, IL</p> <p>Trial ongoing (no phase)</p>	<p>Cilostazol and pentoxifylline Cholesterol-lowering agents Percutaneous angioplasty and stenting Surgery</p>	<p>Decreased pain Improved circulation and mobility Reduced need for amputation Improved quality of life</p>
Cardiac contractility modulation (Optimizer system) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	<p>Optimizer™ system delivers nonexcitatory electrical signals during the absolute refractory period (between beats) to produce more forceful contraction during heartbeat; intended as adjunct to optimal medical therapy.</p> <p>Impulse Dynamics, N.V., Willemstad, Netherlands Antilles</p> <p>Confirmatory trial ongoing</p>	<p>Digitalis Implanted pacemakers and/or defibrillators Optimal medical management</p>	<p>Symptom relief Improved 6-minute walk test Fewer hospital admissions Delayed progression of HF Delayed need for ventricular assist devices Improved quality of life</p>
Cardiac pacing system (Revo) for patients who may require future magnetic resonance imaging	Patients with pacemakers who need to undergo MRI scanning	<p>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.</p> <p>Medtronic, Inc., Minneapolis, MN</p> <p>FDA approved Feb 8, 2011</p>	<p>Currently, no pacemakers exist that can be used in MRI environment Modified MRI environments</p>	<p>Ability for physicians to use MRI for patients who require pacemaker therapy</p>

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	<p>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.</p> <p>Medtronic, Inc., Minneapolis, MN</p> <p>Phase III trial SYMPPLICITY HTN-3 ongoing</p>	Renal artery stents Alpha agonists Alpha blockers Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers Beta blockers Calcium channel blockers Combination medications Diuretics Renin inhibitors	Controlled hypertension without medications Controlled blood pressure to reduce incidence of blindness, heart attacks, kidney failure, and stroke
Catheter-delivered biodegradable adhesive (Sapheon Closure System) for treatment of varicose veins	Patients with varicose veins who are eligible for treatment	<p>While many options exist for treatment of 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.</p> <p>Sapheon, Inc., Santa Rosa, CA</p> <p>Pilot trial completed in United States; Conformité Européene (CE) marked Sept 2011</p>	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	<p>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.</p> <p>Cerenis Therapeutics, Inc., Ann Arbor, MI</p> <p>Phase II trial ongoing</p>	Anacetrapib (in development) Niacin Rosuvastatin RVX-208 (in development)	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	<p>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.</p> <p>Eli Lilly and Co., Indianapolis, IN</p> <p>Phase II trial ongoing</p>	CETP inhibitors in development (anacetrapib, dalcetrapib) Niacin Sclerotherapy	Improved HDL profile Reduced cardiovascular morbidity and mortality Improved quality of life
Dabigatran (Pradaxa) for prevention of thrombosis associated with atrial fibrillation	Patients in whom atrial fibrillation (AF) has been diagnosed	<p>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.</p> <p>Boehringer Ingelheim, Ingelheim, Germany</p> <p>FDA approved Oct 2010</p>	Aspirin Factor Xa inhibitors in development (e.g., apixaban, rivaroxaban) Niacin	Reduced blood clotting Reduced need for monitoring clotting parameters Reduced stroke incidence Improved long-term outcomes
Dual natriuretic peptide receptor agonist (Cenderitide) for treatment of postacute decompensated heart failure	Patients in whom acute decompensated heart failure (ADHF) has been diagnosed	<p>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.</p> <p>Nile Therapeutics, Inc., San Mateo, CA</p> <p>Phase I trial ongoing, expected completion in 1st quarter 2012; FDA granted fast track status; company is seeking "post-ADHF" indication with this drug</p>	Diuretics Natreacor (single natriuretic peptide receptor agonist, approved in U.S. for ADHF)	Reduced hospital readmissions Reduced HF symptom burden Improved cardiovascular outcomes

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Electrical stimulation of carotid baroreceptors (Rheos System) for treatment of drug-resistant hypertension	Patients in whom severe, drug-resistant hypertension has been diagnosed	<p>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.</p> <p>CVRx, Inc., Minneapolis, MN</p> <p>Phase II/III trials ongoing</p>	Optimal medical management	<p>Reduced hypertension</p> <p>Reduced stroke incidence</p> <p>Reduced cardiovascular events</p> <p>Improved quality of life</p>
Elinogrel for prevention of heart attack and stroke and treatment of acute coronary syndrome	Patients in whom acute coronary syndrome has been diagnosed	<p>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.</p> <p>Portola Pharmaceuticals, Inc., South San Francisco, CA Novartis AG, Basel, Switzerland</p> <p>Phase II trial for IV and oral formulations completed; phase III trials planned to begin 2012</p>	<p>Clopidogrel</p> <p>Prasugrel</p> <p>Ticagrelor (Brilinta, 1st reversible oral only P2Y12 ADP receptor antagonist)</p> <p>Ticlopidine</p>	<p>Fewer side effects from anticlotting medication regimen</p> <p>Reduced stroke incidence</p> <p>Reduced heart attack incidence</p> <p>Increased survival</p> <p>Improved quality of life</p>
Factor IXa inhibitor and active control agent (REG2 System) for prevention of venous thromboembolism	Patients in whom risk for venous thromboembolism (VTE) has been diagnosed	<p>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 consists of a subcutaneously administered direct Factor IXa inhibitor, called RB006, which is involved in the clotting cascade and is intended to prevent blood clot formation, and an intravenously administered active control for RB006, called RB007, which is intended to provide predictable reversal of RB006 anticoagulation.</p> <p>Regado Biosciences, Inc., Basking Ridge, NJ</p> <p>Phase I trial completed</p>	<p>Fondaparinux</p> <p>Heparin</p> <p>Low-molecular-weight heparin</p> <p>Vitamin K antagonists</p>	<p>Reversal of anticoagulation</p> <p>Increased survival</p>

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Factor Xa inhibitor (apixaban; Eliquis) for prevention of stroke, and prevention or treatment of venous thromboembolism	Patients at risk of or with a history of deep vein thrombosis (DVT) or pulmonary embolism (PE), or patients with atrial fibrillation (AF) at risk for stroke	<p>Apixaban (Eliquis™, BMS-562247-01) is an oral, highly selective FXa inhibitor intended to reduce the risk of stroke in patients with AF and to prevent or treat venous thromboembolism (VTE).</p> <p>Bristol-Meyers Squibb Co., Princeton, NJ, in joint development with Pfizer, Inc., New York, NY</p> <p>New drug application submitted for stroke prevention in patients with AF; FDA granted priority review; decision date June 28, 2012; phase III trials ongoing for VTE indications. Approved May 2011 by European Medicines Agency for VTE prevention after knee or hip replacement surgery</p>	<p>Aspirin Dabigatran Enoxaparin (Lovenox®) injection Warfarin (Coumadin®) Comparators in development: Biotinylated idraparinux, Idraparinux, Other factor Xa inhibitors</p>	<p>Reduced DVT events Reduced stroke incidence Reduced PE events</p>
Factor Xa inhibitor (betrixaban) for prevention of deep vein thrombosis or pulmonary embolism	Patients at high risk of thrombosis	<p>Betrixaban is a direct coagulation FXa inhibitor and is the only agent with 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 differs from dabigatran (thrombin inhibitor), the only alternative to warfarin on the market; it is primarily eliminated unchanged in the bile so it is metabolized through cytochrome 450 enzyme system.</p> <p>Portola Pharmaceuticals, San Francisco, CA</p> <p>Phase III trial planned for 2012</p>	<p>Aspirin Coumadin® Dabigatran Lovenox® (injectable blood thinner) FXa inhibitor comparators in development: Idraparinux, Biotinylated idraparinux, Other factor Xa inhibitors</p>	<p>Prevention of thrombosis Prevention of pulmonary embolism Decreased stroke events</p>
Factor Xa inhibitor (edoxaban) for prevention of thromboses	Patients at risk for venous thromboembolism (VTE) or with atrial fibrillation (AF)-related stroke	<p>Current standard of care (warfarin) for this indication is associated with limitations, including a narrow therapeutic window and the need for frequent measurements of clotting parameters; no FXa inhibitors are currently approved for use in the U.S. Edoxaban is in a new class of anticoagulants in development designed to inhibit FXa, which is known to be an important component of the coagulation cascade. It is intended to be administered orally, once daily.</p> <p>Daiichi Sankyo, Tokyo, Japan</p> <p>Phase III trial ongoing for VTE indication; phase II trial completed for AF indication; received approval in Japan in Apr 2011 for prevention of VTE after major orthopedic surgery; in the U.S., manufacturer is seeking indications only for VTE and prevention of stroke in patients with AF</p>	<p>Apixaban Aspirin Betrixaban Coumadin® Dabigatran Lovenox® Rivaroxaban</p>	<p>Reduced thrombosis rate Reduced stroke incidence Reduced pulmonary embolism incidence</p>

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Factor Xa inhibitor (otamixaban) for treatment of acute coronary syndrome	Patients in whom acute coronary syndrome (ACS) has been diagnosed	<p>Current anticoagulation therapies for patients with ACS are associated with limitations, including the need for anticoagulation monitoring or dose adjustments in certain populations (e.g., elderly patients, or those with renal impairment). Otamixaban is a reversible, direct selective factor Xa 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.</p> <p>Sanofi, Paris, France</p> <p>Phase III trial ongoing</p>	Fondaparinux Low-molecular-weight heparin Other Factor Xa inhibitors Unfractionated heparin	Reduced need for monitoring or adjusting anticoagulant dose Reduced morbidity and mortality
Factor Xa inhibitor (rivaroxaban, Xarelto) for prevention of stroke	Patients in whom with atrial fibrillation (AF) has been diagnosed	<p>Current standard of care (warfarin) for patients with AF is associated with limitations, including a narrow therapeutic window and the need for frequent measurements of clotting parameters. A recently approved novel medication, dabigatran, operates via a different mechanism of action and requires twice daily dosing. Rivaroxaban (Xarelto®) is a member of a new class of anticoagulants in development that are designed to inhibit Factor Xa, which is known to be an important component of the coagulation cascade. It is administered orally, once daily, and is approved for prevention of venous thromboembolism in patients undergoing knee or hip surgery.</p> <p>Johnson &amp; Johnson, New Brunswick, NJ</p> <p>FDA approved Nov 2011</p>	Apixaban Betrixaban Dabigatran Edoxaban Warfarin	Reduced stroke incidence Reduced morbidity and mortality
Factor Xa inhibitor (rivaroxaban, Xarelto) for prophylaxis of deep vein thrombosis	Patients eligible for anticoagulation (patients in whom risk of thrombosis has been diagnosed)	<p>Rivaroxaban (Xarelto®) is a coagulation factor Xa inhibitor; keeps prothrombin from converting to thrombin, decreasing clot formation; different from dabigatran (thrombin inhibitor), which is only alternative to warfarin on the market. Fewer interactions expected; should not require frequent blood checks like Coumadin®. It is an oral medication taken daily (dabigatran is taken twice a day).</p> <p>Johnson &amp; Johnson, New Brunswick, NJ</p> <p>FDA approved Jul 2011 for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism in patients undergoing knee or hip replacement surgery.</p>	Aspirin Coumadin Dabigatran Lovenox® (injectable blood thinner)	Reduced stroke events

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Factor XI inhibitor (ISIS-FXIRX) for anticoagulation	Patients at risk of aberrant blood clot formation	<p>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 for bleeding.</p> <p>ISIS Pharmaceuticals, Inc., a unit of Johnson &amp; Johnson, New Brunswick, NJ</p> <p>Phase I trial completed; phase II study planned for 2012</p>	<p>Apixaban Aspirin Betrixaban Coumadin® Dabigatran Lovenox® Rivaroxaban</p>	<p>Reduced incidence of aberrant clot formation Reduced thrombosis rate Reduced stroke incidence Reduced pulmonary embolism incidence Reduced morbidity and mortality</p>
Fibrin-specific thrombolytic agent (desmoteplase) for neuroprotection during stroke	Patients in whom acute stroke has been diagnosed	<p>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.</p> <p>H. Lundbeck a/s, Valby, Denmark</p> <p>One phase III trial completed; other phase III trials ongoing</p>	tPA therapy	<p>Increased blood flow to the brain Reversed damage Improved stroke-related outcomes</p>
Freedom driver system for Total Artificial Heart as bridge to heart transplantation	Patients with nonreversible biventricular failure who are candidates for heart transplantation	<p>This 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.</p> <p>SynCardia Systems, Inc., Tucson, AZ</p> <p>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 completed in 2012</p>	Ventricular assist devices outside of the hospital	<p>Restored mobility Possible recovery at home (reduction in hospitalization costs) Extended survival for patients awaiting heart transplantation</p>

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Frontal near-infrared spectroscopy for monitoring stroke recurrence	Hospitalized patients who are being treated for stroke	<p>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 occurring 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.</p> <p>Mayo Clinic, Jacksonville, FL</p> <p>Small pilot trial completed</p>	CT perfusion scan Oxygen probe	<p>Reduced exposure to radiation</p> <p>Reduced need for invasive monitoring procedures</p> <p>Timelier stroke intervention</p> <p>Reduced morbidity from stroke</p>
Gene therapy (Mydicar) for heart failure	Patients in whom heart failure (HF) has been diagnosed (additional trials needed to identify appropriate candidate population)	<p>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.</p> <p>Celladon Corp., La Jolla, CA Targeted Genetics Corp., Seattle, WA</p> <p>Phase II trial ongoing; received FDA fast track status Dec 2011</p>	Current drug therapies	<p>Improved left ventricular ejection fraction</p> <p>Improved cardiovascular outcomes (reduction in cardiovascular events)</p> <p>Improved quality of life</p>
Glial growth factor 2 for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	<p>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.</p> <p>Acorda Therapeutics, Hawthorne, NJ</p> <p>Phase I trial ongoing</p>	<p>Angiotensin-converting enzyme inhibitors</p> <p>Angiotensin receptor blockers</p> <p>Beta blockers</p> <p>Digitalis</p> <p>Diuretics</p> <p>Stem cell therapies</p>	<p>Increased ventricular repair</p> <p>Improved cardiac output</p> <p>Improved cardioprotection</p> <p>Improved long-term cardiac outcomes</p>

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Human monoclonal antibody (BI-204) for treatment of coronary artery disease	Patients in whom coronary artery disease (CAD) has been diagnosed	<p>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.</p> <p>BioInvent International AB, Lund, Sweden Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland</p> <p>Phase II trial ongoing</p>	<p>Mainly statins Other drug therapy Lifestyle changes</p>	<p>Prevent plaque formation Reduced existing plaques Prevent breakdown of unstable plaques Reduced cardiac events in high-risk patients</p>
Icatibant (Firazyr) for treatment of acute hereditary angioedema	Patients in whom acute hereditary angioedema (HAE) of mild, moderate, or severe type has been diagnosed	<p>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.</p> <p>Shire Pharmaceuticals, plc, Dublin, Ireland</p> <p>FDA approved Aug 25, 2011, for treating acute attacks of HAE</p>	<p>Antihistamines C1-INH (concentrate from donor blood) Fresh-frozen plasma Pain relievers and fluids given intravenously</p>	<p>Faster symptom relief of primary symptom Reduced severity of symptoms Reduced mortality</p>
Implantable cardiac monitor for detecting myocardial infarction	Patients at high risk of myocardial infarction (MI)	<p>Implantable electronic device designed to warn patients of an impending MI; measures electrical changes in the heart.</p> <p>Angel Medical Systems, Shrewsbury, NJ</p> <p>Phase III trial ongoing</p>	<p>Conventional, external MI detection technologies Patient report</p>	<p>Earlier detection of impending heart attack Prevention of heart damage Increased overall survival</p>

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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	<p>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).</p> <p>Cardio Polymers, now part of LoneStar Heart, Inc., Laguna Hills, CA</p> <p>Phase II/III trial ongoing</p>	BL-1040 scaffold Drug therapy to prevent HF Emerging stem cell scaffolding therapies	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	<p>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.</p> <p>Sinapis Pharma, Inc., Jacksonville, FL</p> <p>Phase I trial completed; phase II trial planned to begin by late 2011, but not yet registered</p>	tPA	Improved poststroke neuron survival Improved patient outcomes

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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	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 for 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 for cardiovascular events.  VBL Therapeutics, Tel Aviv, Israel  Phase II trial completed	Statins	Reduced risk for 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	<p>HeartWare is developing a left ventricular assist device (LVAD) for treatment of 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.</p> <p>HeartWare International, Inc., Framingham, MA</p> <p>U.S. multicenter late-phase clinical trial under FDA investigational device exemption status ongoing; Conformité Européene (CE) marked in 2009</p>	<p>Optimal medical management Other LVADs Total artificial heart</p>	<p>Improved survival Improved quality of life prior to transplant Reduced incidence of internal bleeding compared with continuous-flow devices</p>
Low-dose tPA for treatment of intraventricular hemorrhage	Patients in whom intraventricular hemorrhage has been diagnosed	<p>The agent tissue plasminogen activator (tPA) is a thrombolytic (clot-busting drug) long used for treatment of 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.</p> <p>Johns Hopkins University, Baltimore, MD</p> <p>Phase III trial ongoing</p>	<p>Intraventricular catheter alone</p>	<p>Improved clot evacuation Decreased time to clot evacuation Improved cardiovascular outcomes</p>

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	<p>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.</p> <p>D-Pharm, Ltd., Rehovot, Israel</p> <p>Phase III trial suspended by trial steering committee in January 2012; investigations are being performed to determine whether study will continue; FDA granted fast track status</p>	tPA	<p>Improved poststroke neuron survival Faster recovery Reduced need for rehabilitation services</p>
Metabolic regulator (ETC-1002) for treatment of dyslipidemia	Patients with cardiovascular disease (CVD), or in whom a risk for CVD has been diagnosed	<p>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.</p> <p>Esperion Therapeutics, Inc., Plymouth, MI</p> <p>Phase II trial completed</p>	Current pharmacotherapy (e.g., statins)	<p>Improved LDL profile Reduced incidence of cardio-metabolic disease Increased overall survival Improved quality of life</p>

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	<p>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.</p> <p>Trophos SA, Marseille, France</p> <p>Phase II trial registered, not yet recruiting</p>	Reperfusion with and without TRO-40303	<p>Reduced myocardial cell death</p> <p>Improved cardiovascular function</p> <p>Increased survival</p>
Mitochondrial-targeted compound (Bendavia) for treatment of ischemia reperfusion injury	Patients experiencing ischemia reperfusion injury during reperfusion post-myocardial infarction and coronary bypass surgery	<p>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.</p> <p>Stealth Peptides, Inc., Newton Centre, MA</p> <p>Phase II trial planned, not yet registered</p>	Angioplasty and stenting Fibrinolytic therapy (i.e., drugs [tissue plasminogen activator] used to break up clots that are blocking a vessel)	<p>Improved electron transport efficiency</p> <p>Maintained mitochondrial respiration and adenosine triphosphate levels</p> <p>Prevented mitochondrial swelling and depolarization</p> <p>Reduced apoptosis</p> <p>Improved cardiovascular outcomes</p>

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	<p>Access to ECG machines is limited in some rural or emergency rescue locations; patients are required to visit health care facilities for ECG readings; "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), 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; 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; manufacturer claims that the device will work in any location with wireless coverage.</p> <p>AliveCor, Seattle, WA</p> <p>Premarket notification for 510(k) clearance from FDA in progress</p>	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 hypercholesterolemia (HoFH) has been diagnosed	<p>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), which in turns lowers plasma lipids. Lomitapide is intended to replace statins. Taken orally.</p> <p>Aegerion Pharmaceuticals, Inc., Cambridge, MA</p> <p>Pivotal phase III trial ongoing; FDA granted orphan drug status; company filed new drug application with FDA Mar 2012</p>	Bile acid-sequestering resins Extracorporeal apheresis Ezetimibe Fibrates (such as gemfibrozil) Nicotinic acid 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	<p>Currently available inotropic pharmacotherapy for HF increases contractility without prolonging systole, which increases oxygen demand, thereby exacerbating myocardial ischemia and the risk for adverse events. Omeclamtiv 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.</p> <p>Cytokinetics, Inc., South San Francisco, CA</p> <p>Phase II trials ongoing</p>	<p>Angiotensin-converting enzyme inhibitors            Angiotensin receptor blockers            Beta blockers            Digitalis            Diuretics            Stem cell therapies</p>	<p>Prolonged systole            Improved heart efficiency            Reduced adverse events            Improved quality of life            Reduced morbidity and mortality</p>
Nitroxyl donor (CXL-1020) for treatment of acute decompensated heart failure	Patients in whom acute decompensated heart failure (HF) has been diagnosed	<p>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.</p> <p>Cardioxyl Pharmaceuticals, Inc., Chapel Hill, NC</p> <p>Phase II trial ongoing</p>	<p>Diuresis (for fluid removal)            Vasodilation (for preload and afterload reduction)            Other intravenous inotropic agents (dobutamine, milrinone)</p>	<p>Improved symptoms, hemodynamics, and clinical status of patients with acute decompensated HF</p>
Off-label minocycline with tPA for treatment of stroke	Patients in whom acute ischemic stroke has been diagnosed	<p>Minocycline, a tetracycline antibiotic, is given with tissue plasminogen activator (tPA) to reduce stroke-associated inflammatory factors and bleeding.</p> <p>Georgia Health Sciences University, Augusta</p> <p>Phase I/II trial completed</p>	<p>Nonsteroidal anti-inflammatory drugs</p>	<p>Reduced bleeding in stroke            Improved overall outcomes</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Off-label sildenafil (Viagra) to improve pediatric exercise tolerance after Fontan surgery for heart defect</p>	<p>Pediatric patients with exercise intolerance after undergoing Fontan operation to correct heart defect</p>	<p>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.</p> <p>Pfizer, Inc., New York, NY (manufacturer)                      Pennsylvania State University, Pennsylvania State Hershey Medical Center, Hershey (investigator)</p> <p>Phase IV trial ongoing</p>	<p>Exercise training</p>	<p>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</p>
<p>Oxygenated pegylated hemoglobin (MP4OX) for treatment of hemorrhagic shock</p>	<p>Patients in whom trauma-related oxygen deprivation (hemorrhagic shock) has been diagnosed</p>	<p>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 for ischemia; intended for use as an adjunctive treatment to standard of care (transfused blood or packed red blood cells).</p> <p>Sangart, Inc., San Diego, CA; MP4OX’s development is part of a Dec 2010 cooperative research and development agreement (CRADA) with the U.S. Navy</p> <p>Phase IIb trial ongoing</p>	<p>Standard of care with and without MP4OX</p>	<p>Improved perfusion of capillaries and oxygenation of ischemic tissues                      Resolution of hemorrhagic shock                      Reduced rate of organ failure                      Improved survival</p>

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PAR-1 antagonist (atopaxar) for prevention of atherothrombosis	Patients in whom a risk of atherothrombosis has been diagnosed	<p>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.</p> <p>Eisai, Inc., Tokyo, Japan</p> <p>Phase II trials completed</p>	Aspirin Clopidogrel	<p>Reduced platelet aggregation</p> <p>Fewer ischemic events</p> <p>Improved bleeding rates</p> <p>Reduced mortality</p>
PCSK9 inhibitor (REGN727/SAR236553) for treatment of hypercholesterolemia	Patients in whom hypercholesterolemia has been diagnosed	<p>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.</p> <p>Sanofi, Paris, France Regeneron Pharmaceuticals, Inc., Tarrytown, NY</p> <p>Phase III trial ongoing</p>	Lipid-lowering agents (e.g., statins)	<p>Improved lipid levels</p> <p>Reduced morbidity</p> <p>Reduced mortality</p>

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<p>Pediatric ventricular assist device (Excor) for pediatric end-stage heart failure</p>	<p>Pediatric patients in whom end-stage heart failure (HF) has been diagnosed</p>	<p>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. This is the only pediatric VAD that is FDA approved.</p> <p>Berlin Heart GmbH, Berlin, Germany</p> <p>FDA approved Dec 2011; designated an orphan product</p>	<p>ECMO</p>	<p>Increased recovery of native heart (when used as destination therapy)                      Increased overall survival                      Reduced adverse events compared with ECMO</p>
<p>PerClot blood-clotting agent for perioperative and postoperative hemostasis</p>	<p>Surgical patients at risk of perioperative and postoperative hemorrhage</p>	<p>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.</p> <p>Cryolife, Inc., Atlanta, GA</p> <p>Company filed investigational device exemption application with FDA in Apr 2011 to begin U.S. trials ongoing; has marketing approval in Europe</p>	<p>Conventional hemostatic techniques (fibrin sealants, mechanical hemostasis) used during surgery</p>	<p>Adequate, timely hemostasis</p>

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Percutaneous annuloplasty (Carillon Mitral Contour System) for functional mitral valve repair	Patients in whom functional mitral regurgitation has been diagnosed	<p>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<sup>®</sup> Mitral Contour System<sup>™</sup> 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.</p> <p>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 Registry. Approved for marketing in Europe in 2009</p>	<p>Optimal medical management Minimally invasive surgery Open surgery</p>	<p>Reduced risk of cardiac events Reduced mitral regurgitation Reduced operative morbidity Reduced mortality Improved quality of life</p>
Percutaneous left atrial appendage occlusion (Watchman) for prevention of atrial fibrillation-associated stroke	Patients with atrial fibrillation who are not good surgical candidates	<p>Intended to block left atrial appendage opening and prevent clots from entering general circulation.</p> <p>Atritech, Inc., Plymouth, MN, acquired by Boston Scientific, Natick, MA</p> <p>Phase III trial ongoing</p>	Long-term anticoagulation therapy	Reduction in stroke risk
Phospholipase A2 inhibitor (darapladib) for treatment of atherosclerosis	Patients with atherosclerosis who are at high risk for myocardial infarction	<p>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 the treatment of 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.</p> <p>GlaxoSmithKline, Middlesex, UK</p> <p>Phase III trials ongoing</p>	<p>Ezetimibe Fibrates Niacin Statins</p>	<p>Improved plaque stability Reduced atherosclerosis Reduced morbidity and mortality</p>

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 have been diagnosed	<p>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.”</p> <p>ev3 Neurovascular, Menlo Park, CA</p> <p>FDA approved Apr 2011; continued followup for 5 years of individuals in the pivotal clinical cohort and continued access cohort required</p>	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	<p>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.</p> <p>Pluristem Therapeutics, Inc., Haifa, Israel</p> <p>Phase I trial ongoing; phase II/III trial planned</p>	<p>Antiplatelet therapy Cilostazol and pentoxifylline (improve walking distance) Cholesterol-lowering agents (statins) Percutaneous angioplasty and stenting Surgery In development: JVS-100 ( repair through recruitment of endogenous stem cells to the damaged organ)</p>	Less pain Increased amputation-free survival rate (amputations and death) Improved quality of life
PMX-60056 for management of coagulation in the use of heparin and low-molecular-weight heparins	Patients receiving heparin or low-molecular-weight heparins (LMWHs) in routine surgical procedures or in cases of bleeding complications	<p>Currently, no drugs are FDA approved to completely reverse the anticoagulant activity of LMWH given during surgery if bleeding becomes uncontrolled. Thus, developing a drug that allows for complete reversal of the anticoagulant activity of both heparin and LMWH has become an area of interest. Synthetic, small-molecule (PMX-60065) is intended to completely reverse anticoagulant activity of heparin or LMWHs and is believed to be the 1st such agent with the potential to do so.</p> <p>PolyMedix, Inc., Radnor, PA</p> <p>Phase II trial ongoing</p>	Protamine	Fast, complete reversal of anticoagulation Reduction in bleeding complications

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Pneumatic abdominal aortic tourniquet (AAT) for treatment of inguinal hemorrhage on the battlefield	Soldiers on the battlefield with inguinal hemorrhage	<p>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.</p> <p>Compression Works, LLC., Birmingham, AL (manufacturer) Speer Operational Technologies, LLC, Greenville, SC (distributor)</p> <p>FDA granted 510(k) clearance in Oct 2011, after expedited review</p>	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	<p>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.</p> <p>Arteriocyte, Inc., Cleveland, OH</p> <p>Phase I trial under investigational device exemption status ongoing</p>	Antiplatelet therapy Cilostazol and pentoxifylline (improve walking distance) Cholesterol-lowering agents (statins) Percutaneous angioplasty and stenting Surgery In development: Placenta-derived cell therapy (PLX-PAD) JVS-100 (encodes Stromal-cell Derived Factor 1, repair through recruitment of endogenous stem cells to the damaged organ)	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
<p>Polymer strands (cPAX system) for treatment of giant and wide-neck cerebral aneurysms</p>	<p>Patients in whom a large, giant and wide-neck cerebral aneurysm has been diagnosed</p>	<p>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 non-invasive computed tomography and MRI scans with little or no artifact for more accurate patient assessment and followup.</p> <p>NeuroVasx, Inc., Maple Grove, MN</p> <p>FDA approved under Humanitarian Device Exemption in Apr 2011</p>	<p>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</p>	<p>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</p>
<p>Positron emission tomography imaging agent (11C-metomidate) for diagnosis of hyperaldosteronism</p>	<p>Patients with diagnosed hypertension that may be secondary to hyperaldosteronism</p>	<p>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.</p> <p>University of Cambridge, Cambridge, UK</p> <p>Pilot trial completed</p>	<p>Adrenal vein sampling</p>	<p>Improved hyperaldosteronism diagnosis Improved management of hyperaldosteronism-associated hypertension Decreased morbidity</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Potassium binder (RLY5016) for prevention of hyperkalemia	Patients in whom heart failure (HF) or HF with underlying renal impairment has been diagnosed	<p>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.</p> <p>Relypsa, Santa Clara, CA</p> <p>Phase II trial completed</p>	Other potassium binders (e.g., sodium polystyrene sulfonate)	<p>Improved side effect profile</p> <p>Decreased incidence of hyperkalemia</p> <p>Optimal medical management of HF</p> <p>Improved long-term cardiac outcomes</p>
Recombinant neuregulin-1 (Neucardin) for treatment of chronic heart failure	Patients in whom heart failure (HF) has been diagnosed	<p>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.</p> <p>Zensun (Shanghai) Sci &amp; Tech Co., Ltd., Shanghai, China</p> <p>Phase III trial ongoing</p>	<p>Emerging stem cell therapies</p> <p>Pharmacotherapy (angiotensin-converting enzyme inhibitors, beta blockers)</p> <p>Polymer scaffolds</p>	<p>Increased cell survival</p> <p>Improved cell metabolism</p> <p>Increased cell proliferation</p> <p>Improved symptoms</p> <p>Improved morbidity and decreased mortality</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Robotic system (CorPath 200) for remotely controlled percutaneous coronary intervention	Patients undergoing percutaneous coronary intervention (PCI)	<p>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.</p> <p>Corindus Vascular Robotics, Inc., Natick, MA</p> <p>Phase II trial ongoing; company pursuing FDA 510(k) clearance</p>	Manually performed PCI	<p>Improved procedural visualization</p> <p>Reduced radiation exposure</p> <p>Reduced physician spinal strain</p> <p>Reduced physician fatigue</p> <p>Increased number of PCI procedures performed</p> <p>Improved patient safety</p>
RVX-208 for treatment of dyslipidemia	Patients with sub-optimal high-density lipoprotein (HDL) levels (dyslipidemia)	<p>Treatment of HDL as a single target is not available. RVX-208 is a novel, small-molecule inducer of apolipoprotein-1 synthesis; intended to generate functional HDL particles (that facilitate reverse cholesterol transport).</p> <p>Resverlogix, Calgary, Alberta, Canada</p> <p>Phase II trials ongoing</p>	Anacetrapib (in development) Niacin Rosuvastatin	<p>Improved HDL levels</p> <p>Decreased plaque burden</p> <p>Improved cardiovascular outcomes</p>
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	<p>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 for 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.</p> <p>Midwest Heart Foundation, Lombard, IL</p> <p>As of April 2012, screenings have been provided to more than 74,000 students.</p>	American Heart Association-recommended screening that includes physical examination and family and personal medical history	<p>Increased detection of potential cardiac abnormalities</p> <p>Earlier diagnosis of abnormalities</p> <p>Reduced incidence of sudden cardiac death</p> <p>Increased costs from screening general student population who would otherwise not be screened by ECG</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Selective serotonin-4 (RO1160367, SER101 ) antagonist for treatment of heart failure</p>	<p>Patients in whom heart failure has been diagnosed</p>	<p>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.</p> <p>Serodus ASA, Oslo, Norway (licensee) F. Hoffmann-La Roche, Basel, Switzerland (developer)</p> <p>Phase I trial completed</p>	<p>Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers Beta blockers Digitalis Diuretics</p>	<p>Increased cardiac output Improved cardioprotection Improved long-term cardiac outcomes</p>
<p>Standardized protocol and integrated system (RACE Project) for treatment and transfer of patients with ST-elevated myocardial infarction</p>	<p>Patients in whom an ST-elevated myocardial infarction (STEMI) has been diagnosed</p>	<p>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).</p> <p>Sponsored by North Carolina Chapter of the American College of Cardiology</p> <p>Pilot study with 436 patients at 55 hospitals completed; data available</p>	<p>Current STEMI practices (vary between hospitals)</p>	<p>Reduced door-in-to-door-out time Reduced time to treatment Improved cardiovascular morbidity Improved mortality outcomes</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Stromal cell-derived factor-1 (JVS-100) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	<p>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.</p> <p>Juventas Therapeutics, Inc., Cleveland, OH</p> <p>Phase I trial ongoing</p>	<p>Angiotensin-converting enzyme inhibitors            Angiotensin receptor blockers            Beta blockers            Digitalis            Diuretics            Mydicar (gene therapy in development)</p>	<p>Increased neovascularization and angiogenesis            Reduced symptom burden            Disease regression or slowed disease progression</p>
Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy	Patients with cardiomyopathy who are at risk for sudden cardiac arrest	<p>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.</p> <p>Cameron Health, Inc., San Clemente, CA (Boston Scientific Corp., Natick, MA, announced in Mar 2012 it was exercising its option to acquire Cameron Health)</p> <p>Premarket approval application submitted to FDA Jan 2012; FDA granted expedited review status; on Apr 26, 2012FDA Circulatory System Devices advisory panel voted 7 to 1 for efficacy and 8-0 for safety in favor of approval; Conformité Européene (CE) marked in 2009</p>	Other implantable defibrillators	<p>Quicker recovery after implantation            Reduced risk of unnecessary shocks            Reduced risk of failures to shock            Improved quality of life</p>
TB-402 for prevention of deep vein thrombosis associated with orthopedic surgery	Patients undergoing orthopedic surgery	<p>More effective antithrombotic therapy is needed for patients undergoing orthopedic surgery. TB-402 is human monoclonal antibody binding to Factor VIII (blood clotting factor); being developed as an anticoagulant for the treatment and prevention of venous thromboembolism post-orthopedic surgery; injected as a single dose intravenous bolus 18–24 hours after total knee replacement surgery; potential to reduce the risk of bleeding events and need for anticoagulation monitoring; overcome poor patient adherence with antithrombotic therapy (single dose).</p> <p>ThromboGenics, Inc., Heverlee, Belgium            BioInvent Inc., Lund, Sweden</p> <p>Phase II trial ongoing</p>	<p>Enoxaparin (Lovenox®)            Low-molecular-weight heparins            Short-term warfarin (Coumadin®) therapy</p>	<p>Decreased adverse effects            Decreased bleeding</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Transcatheter aortic valve (CoreValve) implantation for treatment of severe aortic stenosis	Patients in whom severe aortic stenosis (AS) has been diagnosed	<p>AS occurs in about 4% to 5% of people aged 75 years or older and more than 300,000 people are estimated to 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 replacement performed as an open heart surgery procedure. The transcatheter aortic valve (CoreValve®) 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.</p> <p>Medtronic, Inc., Minneapolis, MN</p> <p>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</p>	Open heart aortic valve surgery In development: Melody® transcatheter aortic valve for severe AS	Improved cardiac function Increased survival 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	<p>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 aortic valve.</p> <p>Edwards Lifesciences, Irvine, CA</p> <p>Phase III pivotal trial ongoing; (PARTNER I and II trials); FDA approved Nov 2011 for use in patients who cannot be treated by open-heart surgery. American Heart Association featured special session on transaortic valve replacement at its meeting in late Nov 2011. U.S. Centers for Medicare &amp; Medicaid Services opened national coverage analysis Sept 2011. Proposed decision memo was released Feb 2012, and national coverage analysis was expected to be completed by Jun 26, 2012.</p>	Optimal medical management Open surgery for valve replacement	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	<p>Minimally invasive transcatheter approach requires transseptal puncture to access the left heart chambers; in lieu of sutures, metal clip (MitraClip®), a flexible metal clip covered in polyester fabric is used. Intended for patients whose valve disease originates mainly from the center of the valve.</p> <p>Evalve, Inc., Menlo Park, CA (being acquired by Abbott Laboratories, Abbott Park, IL)</p> <p>Phase III trial ongoing; Conformité Européene (CE) marked in 2008</p>	<p>Open surgical mitral valve repair</p> <p>Drug therapy for patients for whom surgery is not an option</p>	<p>Improved quality of life for patients who are not good surgical candidates</p> <p>Reduction in mitral regurgitation and associated cardiovascular outcomes</p> <p>Decreased cost because of slowing disease progression</p> <p>Decreased cost compared with open surgery</p>
Transcatheter pulmonary valve (Sapien) implantation for treatment of pulmonary valve disease	Pediatric patients in whom a malformed pulmonary valve has been diagnosed	<p>Interventional cardiac catheterization procedure using the Sapien stent valve to replace a defective or worn-out pulmonary valve.</p> <p>Edwards Lifesciences, Irvine, CA</p> <p>Clinical trial ongoing under FDA investigational device exemption status; company intends to seek humanitarian device exemption from FDA</p>	Open heart surgery	<p>Accurate deployment of valve</p> <p>Avoided open surgery</p> <p>Reduced hospital stay</p> <p>Reduced pain</p> <p>Reduced bleeding/transfusion</p> <p>Quicker recovery and return to normal activity</p> <p>Improved quality of life</p>

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	<p>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.</p> <p>Cerevast Therapeutics, Inc., Redmond, WA</p> <p>Phase I/II trial completed; phase III trial registered, but not yet recruiting</p>	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	<p>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.</p> <p>Neurocrine Biosciences, Inc., San Diego, CA</p> <p>Trials ongoing (conducted by Centre for Cardiovascular Sciences at The University of Edinburgh through a British Heart Foundation grant )</p>	Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers Beta blockers Digitalis 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	<p>CardioFit® vagus nerve stimulation is an implantable device intended to improve heart-pumping capacity in patients with severe congestive HF.</p> <p>BioControl Medical, Yehud, Israel</p> <p>Phase III trial ongoing</p>	Optimal medical management Minimally invasive heart surgery Ventricular assist devices Heart transplantation	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	<p>Many factors contribute to patient nonadherence with hypertension treatment; therefore, hypertension often remains uncontrolled or poorly controlled, contributing to a patient's risk for 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.</p> <p>PhaseBio Pharmaceuticals, Inc., Malvern, PA</p> <p>Phase I trial ongoing</p>	<p>Angiotensin-converting enzyme inhibitors                      Angiotensin receptor blockers                      Beta blockers                      Calcium channel blockers                      Combination medications                      Diuretics                      Renin inhibitors</p>	<p>Improved control of hypertension                      Reduced risk for cardiovascular events                      Reduced morbidity                      Reduced mortality from hypertension</p>
Warm oxygenated blood perfusion (Organ Care System) for preservation of donor hearts	Patients in whom a need for a heart transplant has been diagnosed	<p>Currently, donor hearts being transported for transplantation are stopped and transported on ice, in a cooler (i.e., cold ischemic storage). This method is associated with limitations, such as a narrow treatment window, the potential for damage, and the inability to test the heart for function. As a result, only about 30% to 40% of suitable donor hearts are used for transplant. The Organ Care System (OCS™) is a heart transplant system that is intended to pump warm, oxygenated, nutrient-rich donor blood through the organ until it is implanted, thereby keeping the heart in a "living" state as it is transported. The manufacturer states that with this method, the heart may withstand longer periods of time outside of the body, be less vulnerable to damage during transportation, and be able to be tested for function and tissue matching. The system has attached consoles to monitor heart function during transport.</p> <p>TransMedics, Inc., Andover, MA</p> <p>Phase II/III trial ongoing</p>	Cold ischemic storage	<p>Improved patient outcomes                      Increased utilization of available organs                      Expanded pool of potential donor hearts</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Wireless cardiac resynchronization therapy (WiCS) for treatment of heart failure	Patients in whom heart failure has been diagnosed	<p>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.</p> <p>EBR Systems, Inc., Sunnyvale, CA Cambridge Consultants, Ltd., Cambridge, UK</p> <p>Phase I trial ongoing</p>	Biventricular pacing with leads	<p>Improved cardiac pacing Reduced need for reoperation because of lead failure Shortened implantation procedure time Reduced morbidity Reduced mortality</p>
Wireless monitoring system (Champion) for management of heart failure	Patients in whom moderately severe heart failure (HF) has been diagnosed	<p>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.</p> <p>CardioMEMS, Inc., Atlanta, GA</p> <p>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</p>	Weight monitoring (for fluid retention) Symptom monitoring	<p>Improved clinician access to changes in patient symptoms Earlier medical intervention Reduced HF-related hospitalizations Improved morbidity and mortality</p>

**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 II trial planned for late 2012	Donepezil Galantamine Memantine Rivastigmine	Delayed memory loss Delayed cognitive decline Longer maintenance of independent living
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, though 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	Bapineuzumab Ponezumab Solanezumab	Reduced a-beta load in brain Slowed progression of AD Increased survival Improved quality of life
Anti-amyloid 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; there is a need 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	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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
AZD1446 for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	<p>AZD1446 is a selective modulator of alpha4beta2.</p> <p>Targacept, Inc., Winston-Salem, NC, with AstraZeneca, London, UK</p> <p>Phase II trial completed; additional phase II trial planned</p>	Medications to slow progression of AD	<p>Delayed progression of AD symptoms</p> <p>Delayed need for intensive assistance with activities of daily living</p> <p>Improved quality of life</p> <p>Improved functional capacity</p>
Bapineuzumab for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	<p>Human monoclonal antibody intended to promote clearance of beta amyloid (a-beta) protein from damaged sites of the brain. Intended to minimize 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); current drug therapy has nonspecific antibodies that interact with many other brain processes.</p> <p>Janssen Alzheimer Immunotherapy, Dublin, Ireland Pfizer, Inc., New York, NY</p> <p>Phase III trials ongoing</p>	Other drug therapy for AD	<p>Halted or delayed disease progression</p> <p>Preserved cognitive function</p> <p>Preserved memory</p> <p>Improved quality of life</p> <p>Ability to live independently longer</p>
Beta-amyloid immunotherapy (CAD-106) for Alzheimer's disease	Patients in whom mild to severe Alzheimer's disease (AD) has been diagnosed	<p>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.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Phase II clinical trials ongoing; filing planned for after 2015</p>	Donepezil Galantamine Memantine Rivastigmine	<p>Reduced a-beta load in brain</p> <p>Regression or slowing of disease progression</p> <p>Reduced morbidity and mortality</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Beta-amyloid monoclonal antibody (RG1450, gantenerumab) for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	<p>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.</p> <p>F. Hoffmann-La Roche, Ltd., Basel, Switzerland</p> <p>Phase II trial ongoing</p>	Donepezil Galantamine Memantine Rivastigmine	Slowed disease progression, or regression Reduced morbidity Improved quality of life
Beta-amyloid monoclonal antibody (solanezumab, LY2062430) for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	<p>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 human 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.</p> <p>Eli Lilly &amp; Co., Indianapolis, IN</p> <p>Two phase III trials ongoing (EXPEDITION; EXPEDITION II)</p>	Bapineuzumab Cholinesterase inhibitors Memantine	Decreased a-beta load in brain Slowed or halted disease progression Improved memory and cognition Improved survival 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	<p>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.</p> <p>ProteoTech, Inc., Kirkland, WA Tasly Pharmaceuticals, Inc., Rockville, MD</p> <p>Phase I trial ongoing</p>	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	<p>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.</p> <p>Bristol-Myers Squibb, New York, NY</p> <p>Phase II trials ongoing</p>	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	<p>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.</p> <p>EnVivo Pharmaceuticals, Watertown, MA</p> <p>Phase I trial ongoing</p>	Donepezil Galantamine Memantine Rivastigmine	Slowed disease progression, or regression Improved long-term outcomes Improved quality of life
Handheld event-related potential/quantitative electroencephalography system (Cognition) for diagnosis of Alzheimer's disease	Patients in whom a diagnosis of Alzheimer's disease (AD) is suspected	<p>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. There is an unmet need for diagnostic/screening tools that can detect the condition before significant loss of memory, cognition, and activities of daily living occur. Cognition™ 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.</p> <p>Neuronetrix, Inc., Louisville, KY</p> <p>Trial ongoing (no phase listed)</p>	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
Immunoglobulin intravenously for treatment of Alzheimer's disease	Patients in whom mild to moderate AD has been diagnosed	<p>No effective treatments for slowing the progression of AD are available. Intravenous immunoglobulin (IVIG) infusion is approved for treatment of 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.</p> <p>Baxter International, Inc., Deerfield, IL</p> <p>Phase III trial ongoing</p>	Donepezil Galantamine Memantine Rivastigmine	Reduced a-beta load in brain Halted or 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
Insulin sensitizer (MSDC-0160) for treatment of Alzheimer's disease	Patients in whom mild Alzheimer's disease (AD) has been diagnosed	<p>Disease-modifying treatments for AD are not available; available drugs treat only symptoms, not the underlying causes of AD. 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.</p> <p>Metabolic Solutions Development Co., LLC, Kalamazoo, MI</p> <p>Phase II trial ongoing; the manufacturer received a \$773,000 grant from the Alzheimer's Drug Discovery Foundation to conduct a pilot phase IIa trial for this indication</p>	Cholinesterase inhibitors Memantine	Delay or halt in progression of AD Improved long-term outcomes Improved quality of life
Nicotine patch for treatment of mild cognitive impairment	Patients in whom mild cognitive impairment (MCI) has been diagnosed	<p>MCI may be a precursor to Alzheimer's disease (AD). No medications are approved by the FDA 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.</p> <p>University of Vermont, Burlington</p> <p>Trial completed</p>	Pharmacotherapy for AD	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	<p>MCI may be a precursor to Alzheimer's disease (AD). No medications are approved by FDA for MCI. Atomoxetine (Strattera®) is an oral selective norepinephrine reuptake inhibitor (SNRI) that is approved by FDA to improve attention span and decrease 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 utility 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.</p> <p>Eli Lilly and Co., Indianapolis, IN (manufacturer) Emory University, Atlanta, GA, with the National Institute on Aging, Bethesda, MD (investigators)</p> <p>Phase II trial registered; not yet open for participant recruitment</p>	Pharmacotherapy used for more advanced AD	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	<p>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.</p> <p>Eisai Co., Ltd., Tokyo, Japan (manufacturer) Case Western Reserve University School of Medicine, Cleveland, OH (investigator)</p> <p>Preclinical trial completed; drug can be prescribed off label in the U.S.</p>	Donepezil Galantamine Memantine Rivastigmine	Reduced a-beta load in brain Regression or slowing of disease progression Reduced morbidity Reduced 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	<p>No disease-modifying interventions for AD are currently available. This intervention represents a new mechanism of action for the treatment of 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 for 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.</p> <p>HealthPartners Research Foundation, Minneapolis, MN University of Kansas, Lawrence University of Washington, Seattle</p> <p>Phase II trials completed</p>	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	<p>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.</p> <p>AstraZeneca, London, UK</p> <p>Phase II trial completed; Phase I trial ongoing</p>	Other F18 agents in development: 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 injection (Amyvid) for detecting beta-amyloid plaques	Patients suspected of having beta amyloid (a-beta) - associated disease	<p>No method is available to detect a-beta in living patients suspected of having an a-beta-associated disease (e.g., Alzheimer's disease, Lewy body dementia, Guam Parkinson dementia complex). Florbetapir F18 (Amyvid™) is a radiopharmaceutical that binds specifically to a-beta and is visualized by PET. 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.</p> <p>Avid Radiopharmaceuticals, a subsidiary of Eli Lilly &amp; Co., Indianapolis, IN</p> <p>FDA approved Apr 2012 for detecting beta-amyloid plaques</p>	No current method of detecting a-beta in live patients Flutemetamol in development for same indication	Increased sensitivity and specificity of a-beta plaque detection
Positron emission tomography imaging agent flutemetamol for diagnosis of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) is suspected	<p>A positron emission tomography (PET) imaging agent to detect normal or raised amyloid levels and confirm a diagnosis of AD.</p> <p>General Electric Co., Fairfield, CT (GE Healthcare, Chalfont St. Giles, UK)</p> <p>Phase III trials ongoing</p>	Blood tests and other biomarkers Clinical exam and history Other imaging agents used with PET	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	<p>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.</p> <p>Ceregene, Inc., San Diego, CA</p> <p>Phase II trial ongoing</p>	Currently, no treatment exists for changing the underlying neurobiology of the disease Drug therapies for relief from cognitive symptoms	<p>Reduced apoptosis (programmed cell death)</p> <p>Reduced brain degeneration</p> <p>Preserved cognition</p> <p>Preserved memory</p> <p>Preserved independence</p> <p>Reduced need for caregivers</p> <p>Improved quality of life</p>

**Table 5. AHRQ Priority Condition: 05 Depression and Other Mental Health Disorders: 37 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	<p>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.</p> <p>Department of Veterans Affairs</p> <p>Trials completed</p>	Pharmacotherapy Psychotherapy	Reduced symptoms Improved quality of life
Antipsychotic (pomaglumetad methionil) for treatment of schizophrenia	Patients in whom schizophrenia has been diagnosed	<p>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.</p> <p>Eli Lilly &amp; Co., Indianapolis, IN</p> <p>Phase III trials ongoing</p>	Atypical antipsychotic drugs (e.g., Seroquel®, Zyprexa®)	Reduced symptoms Reduced side effects compared with other drugs Improved quality of life
Bright-light therapy for nonseasonal major depressive disorder	Patients in whom nonseasonal major depressive disorder (MDD) has been diagnosed	<p>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.</p> <p>National Institute of Mental Health, Bethesda, MD</p> <p>Trial completed</p>	Antidepressant medication (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, etc.) Psychotherapy Combination therapy	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
<p>Citizen soldier peer support outreach program (Buddy-to-Buddy) for returning veterans</p>	<p>Returning veterans in whom mental health or substance abuse conditions have been, or may be, diagnosed</p>	<p>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.</p> <p>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</p> <p>Fully implemented in Michigan; outcomes evaluation is ongoing</p>	<p>No peer support Professional only support Vet-to-Vet (peer support group meeting) program</p>	<p>Increased access for veterans to medical and psychological support resources Improved mental health outcomes Improved substance abuse outcomes Improved quality of life</p>
<p>Cortisol antagonist (mifepristone, Korlym) for treatment of psychotic depression</p>	<p>Patients in whom psychotic depression has been diagnosed</p>	<p>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.</p> <p>Corcept Therapeutics, Menlo Park, CA</p> <p>Phase III trial ongoing; FDA granted fast track status</p>	<p>Antipsychotics in combination with antidepressants Electroconvulsive therapy</p>	<p>Improvement in psychotic symptoms Reduced suicide rate Improved quality of life</p>

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	<p>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).</p> <p>St. Jude Medical, Inc., St. Paul, MN</p> <p>Pilot trial completed, pivotal trial planned</p>	<p>DBS using Medtronic device                      Deep transcranial magnetic stimulation                      Reclaim System in anterior capsule                      Repetitive transcranial magnetic stimulation                      Vagus nerve stimulation</p>	<p>Reduced symptom burden                      Improved quality of life</p>
Deep brain stimulation (Reclaim system) therapy for severe obsessive-compulsive disorder	Patients in whom severe obsessive-compulsive disorder (OCD) has been diagnosed	<p>Electrode leads (Reclaim™ system) connected from chest to anterior limb of the internal capsule stimulate the patient's brain.</p> <p>Medtronic, Inc., Minneapolis, MN</p> <p>Approved under humanitarian device exemption as adjunct to medications and alternative to anterior capsulotomy in patients whose disease has failed to respond to 3 selective serotonin reuptake inhibitors</p>	<p>Anterior capsulotomy                      Combination therapy                      Drug therapy alone                      Psychotherapy alone</p>	<p>Reduced scores on OCD measures                      Improved quality of life</p>
Deep brain stimulation (Reclaim system) therapy for treatment-resistant depression	Patients in whom treatment-resistant depression has been diagnosed	<p>Neurostimulator (Reclaim system) implanted subcutaneously in chest; intended to deliver controlled electrical stimulation to targeted parts of the brain via thin wire electrodes.</p> <p>Medtronic, Inc., Minneapolis, MN</p> <p>Phase III trial ongoing</p>	<p>Antidepressant medications                      Electroconvulsive therapy                      Transcranial magnetic stimulation                      Vagus nerve stimulation</p>	<p>Reduced scores on depression scales                      Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Deep brain stimulation therapy for Tourette's syndrome</p>	<p>Patients in whom Tourette's syndrome (TS) has been diagnosed</p>	<p>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.</p> <p>University of Florida, Gainesville</p> <p>Trial ongoing (no phase listed) at University of Florida; University holds only FDA investigational device exemption approved for DBS for TS in U.S.</p>	<p>Antidepressants Botulinum toxin type A (Botox®) injections Central adrenergic inhibitors Fluphenazine Pimozide Stimulant medications</p>	<p>Reduced symptom burden Improved quality of life</p>
<p>Dimethoxybenzylidene anabaseine for treatment of schizophrenia</p>	<p>Patients in whom schizophrenia has been diagnosed</p>	<p>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 treatment of 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.</p> <p>Department of Veterans Affairs</p> <p>Phase II trial ongoing</p>	<p>Atypical antipsychotics Other NNR agonists in development</p>	<p>Improved cognitive function Improved clinical schizophrenia rating scales Improved quality of life</p>
<p>Extended intensive psychotherapy assisted by MDMA (methylenedioxyamphetamine) for treatment of posttraumatic stress disorder</p>	<p>Patients in whom treatment-refractory posttraumatic stress disorder (PTSD) has been diagnosed</p>	<p>Methylenedioxyamphetamine (MDMA; ecstasy) has pharmacologic effects that include serotonin release, 5HT2 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 methylenedioxyamphetamine 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.</p> <p>Funded by Multidisciplinary Association for Psychedelic Studies, Santa Cruz, CA</p> <p>Phase II trial ongoing, with permission from FDA and the U.S. Drug Enforcement Administration</p>	<p>Combination therapy Intensive psychotherapy alone SSRIs alone</p>	<p>Improved efficacy of intensive psychotherapy sessions Improved rating scales (e.g., Clinician-Administered PTSD Scale) Improved quality of life</p>

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	<p>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).</p> <p>BioLineRx, Ltd., Jerusalem, Israel Cypress Bioscience, Inc., San Diego, CA</p> <p>Phase II/III trial ongoing</p>	Atypical antipsychotics Dimethoxybenzylidene anabaseine TC-5619	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	<p>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.</p> <p>Addex Pharmaceuticals, Geneva, Switzerland Ortho-McNeil-Janssen Pharmaceuticals, Inc., Titusville, NJ</p> <p>Phase IIa trial ongoing</p>	Atypical antipsychotics (e.g., quetiapine)	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)	<p>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.</p> <p>Chugai Pharmaceutical subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland</p> <p>Phase III trials ongoing; filing anticipated in 2013</p>	<p>Novel mechanism of action, so no comparators in class</p> <p>Atypical antipsychotics (e.g., quetiapine)</p> <p>Lithium</p>	<p>Meaningful reduction in negative symptoms of schizophrenia, as measured by clinical rating scales (e.g., Positive and Negative Syndrome Scale)</p> <p>Improved personal and social functioning</p>
Glycine-site functional partial agonist selective modulator of NMDAR (GLYX-13) for treatment-resistant depression	Patients in whom treatment-resistant depression has been diagnosed	<p>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.</p> <p>Naurex, Inc., Evanston, IL</p> <p>Phase II trials ongoing</p>	<p>Cognitive behavior therapy</p> <p>Combination treatment</p> <p>Other NMDAR modulators (e.g. ketamine)</p> <p>Psychotherapy</p> <p>Selective serotonin reuptake inhibitors</p>	<p>Improved score on standardized depression measures</p> <p>Reduced side effects</p> <p>Improved quality of life</p>
Lisdexamfetamine (Vyvanse) for treatment of negative symptoms in schizophrenia	Patients in whom schizophrenia has been diagnosed	<p>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.</p> <p>Shire Pharmaceuticals, plc, Dublin, Ireland</p> <p>Phase II trial completed</p>	<p>Atypical antipsychotics</p> <p>BL-1020 (in development)</p> <p>RG-1678 (in development)</p> <p>RO4917838 (in development)</p>	<p>Reduced negative symptoms</p> <p>Improved social functioning</p> <p>Improved quality of life</p>

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	<p>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.</p> <p>Shire Pharmaceuticals, plc, Dublin, Ireland</p> <p>Phase III trials ongoing</p>	Other amphetamines	<p>Improved symptoms on major depression scales</p> <p>Improved quality of life</p>
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	<p>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.</p> <p>Various research institutions, including Northwestern University, Evanston, IL, and McNally Laboratory at Harvard University, Cambridge, MA</p> <p>Clinical trials ongoing</p>	In-person psychotherapy Internet-delivered (nonmobile phone) psychotherapy	<p>Improved performance on mental health rating scales</p> <p>Reduced morbidity</p> <p>Reduced mortality</p> <p>Improved quality of life</p>

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	<p>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-HT<sub>3</sub> and 5-HT<sub>7</sub> receptor antagonist, 5-HT<sub>1A</sub> receptor agonist, 5-HT<sub>1B</sub> 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.</p> <p>Takeda Pharmaceutical Co., Ltd., Osaka, Japan, jointly with H. Lundbeck a/s, Valby, Denmark</p> <p>Phase III trials ongoing</p>	<p>Combination therapy Deep brain stimulation Electroconvulsive therapy Other antidepressants Psychotherapy Transcranial magnetic stimulation Vagus nerve stimulation</p>	<p>Improved scores on validated depression instruments Reduced side effects including sexual dysfunction Improved quality of life</p>
Nicotinic alpha-7 agonist (EVP-6124) for treatment of cognitive symptoms of schizophrenia	Patients in whom schizophrenia has been diagnosed	<p>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.</p> <p>EnVivo Pharmaceuticals, Watertown, MA</p> <p>Phase II trial completed; phase III trials planned for 2012</p>	<p>Atypical antipsychotics Other nicotinic agonists in development</p>	<p>Improved cognitive symptoms Improved social functioning Improved quality of life</p>
Nicotinic receptor (TC-5619) agonist for treatment of schizophrenia	Patients in whom schizophrenia has been diagnosed	<p>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.</p> <p>Targacept, Winston-Salem, NC</p> <p>Phase II trial completed, additional phase II trial ongoing</p>	<p>Atypical antipsychotics Other NNR agonists in development</p>	<p>Improved cognitive symptoms Improved social functioning Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label acamprosate for treatment of binge-eating disorder	Patients in whom binge-eating disorder has been diagnosed	<p>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. Acamprosate is a glutamate receptor modulator that acts as an antagonist to the N-methyl-D-aspartate receptor (NMDAR), and is approved for the treatment of alcohol dependence. It has been suggested that addiction (e.g., alcohol dependence) and binge-eating disorder are pathophysiologically related, in that they both are moderated by reward circuitry in the brain. Additionally, in patients with alcohol dependence, acamprosate has been shown to reduce food craving and weight gain. In a clinical trial, the drug is being dosed as an oral tablet, administered 3 times daily.</p> <p>Lindner Center of Hope, Mason, OH</p> <p>Phase II/III trial completed</p>	Antiepileptics Selective norepinephrine reuptake inhibitors Selective serotonin-norepinephrine reuptake inhibitors	Improved symptoms of binge eating Decreased morbidity and mortality
Off-label armodafinil for treatment of binge-eating disorder	Patients in whom binge-eating disorder has been diagnosed	<p>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 is a wakefulness-promoting drug with an unknown mechanism of action; it is approved under the brand name Nuvigil® for the treatment of 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.</p> <p>Cephalon, Inc., acquired by Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, in Oct 2011 (manufacturer) Lindner Center of Hope, Mason, OH (investigator)</p> <p>Phase III trial ongoing</p>	Antiepileptics Selective norepinephrine reuptake inhibitors Selective serotonin-norepinephrine reuptake inhibitors	Improved symptoms of binge eating Decreased morbidity and mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label ketamine for treatment-resistant severe depression	Patients in whom treatment-resistant major depressive disorder or bipolar depression has been diagnosed	<p>Oral N-methyl-D-aspartate (NMDA; ketamine, a recreational drug) for rapid (within 40 minutes) relief of severe treatment-resistant depression.</p> <p>National Institutes of Health, Bethesda, MD</p> <p>Phase II trial ongoing</p>	<p>Cognitive behavior therapy</p> <p>Combination therapies</p> <p>Electroconvulsive therapy</p> <p>Other antidepressant medicines</p> <p>Psychotherapy</p> <p>Transmagnetic stimulation</p>	<p>Rapid response</p> <p>Improved treatment adherence</p> <p>Reduced symptoms</p> <p>Improved quality of life</p>
Off-label mifepristone (Mifeprex) for treatment of anxiety-associated cognitive impairment	Patients in whom cognitive impairment, secondary to anxiety, has been diagnosed	<p>Cognitive impairment associated with anxiety can lead to disability, reduced treatment response, and dementia. No treatments are approved for treatment of cognitive impairment. Though 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 this labeled indication change.</p> <p>National Institute of Mental Health, Bethesda, MD</p> <p>Phase III trial registered, not yet recruiting</p>	Cholinesterase inhibitors	<p>Improved memory and executive function</p> <p>Improved morbidity (dementia, disability)</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label oxytocin for treatment of social cognition deficits associated with schizophrenia	Patients in whom schizophrenia has been diagnosed	<p>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.</p> <p>Several institutions, including University of California, Los Angeles, and University of North Carolina, Chapel Hill</p> <p>Clinical trials completed</p>	Psychotherapeutic intervention	Improved social cognition Improved quality of life
Off-label riluzole (Rilutek) for treatment of major depressive disorder	Patients in whom treatment-resistant major depressive disorder (MDD) has been diagnosed	<p>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 treatment of 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.</p> <p>Sanofi, Paris, France (manufacturer) National Institute of Mental Health, Bethesda, MD (investigator)</p> <p>Phase II trials ongoing</p>	Antidepressant pharmacotherapy (selective serotonin reuptake inhibitors) Deep brain stimulation Electroconvulsive therapy Psychotherapy Transcranial magnetic stimulation Vagus nerve stimulation	Glutamatergic modulation Improved MDD symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label sodium oxybate for treatment of binge-eating disorder	Patients in whom binge-eating disorder has been diagnosed	<p>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 treatment of 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.</p> <p>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)</p> <p>Phase II/III trial completed; regulated as a Class III controlled substance by FDA and U.S. Drug Enforcement Agency</p>	Antiepileptics Selective norepinephrine reuptake inhibitors Selective serotonin-norepinephrine reuptake inhibitors	Improved symptoms of binge eating Improved morbidity and mortality
Off-label venlafaxine (Effexor) for treatment of compulsive hoarding	Patients with compulsive hoarding habits who have no other identified psychiatric morbidity	<p>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.</p> <p>Pfizer, Inc., New York, NY (manufacturer) University of California, San Diego (investigator)</p> <p>Clinical trial completed</p>	Psychotherapy SSRIs	Improved scores on hoarding 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
Reversible inhibitor of monoamine oxidase A (TriRima) for treatment-resistant depression	Patients in whom treatment-resistant depression has been diagnosed	<p>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.</p> <p>CeNeRx BioPharma, Inc., Cary, NC</p> <p>Phase II trials ongoing</p>	<p>Aurorix (only approved reversible inhibitor of MAO-A; not marketed in U.S.; approved in other countries)</p> <p>MAO inhibitors</p> <p>Selective serotonin reuptake inhibitors</p>	<p>Improved score on validated depression scales</p> <p>Reduced serious cardiovascular side effects associated with other MAO-A inhibitors</p>
RO4917838 for treatment of negative symptoms of schizophrenia	Patients in whom schizophrenia has been diagnosed	<p>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.</p> <p>F. Hoffmann-La Roche Ltd., Basel, Switzerland</p> <p>Phase III trials ongoing</p>	<p>Current drug therapy for schizophrenia (positive symptoms, e.g., hallucinations)</p>	<p>Symptom improvement</p> <p>Improved quality of life</p>
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 (SSRIs)	<p>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.</p> <p>Euthymics Biosciences, Inc., Cambridge, MA</p> <p>Phase II/III trial ongoing</p>	<p>Deep brain stimulation</p> <p>Electroconvulsive therapy</p> <p>Psychotherapy</p> <p>Transcranial magnetic Vagus nerve stimulation</p> <p>Medicines:</p> <p>SSRIs</p> <p>Serotonin norepinephrine reuptake inhibitors</p>	<p>Increased serotonin, norepinephrine, and dopamine neurotransmission</p> <p>Improvement in symptoms, as measured by standard depression rating scales</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Synthetic neurosteroid (Ganaxolone) for treatment of posttraumatic stress disorder	Patients in whom posttraumatic stress disorder (PTSD) has been diagnosed	<p>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.</p> <p>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)</p> <p>Phase II trial ongoing</p>	<p>Acupuncture (in development) Counseling (e.g., cognitive behavior therapy; group therapy) Selective serotonin reuptake inhibitors</p>	<p>Improved symptoms Improved quality of life</p>
Text-messaging therapy for bulimia nervosa	Patients in whom bulimia nervosa has been diagnosed	<p>Feelings of shame affect willingness to undergo treatment, and access to treatment and duration of treatment are significant issues with eating disorders because of chronic nature of the disorders. New approaches to behavioral therapies that engage participants ongoing are needed. In this program, participants send 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.</p> <p>University of North Carolina at Chapel Hill</p> <p>Trial completed (phase not reported)</p>	<p>Antidepressant medication Cognitive behavior therapy and other psychological counseling Combination therapy Nutritional counseling</p>	<p>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</p>

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 major depressive disorder	Patients in major depressive disorder (MDD) has been diagnosed	<p>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).</p> <p>University of California, Los Angeles, and NeuroSigma, Inc., Los Angeles, CA</p> <p>Phase II trial ongoing</p>	<p>DBS Electroconvulsive therapy Pharmacotherapy rTMS VNS</p>	<p>Improved depression symptoms Improved quality of life</p>
Trigeminal nerve stimulation (eTNS) for treatment of posttraumatic stress disorder	Patients in whom posttraumatic stress disorder (PTSD) has been diagnosed	<p>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).</p> <p>University of California, Los Angeles, and NeuroSigma, Inc., Los Angeles, CA</p> <p>Phase I trial ongoing</p>	<p>Pharmacotherapy Psychotherapy</p>	<p>Improved symptom burden Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Wisdom therapy for posttraumatic embitterment disorder	Patients in whom posttraumatic embitterment disorder (PTED) has been diagnosed	<p>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.</p> <p>First described by Michael Linden, Charité University Hospital, Berlin, Germany</p> <p>Pilot trial completed</p>	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: 14 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	<p>There is no cure 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 <i>FMR1</i> gene that basically turn off the gene; it is the most common known heritable cause of cognitive and behavioral disability. Normal <i>FMR1</i> 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.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Phase II/III trials ongoing</p>	<p>Physical and behavioral interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living</p> <p>Medications:                      Antipsychotics                      Central nervous system stimulants                      Clonidine (Catapres®)                      Folic acid                      Selective serotonin reuptake inhibitors</p>	Change baseline in behavioral symptoms using the Aberrant Behavior Checklist

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Functional magnetic resonance imaging for differentiating autism from bipolar and other behavioral disorders in children	Children suspected of having autistic spectrum disorder	<p>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 two 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.</p> <p>Institute of Psychiatry, King's College, London, UK</p> <p>Phase I trial completed on autism and bipolar disorder; other trials ongoing</p>	Assessments based on interviews and behavior observation	<p>Early diagnosis</p> <p>Early intervention and treatment</p> <p>Improved quality of life</p>
Ganaxolone for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	<p>There is no cure FXS; medications and behavioral interventions alleviate individual symptoms but do not address the cause of FXS. Individuals with FXS have DNA mutations in the <i>FMR1</i> 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 the 3beta-methylated synthetic analog of the neurosteroid 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.</p> <p>Marinus Pharmaceuticals, Inc., Branford, CT</p> <p>Early phase trial planned to start in 1st half of 2012, but no trials registered in the National Clinical Trials database as of April 2012</p>	<p>Physical and behavioral intervention including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living</p> <p>Medications:</p> <ul style="list-style-type: none"> <li>Antipsychotics</li> <li>Central nervous system stimulants</li> <li>Clonidine (Catapres®)</li> <li>Folic acid</li> <li>Selective serotonin reuptake inhibitors</li> </ul> <p>To address sleep disturbances</p> <p>To treat seizures and mood instability</p>	<p>Improved behavior and cognitive measures</p> <p>Increased sociability and communication</p> <p>Improved scores on scales of sociability</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mecasermin (Increlex) for treatment of Rett's syndrome	Children aged 2–12 years in whom Rett's syndrome has been diagnosed	<p>Mecasermin (Increlex®) is a synthetic form of insulin-like growth factor-1 to stimulate synaptic maturation and is intended to improve cognitive function in children with Rett's syndrome.</p> <p>Ipsen (acquired developer Tercica, Inc.), Paris, France</p> <p>Phase I/II trial ongoing</p>	Educational programs	Improved neurodevelopmental symptoms (severe cognitive, motor, and language problems and autistic behaviors)
N-acetylcysteine for treatment of autism	Children receiving a diagnosis of autism	<p>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 treatment of autism spectrum disorders, NAC is being administered orally, 600 mg 3 times daily, with a maximum dose of 4,200 mg/day.</p> <p>Stanford University School of Medicine, Stanford, CA, and Indiana University School of Medicine, Indianapolis, in collaboration with National Alliance for Autism Research, Princeton, NJ</p> <p>Stanford University School of Medicine: phase II trial completed Indiana University School of Medicine: phase II trial completed</p>	<p>Behavioral programs for autistic children Risperidone</p> <p>Off-label treatments, (e.g., acetylcholinesterase inhibitors, alpha-2 adrenergic agonists, carnitine) Immunomodulation and anti-inflammatory treatments Melatonin Naltrexone Oxytocin Tetrahydrobiopterin</p>	<p>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</p>
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	<p>ND0801 dermal patch is intended to work by preventing desensitization of neural nicotinic receptors, thereby improving cognition and focus.</p> <p>NeuroDerm, Ltd., Ness Ziona, Israel</p> <p>Phase IIa trial ongoing</p>	Standard medications for ADHD	<p>Cognitive improvement Fewer side effects than current ADHD stimulant medications Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Off-label donepezil (Aricept) for treatment of fragile X syndrome</p>	<p>Patients in whom fragile X syndrome (FXS) has been diagnosed</p>	<p>There is no cure 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 <i>FMR1</i> 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. Approved to treat mild, moderate, and severe Alzheimer's disease and is under study for various other types of cognitive impairment, including Down syndrome.</p> <p>Under study by Autism Speaks, New York, NY; National Institute of Mental Health, Rockville, MD; and Stanford University, Stanford, CA</p> <p>Phase II trial ongoing</p>	<p>Physical and behavioral intervention including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living</p> <p>Medications: Antipsychotics Central nervous system stimulants Clonidine (Catapres®) Folic acid Selective serotonin reuptake inhibitors</p>	<p>Improvements in specific measures of behavior and cognition Improved scores on behavior assessments Improved scores on working memory tests</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Off-label intranasal oxytocin for treatment of social dysfunction in autism spectrum disorders</p>	<p>Patients in whom autistic spectrum disorder (ASD) or Asperger's syndrome has been diagnosed</p>	<p>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. Clinical trial dose: 0.4 IU/kg of body weight morning and lunch.</p> <p>Montefiore Medical Center, Bronx, NY; Mount Sinai School of Medicine, New York, NY; Victoria Apotheke, Zurich, Switzerland is the source of the oxytocin; trial is funded by U.S. Department Of Defense, Washington, DC, University of Illinois, Urbana, and Holland Bloorview Kids Rehabilitation Hospital, Toronto, Ontario, Canada</p> <p>Phase II trials ongoing</p>	<p>Applied behavior analysis                      Floor time                      Gluten-free, casein-free diet                      Occupational therapy                      PECS (communicate using picture cards)                      PRT (teach language, decrease disruptive/self-stimulatory behaviors)                      Relationship development intervention                      SCERTS (practices and strategies from other approaches)                      Sensory integration therapy                      Speech therapy                      TEACCH (special education program)                      Verbal behavior intervention</p>	<p>Improved Diagnostic Analysis of Nonverbal Accuracy results                      Improved Change Social Responsivity Scale score                      Improved Change Clinical Global Impressions Scale - Improvement score</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label minocycline for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	<p>There is no cure 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 <i>FMR1</i> 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 treatment of 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.</p> <p>University of California, Davis; FRAXA Research Foundation (in collaboration with Fragile X Foundation of Canada), Toronto, Ontario, Canada</p> <p>Pilot trial and unphased trial ongoing</p>	<p>Medications to address sleep and behavior and mood symptoms: Antipsychotics Central nervous system stimulants Clonidine (Catapres®) Folic acid Selective serotonin reuptake inhibitors</p>	<p>Improved behavior, perceptual and cognitive development Improved daily living skills Improved gross motor skill development Increased sociability and communication Improved speech and language</p>
RO4917523 for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	<p>There is no cure 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 <i>FMR1</i> gene that basically turn off the gene; it is the most common known heritable cause of cognitive and behavioral disability. Normal <i>FMR1</i> 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.</p> <p>F. Hoffmann-La Roche, Ltd., Basel, Switzerland</p> <p>Phase II trial completed</p>	<p>Physical and behavioral intervention including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Medications: Antipsychotics Central nervous system stimulants Clonidine (Catapres®) Folic acid Selective serotonin reuptake inhibitors To address sleep disturbances To treat seizures and mood instability</p>	<p>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</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
STX107 for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	<p>There is no cure 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 <i>FMR1</i> gene that basically turn off the gene; it is the most common known heritable cause of cognitive and behavioral disability. Normal <i>FMR1</i> 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.</p> <p>Seaside Therapeutics, Inc., Cambridge, MA</p> <p>Phase II trial ongoing</p>	<p>Physical and behavioral intervention including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living</p> <p>Medications: Antipsychotics Central nervous system stimulants Clonidine (Catapres®) Folic acid Selective serotonin reuptake inhibitors</p> <p>To address sleep disturbances To treat seizures and mood instability</p>	<p>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</p>
STX209 (arbaclofen) for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	<p>There is no cure 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 <i>FMR1</i> 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.</p> <p>Seaside Therapeutics, Inc., Cambridge, MA</p> <p>Phase III trials ongoing</p>	<p>Physical and behavioral intervention including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living</p> <p>Medications: Antipsychotics Central nervous system stimulants Clonidine (Catapres®) Folic acid Selective serotonin reuptake inhibitors</p> <p>To address sleep disturbances To treat seizures and mood instability</p>	<p>Improved behavioral and cognitive measures Increased sociability and communication</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>STX209 (arbaclofen) for treatment of social withdrawal in autism spectrum disorder</p>	<p>Patients in whom an autism spectrum disorder (ASD) has been diagnosed</p>	<p>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.</p> <p>Seaside Therapeutics, Inc., Cambridge, MA</p> <p>Phase II trials ongoing</p>	<p>Applied behavior analysis                      Floor time                      Gluten free, casein free diet (GFCF)                      Occupational therapy                      PECS (communicate using picture cards)                      PRT (teach language, decrease disruptive/self-stimulatory behaviors)                      Relationship development intervention                      SCERTS (practices and strategies from other approaches)                      Sensory integration therapy                      Speech therapy                      TEACCH (special education program)                      Verbal behavior intervention                      Investigational:                      Oxytocin nasal                      Brief parent-mediated intervention                      Friendship training program</p>	<p>Improvement in Aberrant Behavior Checklist-Social Withdrawal Subscale</p>
<p>Trigeminal nerve stimulation (eTNS) for treatment of attention-deficit/hyperactivity disorder</p>	<p>Patients in whom attention-deficit hyperactivity disorder (ADHD) has been diagnosed</p>	<p>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.</p> <p>University of California, Los Angeles, and NeuroSigma, Inc., Los Angeles, CA</p> <p>Phase I trial ongoing</p>	<p>Behavioral therapies                      Combination therapies                      Drug therapies</p>	<p>Improved behavior and focus                      Improved quality of life</p>

**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
AKB-9778 for treatment of diabetic macular edema	Patients in whom diabetic macular edema has been diagnosed	<p>Currently, no pharmacotherapy is approved for treatment of 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.</p> <p>Akebia Therapeutics, Inc., Cincinnati, OH</p> <p>Phase I trial complete; company was expected to start a Phase 1b/2a trial in 2nd quarter 2012</p>	<p>Intravitreal triamcinolone acetonide with or without laser photocoagulation                      PF-04523655 (under development)                      Laser photocoagulation alone                      Vascular endothelial growth factor antagonists (bevacizumab, pegaptanib, ranibizumab)</p>	<p>Improved visual acuity                      Halted loss of vision                      Increased contrast sensitivity                      Improved quality of life</p>
Allogeneic fecal enema for treatment of metabolic syndrome in obese patients	Obese patients in whom metabolic syndrome (at least 3 of 5 National Cholesterol Education Project metabolic syndrome criteria) has been diagnosed	<p>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.</p> <p>Academic Medical Center/University of Amsterdam, the Netherlands</p> <p>Pilot trial completed</p>	<p>Antiobesity drugs                      Bariatric surgery                      Dietary and exercise changes</p>	<p>Improved fecal flora composition                      Weight loss                      Resolution of metabolic syndrome</p>

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	<p>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.</p> <p>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</p> <p>Phase I/II trial and phase II trials ongoing; FDA granted orphan drug designation</p>	Dietary and lifestyle changes Various modifications to insulin	Reduced daily insulin usage Improved glycosylated hemoglobin (HbA <sub>1c</sub> ) 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	<p>Research has implicated inflammation in the development of insulin resistance associated with T2DM; however, no anti-inflammatory treatments are currently approved for treatment of T2DM. Anakinra is a recombinant protein inhibitor of interleukin-1 (IL-1) receptors that has been approved since 2001 for treatment of 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.</p> <p>Amgen, Inc., Thousand Oaks, CA (manufacturer) Radboud University Nijmegen, the Netherlands; University Hospital, Zurich, Switzerland; and Steno Diabetes Center, Gentofte, Denmark (investigators)</p> <p>Phase II/III trials ongoing</p>	Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Achieved target glycosylated hemoglobin (HbA <sub>1c</sub> ) 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	<p>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.</p> <p>Derma Sciences, Princeton, NJ</p> <p>Phase II trial completed; company anticipates phase III trial to commence in 2nd half of 2012</p>	<p>Acellular wound matrices Cellular wound matrices Hyperbaric oxygen therapy Negative pressure wound therapy</p>	<p>Increased percentage of ulcers healed Decrease in ulcer size</p>
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	<p>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.</p> <p>Various manufacturers</p> <p>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</p>	<p>External insulin pump Injected insulin</p>	<p>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</p>
Atrasentan for treatment of chronic kidney disease in type 2 diabetes	Patients with type 2 diabetes mellitus who have chronic kidney disease (CKD)	<p>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.</p> <p>Abbott Laboratories, Abbott Park, IL</p> <p>Phase II trial completed</p>	<p>Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride) Various drugs under development</p>	<p>Reduced urine albumin-to-creatinine ratio Improved kidney function Improved quality of life</p>

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	<p>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.</p> <p>Various academic research centers and manufacturers</p> <p>Mid-to-late phase trials completed and ongoing</p>	Dietary and exercise changes Drugs such as metformin	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	<p>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.</p> <p>Oxford Medical Diagnostics, Oxford, UK</p> <p>Early phase trials planned</p>	Conventional glucose testing from blood samples	Improved adherence with blood glucose testing
Breath analysis (laser-based) for diagnosing diabetes	Patients at risk of type 1 or type 2 diabetes mellitus	<p>Uses laser-based gas analysis; intended to provide a rapid, noninvasive method for diagnosis.</p> <p>Avacta Group, plc, York, UK Oxford Medical Diagnostics, Oxford, UK</p> <p>Unphased trial ongoing</p>	Blood glucose testing	<p>More patients screened and diagnosed</p> <p>Diagnosis earlier in disease course</p> <p>Faster, point-of-service diagnosis</p>
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	<p>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.</p> <p>Generex Biotechnology Corp., Toronto, Ontario, Canada</p> <p>Phase III trial completed; FDA approved for patients with life-threatening T1DM or T2DM with no other treatment options Sept 2009</p>	Adjunct to other insulin products	<p>Achieved target glycosylated hemoglobin (HbA<sub>1c</sub>) levels</p> <p>Reduced glycemic excursions related to meals</p> <p>Prevented onset of T2DM in prediabetic individuals</p> <p>Delayed insulin dependence in T2DM</p> <p>Improved quality of life</p>

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	<p>Research has implicated inflammation in the development of insulin resistance associated with T2DM; however, there are no currently approved anti-inflammatory treatments for 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.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Phase II/III trial completed</p>	<p>Anakinra (IL-1 inhibitor in development)                      Insulin sensitizers (pioglitazone, rosiglitazone)                      Metformin                      Sitagliptin                      Sulfonylurea drugs (glimepiride)</p>	<p>Glycosylated hemoglobin (HbA<sub>1c</sub>) level control                      Desired fasting glucose level control                      Resolved insulin sensitivity</p>
Chemokine receptor antagonist (CCX140) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	<p>While 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.</p> <p>ChemoCentryx, Inc., Mountain View, CA</p> <p>Phase II trial completed, with 2 phase II trials ongoing</p>	<p>Dietary and exercise changes                      Traditional diabetes medications</p>	<p>Improved glycosylated hemoglobin (HbA<sub>1c</sub>) levels                      Reduced hyperglycemic episodes                      Halted or delayed secondary complications (i.e., nephropathy)</p>
C-peptide replacement therapy (Ersatta™) for treatment of diabetic peripheral neuropathy	Patients in whom diabetic peripheral neuropathy has been diagnosed	<p>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 the treatment of various secondary complications of diabetes.</p> <p>Cebix, Inc., La Jolla, CA</p> <p>Phase Ib trial ongoing; FDA has granted Ersatta fast track status for diabetic peripheral neuropathy</p>	<p>Analgesics                      Antiepileptics                      Duloxetine (antidepressant),                      Lidocaine patches                      Pregabalin (anticonvulsant)                      Selective serotonin reuptake inhibitors                      Serotonin-norepinephrine reuptake inhibitors                      Tricyclic antidepressants</p>	<p>Reduced patient-reported pain on visual analog scale                      Improved quality of life</p>

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	<p>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, with strong bonds with carbon; this affinity may impact 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.</p> <p>Concert Pharmaceuticals, Inc., Lexington, MA</p> <p>Phase II trial ongoing</p>	<p>Controlling high blood pressure is the most effective way of slowing kidney damage from diabetic nephropathy</p> <p>Angiotensin-converting enzyme inhibitors</p> <p>Angiotensin receptor blockers</p> <p>Dialysis (once end-stage kidney disease develops)</p> <p>Kidney transplantation</p>	<p>Protect kidney function and slow disease progression when added to existing therapy</p> <p>Delay/prevent kidney transplantation</p>
DB 959 (PPAR agonist) delta/gamma for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus has been diagnosed	<p>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.</p> <p>DARA Biosciences, Inc., Raleigh, NC</p> <p>Phase Ib trial completed; phase IIa planned for 2012</p>	<p>Non-PPAR agonist drugs</p> <p>Other agonist drugs that can cause weight gain and do not improve lipid profile</p>	<p>Achieved target glycosylated hemoglobin (HbA<sub>1c</sub>) levels</p> <p>Improved lipid profile</p>
Docosahexaenoic acid and salicylate conjugate (CAT-1004) for treatment of type 2 diabetes mellitus	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	<p>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.</p> <p>Catabasis Pharmaceuticals, Inc., Cambridge, MA</p> <p>Phase I trial completed with 1 phase I trial ongoing</p>	<p>Behavior, dietary and exercise changes</p> <p>Various approved drugs for treating T2DM</p> <p>Various drugs currently under investigation for treating T2DM (e.g., sodium-glucose cotransporter-2 inhibitors)</p>	<p>Decreased inflammation and insulin resistance</p> <p>Near-normal glycosylated hemoglobin (HbA<sub>1c</sub>) levels</p> <p>Halted or delayed acute and secondary complications</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Exenatide (Byetta) continuous subcutaneous (Duros, or ICTA 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	<p>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.</p> <p>Amylin Pharmaceuticals, Inc., San Diego, CA (drug) Intarcia Therapeutics, Inc., Hayward, CA (device)</p> <p>Duros technology is FDA approved for drug delivery; exenatide formulation for use with pump is under study; in Nov 2011, Eli Lilly and Co. returned all development rights of exenatide to Amylin; phase II trial completed; phase III trial ongoing</p>	Injected exenatide Metformin	Improved glycosylated hemoglobin (HbA <sub>1c</sub> ) levels Weight loss Reduced side effects (nausea)
Exenatide extended-release (Bydureon) for treatment of diabetes	Patients with type 2 diabetes mellitus (T2DM) who take oral agents for control	<p>Extended-release exenatide (Bydureon™), a version of Byetta (approved in 2005) is taken by injection once a week.</p> <p>Amylin Pharmaceuticals, Inc., San Diego, CA Alkermes, Inc., Waltham, MA</p> <p>FDA approved Jan 27, 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. The company is also required to conduct a double-blind, placebo-controlled trial 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.</p>	Oral agents taken daily	Blood sugar control Cardiovascular changes (QTc segment prolongation arrhythmias)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema	Patients in whom diabetic macular edema has been diagnosed	<p>No FDA-approved drug therapy is available for treatment of 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.</p> <p>Alimera Sciences, Alpharetta, GA</p> <p>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, while pursuing approval in Canada and EU.</p>	Laser photocoagulation Intravitreal triamcinolone acetonide with or without laser photocoagulation. VEGF antagonists (bevacizumab, pegaptanib, ranibizumab)	Increased visual acuity Increased contrast sensitivity Improved quality of life
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	<p>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.</p> <p>Genfit Corp., Lille, France</p> <p>Phase II trial completed</p>	Drugs for treating diabetes Drugs for treating prediabetes (metabolic syndrome)	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	<p>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.</p> <p>Oramed Pharmaceuticals, Inc., Jerusalem, Israel</p> <p>Phase II trial ongoing</p>	Injected exenatide Injected liraglutide	Near-normal glycosylated hemoglobin (HbA <sub>1c</sub> ) levels Improved fasting glucose levels Improved insulin sensitivity Reduced 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 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 injection or infusion Islet cell transplantation	Preserved islet cell function Reduced need for insulin injections Reduced incidence of diabetes acute and secondary complications
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 injection or insulin infusion Islet cell 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	External insulin infusion pump Injected insulin 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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ipeglimin for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	<p>Despite available treatments for T2DM, a need exists for more effective treatments. Ipeglimin 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. Ipeglimin 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.</p> <p>Poxel S.A., Lyon, France</p> <p>Phase II trial completed</p>	Dietary and exercise changes Traditional T2DM medications	Improved glycosylated hemoglobin (HbA <sub>1c</sub> ) 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	<p>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.</p> <p>Beta-Stim Ltd., Caesarea, Israel</p> <p>Phase I trial ongoing</p>	Dietary and exercise changes Diabetes medications Injected insulin Subcutaneous insulin pump	Achieved normal blood glucose levels Delayed or halted progression of disease Reduced secondary complications
Inhaled insulin (Afrezza) for treatment of diabetes	Patients with type 1 or type 2 diabetes mellitus who require insulin injections	<p>Inhaled insulin (Afrezza®) to control blood glucose levels.</p> <p>MannKind Corp., Valencia, CA</p> <p>Mid-phase trials ongoing; in Mar 2010, company received complete response letter from FDA questioning whether the inhaler used in clinical 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, trials are not yet registered on National Clinical Trials database</p>	Injected insulin Insulin pump therapy Other inhaled insulin products	Decreased blood glucose levels Better glycemic control Delayed or halted progression of complications Improved patient acceptance Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
InsuPatch for improving insulin absorption in type 1 diabetes	Patients with type 1 diabetes mellitus who use an insulin pump	<p>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.</p> <p>InsuLine Medical, Ltd., Petach-Tikvah, Israel</p> <p>Phase III trial completed</p>	Insulin delivered via a pump, but without heat	<p>Improved insulin absorption</p> <p>Decreased frequency and severity of adverse events</p> <p>Avoidance of glycemic excursions</p>
Leptin analog (Metreleptin) for treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus has been diagnosed	<p>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.</p> <p>University of Texas Southwestern Medical Center, Dallas (in collaboration with Juvenile Diabetes Foundation, New York, NY, and Amylin Pharmaceuticals, Inc., San Diego, CA)</p> <p>Phase I trial ongoing</p>	Insulin alone	<p>Better blood sugar control</p> <p>Improved lipid and cholesterol profile</p>

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 mellitus	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	<p>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.</p> <p>Metabolic Solutions Development Co., LLC, Kalamazoo, MI</p> <p>Phase IIa trial complete; phase IIb trial ongoing; 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</p>	First generation TZDs: Pioglitazone Rosiglitazone Troglitazone Other various drugs	Decreased HA <sub>1c</sub> 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	<p>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.</p> <p>GlaxoSmithKline, Middlesex, UK</p> <p>Phase II trial completed</p>	Antinausea agents (e.g., prochlorperazine, ondansetron, diphenhydramine) 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 for type 2 diabetes mellitus (T2DM)	<p>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 for prediabetes and/or T2DM.</p> <p>VeraLight, Inc., Albuquerque, NM</p> <p>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; Conformité Européene (CE) mark and Health Canada License approvals</p>	<p>Blood-based diabetes screening tests Breath analysis glucose screening (under development) Sweat conductance glucose screening (under development)</p>	<p>Delayed or prevented secondary complications Increased screening adherence Increased rate of early diagnosis Improved quality of life</p>
Off-label salsalate for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	<p>Research has demonstrated a link between T2DM progression and inflammation. Salsalate is a widely available anti-inflammatory derivative of salicylic acid; while 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.</p> <p>Joslin Diabetes Center, Boston, MA; various academic research centers</p> <p>Phase II/III trial completed</p>	<p>Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)</p>	<p>Achieved target glycosylated hemoglobin (HbA<sub>1c</sub>) levels Desired fasting glucose level control Resolved insulin sensitivity</p>

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	<p>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.</p> <p>Oramed Pharmaceuticals, Inc., Jerusalem, Israel</p> <p>Phase IIb trial completed</p>	<p>Inhaled/intranasal insulin                      Injected insulin</p>	<p>Near-normal glucose targets                      Improved glycosylated hemoglobin (HbA<sub>1c</sub>) levels                      Improved patient adherence with insulin regimen                      Reduced acute and secondary complications</p>
Oral neuronal alpha-7 neural nicotinic receptor modulator (TC-6987) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	<p>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.</p> <p>Targacept, Inc., Winston Salem, NC</p> <p>Phase II trials ongoing</p>	<p>Insulin sensitizers (pioglitazone, rosiglitazone)                      Metformin                      Sitagliptin                      Sulfonylurea drugs (glimepiride)</p>	<p>Improved fasting glucose levels                      Achieved target glycosylated hemoglobin (HbA<sub>1c</sub>) levels                      Decreased insulin sensitivity                      Delayed disease progression                      Avoidance of secondary complications of diabetes</p>
Otelixizumab (TRX4) for early treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus has been diagnosed within the past 90 days	<p>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.</p> <p>Tolerx, Inc., Cambridge, MA                      GlaxoSmithKline, Middlesex, UK</p> <p>Phase III trial completed; GSK announced Mar 11, 2011 that drug did not meet primary endpoint; GSK stated it will explore additional dosing regimens to inform decisions about future clinical development of the compound</p>	<p>Drugs that do not address beta cell function, but only control disease symptoms</p>	<p>Improved C-peptide levels, which indicate beta cell function                      Improved glycemic control                      Daily insulin required                      Reduced side effects</p>

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	<p>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 one 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 physician's office rather than as a self-administered drug (or self-administered insulin).</p> <p>Andromeda Biotech, Ltd., Yavne, Israel</p> <p>Phase III trial complete; 2nd confirmatory phase III trial ongoing</p>	<p>Diamyd (in development) Insulin injection or insulin infusion Islet cell transplantation Pancreas transplantation</p>	<p>Improved beta-cell function (measured as change from baseline in stimulated C-peptide secretion during a mixed-meal tolerance test) Increased glycemic control.</p>
PF-04523655 (PF-655) for treatment of diabetic macular edema	Patients in whom diabetic macular edema has been diagnosed	<p>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 <i>RTP-801</i> 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.</p> <p>Quark Pharmaceuticals, Inc., Fremont, CA, in cooperation with Pfizer, Inc., New York, NY</p> <p>Phase IIb trial completed; 1 phase IIb trial ongoing</p>	<p>Laser photocoagulation Intravitreal triamcinolone acetonide with or without laser photocoagulation Vascular endothelial growth factor antagonists (bevacizumab, pegaptanib, ranibizumab)</p>	<p>Improved visual acuity Halted loss of vision Improved contrast sensitivity Improved quality of life</p>
Porcine-derived cell transplant (DiabeCell) for treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus (T1DM) has been diagnosed	<p>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 will eliminate the need for immunosuppressants.</p> <p>Living Cell Technologies, Ltd., Sydney, Australia</p> <p>Phase IIb trial completed late 2010; phase I/IIa trial on 10 patients completed in Russia; phase II trial ongoing in New Zealand</p>	<p>Human islet cell transplants Insulin injection Insulin pump Pancreas transplantation</p>	<p>Reduced graft rejection Freedom from immunosuppressive drugs posttransplant Reduced insulin independence Improved quality of life</p>

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	<p>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.</p> <p>Sanuwave, Inc., Alpharetta, GA</p> <p>Phase III trial completed; Dec 2011, FDA issued a major deficiency letter in response to the premarket approval application for dermaPACE</p>	<p>Acellular wound matrices Cellular wound matrices Hyperbaric oxygen therapy Negative pressure wound therapy</p>	<p>Increased percentage of ulcers healed Shortened time to complete healing Reduced ulcer size Reduced incidence of gangrene Reduced incidence of amputation</p>
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	<p>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.</p> <p>NephroGenex, Inc., Research Triangle Park, NC</p> <p>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</p>	<p>Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers Antihypertensive agents C-peptide Dietary modification Dialysis Hypoglycemic agents Kidney transplantation</p>	<p>Reduced disease progression (as measured by serum creatinine and biomarkers) Improved renal function Reduced complications of diabetic nephropathy Increased survival Improved quality of life</p>

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	<p>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).</p> <p>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Novartis AG, Basel, Switzerland</p> <p>Positive results reported from 2 phase III trials; biologics license application submission was expected within 2011, but no action has been taken as of Jan 2012; in Nov 2011, UK National Health Service rejected coverage of the drug for this indication citing it did not meet its requirement for being cost-effective</p>	<p>Intravitreal triamcinolone acetonide (steroid) Laser photocoagulation Panretinal photocoagulation Vitrectomy</p> <p>Experimental treatments: C-peptide Oligomeric proanthocyanidin (pine bark extract)</p>	<p>Improved vision Stabilized vision Reduced side effects of existing treatment Improved quality of life</p>
Sodium-glucose cotransporter (LX4211) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	<p>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.</p> <p>Lexicon Pharmaceuticals, Inc., The Woodlands, TX</p> <p>Phase II trial completed</p>	Alpha-glucosidase inhibitors (acarbose and miglitol), which interfere with absorption of some glucose-containing nutrients	<p>Rapid improvement in glycemic control Improved blood pressure Improved triglyceride levels Weight loss</p>

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	<p>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.</p> <p>Astellas Pharma, Inc., Tokyo, Japan</p> <p>Phase III trials ongoing in Japan</p>	Other diabetes medications that do not result in weight loss	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	<p>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.</p> <p>Boehringer Ingelheim GmbH, Ingelheim, Germany</p> <p>Phase III trial completed; phase III trials ongoing</p>	Pioglitazone Pioglitazone plus metformin	Improved glycosylated hemoglobin (HbA <sub>1c</sub> ) 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	<p>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.</p> <p>Johnson &amp; Johnson, New Brunswick, NJ</p> <p>Phase III trials ongoing</p>	<p>Dietary and exercise changes Other SGLT2 inhibitors under investigation Various approved drugs for treatment of T2DM</p>	<p>Near-normal glycosylated hemoglobin (HbA<sub>1c</sub>) levels Weight loss Fewer hypoglycemic events Halted or delayed acute and secondary complications</p>
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	<p>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.</p> <p>Bristol-Myers Squibb, New York, NY AstraZeneca, London, UK</p> <p>In Jan 2012 FDA rejected dapagliflozin for this indication and issued a complete response letter to the company.</p>	<p>Glipizide plus metformin</p>	<p>Achieved target glycosylated hemoglobin (HbA<sub>1c</sub>) levels Weight loss Decreased hypoglycemic events Halted or delayed secondary complications of diabetes</p>

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	<p>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.</p> <p>Chugai Pharmaceuticals Co., Ltd., Tokyo, Japan</p> <p>Phase III trial ongoing</p>	<p>Dietary and exercise changes Other SGLT2 inhibitors under investigation Various approved drugs for treatment of T2DM</p>	<p>Near-normal glycosylated hemoglobin (HbA<sub>1c</sub>) levels Weight loss Decreased hypoglycemic events Halted or delayed acute and secondary complications</p>
Sodium-glucose cotransporter-2 inhibitor (TS-071) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	<p>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.</p> <p>Taisho Pharmaceutical Co., Ltd., Tokyo, Japan</p> <p>Phase II trial ongoing</p>	<p>Dietary and exercise changes Other SGLT2 inhibitors under investigation Various approved drugs for treating T2DM</p>	<p>Near-normal glycosylated hemoglobin (HbA<sub>1c</sub>) levels Weight loss Fewer hypoglycemic events Halted or delayed acute and secondary complications</p>

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	<p>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.</p> <p>EyeSense GmbH, Grosssostheim, Germany</p> <p>Phase II trial ongoing (in Germany); unknown when/if U.S. trials will be undertaken</p>	Conventional 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 mellitus-associated leg ulcers	Patients with venous leg wounds and foot ulcers associated with type 2 diabetes mellitus (T2DM)	<p>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 treatment of chronic wounds for patients with T2DM. Nexagon is administered topically (1 or 3 mg/mL used with compression dressings).</p> <p>CoDa Therapeutics, Inc., San Diego, CA</p> <p>Phase II trial completed; phase II trials ongoing</p>	Antibiotics Steroids/anti-inflammatories Surgery (i.e., 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
Triolet anti-inflammatory (HE3286) for treatment of obesity-induced type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	<p>Research has implicated inflammation in the development of insulin resistance associated with T2DM; however, no anti-inflammatory treatments for obesity-induced T2DM are available. Triolet® 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 Triolet is believed to be the 1st in a new class of insulin sensitizers to target obesity-mediated dysregulated metabolism.</p> <p>Harbor BioSciences, Inc., San Diego, CA</p> <p>Phase IIa trial completed and did not reach primary endpoints, but a reanalysis of data under FDA's guidance examined body mass index 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.</p>	<p>Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)</p>	<p>Improved blood glucose levels Reduced glycemic excursions</p>
Ultra-long-acting insulin (Degludec) for treatment of type 2 diabetes	Patients with type 2 diabetes mellitus who require oral medication, insulin, or both	<p>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.</p> <p>Novo Nordisk a/s, Bagsvaerd, Denmark</p> <p>Phase IIIa trials completed for Degludec and DegludecPlus; phase III trial initiated May 2011; Sept 2011, Novo Nordisk filed NDAs with the FDA for Degludec and DegludecPlus</p>	<p>Insulin glargine (Lantus®), a long-acting basal insulin taken once daily Regular insulin</p>	<p>Achieved target glycosylated hemoglobin (HbA<sub>1c</sub>) levels Reduced progression of complications Improved quality of life</p>

**Table 8. AHRQ Priority Condition: 08 Functional Limitations and Disability: 168 Interventions**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
1-deoxyno-jirimycin (AT2220) to enhance efficacy of enzyme replacement therapy for Pompe disease	Patients in whom late-onset Pompe disease has been diagnosed	<p>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.</p> <p>Amicus Therapeutics, Inc., Cranbury, NJ</p> <p>Phase II trial ongoing; a phase II study recently terminated</p>	Alpha-glucosidase enzyme replacement therapy (Myozyme, Lumizyme) with and without AT2220	<p>Decreased muscle atrophy, increased strength and function</p> <p>Improved pulmonary function and/or ventilation conditions</p> <p>Reduced cardiomyopathy</p> <p>Reduced fatigue</p> <p>Improved quality of life</p>
Alemtuzumab (Lemtrada) for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	<p>Alemtuzumab 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.</p> <p>Genzyme Corp., Cambridge, MA</p> <p>Phase III trial ongoing; FDA approved for treatment of refractory chronic lymphocytic leukemia; expected to file for regulatory approval in 1st half of 2012</p>	Fingolimod Glatiramer acetate Interferons Mitoxantrone Natalizumab	<p>Reduced frequency of relapse</p> <p>Slowed disease progression</p> <p>Improved quality of life</p>

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	<p>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.</p> <p>Cytonet GmbH &amp; Co., KG, Weinheim, Germany</p> <p>Phase II trials ongoing in U.S. and Europe</p>	<p>Dietary management Ammonia scavengers (sodium phenylbutyrate, sodium benzoate) Urea cycle enzyme catalysts (L-citrulline, L-arginine)</p>	<p>Changes in 13C urea formation Reduced frequency and severity of metabolic crises</p>
ALN-TTR01/RNAi for treatment of <i>TTR</i> -mediated amyloidosis	Patients in whom ATTR amyloidosis has been diagnosed	<p>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 (<i>TTR</i>) 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 <i>TTR</i> gene and serum levels of TTR.</p> <p>Alnylam Pharmaceuticals, Cambridge, MA</p> <p>Phase 1 trial ongoing</p>	Liver transplantation	<p>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</p>

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Alpha-tocopherol quinone (EPI-A0001) for treatment of Friedreich's ataxia	Patients in whom Friedreich's ataxia (FA) has been diagnosed	<p>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 treatment of 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.</p> <p>Edison Pharmaceuticals, Inc., Mountain View, CA</p> <p>Phase IIa trial completed; FDA granted orphan drug and fast track status</p>	<p>Drugs under investigation: Idebenone (Phase III) Deferiprone EGb761 EPI-743 OX1 Pioglitazone Resveratrol TAT-Frataxin</p> <p>Counseling Physical therapy Speech therapy Walking aids or wheelchairs</p>	<p>Improved neurologic function (assessed by Friedreich's Ataxia Rating Scale) Improved quality of life</p>
Amino-benzothiazole (dexpramipexole) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	<p>Only 1 agent (riluzole) is FDA approved for treatment of 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.</p> <p>Biogen Idec International GmbH, Zug, Switzerland Knopp Bioscience, Pittsburgh, PA</p> <p>Phase III trial ongoing; FDA granted fast track and orphan drug status</p>	Riluzole	<p>Increased survival Delayed disease progression Improved symptoms Improved quality of life</p>

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Ampakine (CX-1739) for treatment of obstructive sleep apnea	Patients in whom obstructive sleep apnea (OSA) has been diagnosed	<p>No pharmacotherapies are FDA approved for treatment of 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.</p> <p>Cortex Pharmaceuticals, Inc., Irvine, CA</p> <p>Phase IIa trial ongoing</p>	CPAP Oral appliances Surgery	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	<p>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-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.</p> <p>Ashok Gupta, holistic medicine practitioner, London, UK Ann Vincent, M.D., Mayo Clinic, Rochester, MN</p> <p>Trial ongoing (unphased); sold as a proprietary program; currently clinically implementable</p>	Dietary restrictions Gentle stretching Lifestyle changes Nutritional supplementation Pharmacotherapies to treat sleep disorders Prevention of overexertion Stress reduction	Improved ability to perform daily activities Reduced symptoms Improved quality of life

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Amygdala retraining program for treatment of fibromyalgia	Patients in whom fibromyalgia has been diagnosed	<p>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.</p> <p>Ashok Gupta, holistic medicine practitioner, London, UK Ann Vincent, M.D., Mayo Clinic, Rochester, MN</p> <p>Trial ongoing (unphased); sold as a proprietary program; currently clinically implementable</p>	<p>Duloxetine Fluoxetine Gabapentin Lorazepam Milnacipran Pregabalin Stress reduction Tricyclic antidepressants</p>	<p>Improved ability to perform daily activities Reduced symptoms Improved quality of life</p>
Antisense molecule (ISIS-SMNRx) for treatment of spinal muscular atrophy	Children in whom spinal muscular atrophy (SMA) has been diagnosed	<p>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.</p> <p>ISIS Pharmaceuticals, Inc., a unit of Johnson &amp; Johnson, Inc., New Brunswick, NJ Biogen Idec International GmbH, Zug, Switzerland Phase I trial ongoing; FDA granted fast track and orphan drug status</p>	Supportive therapy	<p>Reduced symptoms Improved motor function Improved quality of life</p>

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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	<p>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 experience 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; 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.</p> <p>University of Texas Health Science Center at Houston Medical School</p> <p>Phase I trial completed with 10 patients; procedure performed under an investigational new drug (IND) process because of the manipulation of the cells</p>	There are no effective treatments to protect or promote repair of the brain in TBI-injured children	<p>Reduced adverse neurologic events (seizures, change in Glasgow coma scale, cerebral vascular accident)</p> <p>Reduced disability</p> <p>Reduced infectious morbidity and secondary organ injury</p> <p>Improved cognitive function</p>
Autologous cell preparation and spraying system (ReCell) for treatment of burn wounds	Patients in need of therapy for skin burns	<p>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.</p> <p>Avita Medical, Ltd., Cambridge, UK</p> <p>Clinical trials completed</p>	Cultured epithelial autograft Donor stem cell transplantation and skin printing Wound débridement	<p>Improved wound healing</p> <p>Decreased postsurgical blister and skin damage</p> <p>Improved quality of life</p>
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	<p>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).</p> <p>Union Memorial Hospital’s Curtis National Hand Center, Baltimore, MD</p> <p>First reported procedure completed Aug 2011</p>	Conventional ligament reconstruction surgery	<p>Decreased wrist pain</p> <p>Decreased risk of wrist arthritis</p> <p>Improved wrist function</p> <p>Improved quality of life</p>

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Autologous mesenchymal stem cell therapy (NurOwn) for amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis has been diagnosed	<p>NurOwn™ differentiated autologous adult stem cell therapy. The technology collects from the patient adult human mesenchymal stem cells from autologous bone marrow and processes the cells in vitro using a proprietary process in which the cells are intended to differentiate into astrocyte-like cells capable of releasing neurotrophic factors, including glial-derived neurotrophic factor; cells are then reinfused through either a single intrathecal injection into the cerebrospinal fluid or multiple intramuscular injections into biceps or triceps.</p> <p>BrainStorm Cell Therapeutics, New York, NY</p> <p>Phase I/II trial ongoing; FDA granted orphan drug status in Feb 2011; company stated intention to pursue FDA regulatory approval</p>	Riluzole Physical therapy and assistive technology (speaking tubes, motored chairs, etc.)	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	<p>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-rich and platelet-rich medium for 12 days; the mix of cultured bone marrow cells (stem and progenitor) is transplanted to the patient in an effort to regenerate damaged nerve, bone, skin, and vessels from maxillary and mandibular ORN (hard and soft tissue).</p> <p>POLUSA Hospital, Lugo, Spain</p> <p>Pilot trial completed</p>	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
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)	<p>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.</p> <p>Procedure uses existing technologies and is in early diffusion in Europe and U.S.; 1st reported by University of Ferrara, Italy</p> <p>Clinical trials under way to further assess validity</p>	Corticosteroids Disease modifying drugs Fingolimod Interferons	Improved cognitive and motor function Reduced relapse Reduced lesions on imaging Improved quality of life

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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)	<p>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.</p> <p>Reata Pharmaceuticals, Inc., Irving, TX</p> <p>Phase III trial ongoing</p>	<p>Dialysis</p> <p>Human recombinant erythropoietin to treat anemia</p> <p>Kidney transplantation</p> <p>Management of diabetes or high blood pressure</p> <p>Palliative care</p>	<p>Prevention of kidney failure, dialysis or kidney transplantation</p> <p>Improved glomerular filtration rate</p> <p>Improved renal function</p> <p>Improved CKD stage</p>
Beta-3 adrenoceptor agonist (Mirabegron) for treatment of overactive bladder	Patients in whom overactive bladder leading to urinary incontinence has been diagnosed	<p>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.</p> <p>Astellas Pharma, Inc., Tokyo, Japan</p> <p>Phase III trials completed; new drug application (NDA) submitted to FDA in Aug 2011; Nov 2011, FDA accepted the NDA filing; Apr 2012, FDA advisory panel is expected to review NDA</p>	<p>Behavioral therapy in combination with bladder relaxing drugs (e.g., darifenacin, oxybutynin, oxybutynin skin patches, solifenacin, tolterodine, trospium)</p> <p>Onabotulinum toxin A</p> <p>Sacral nerve stimulation</p> <p>Surgical treatment (bladder enlargement, cystectomy)</p>	<p>Decreased urge to urinate</p> <p>Decreased urination episodes per week</p> <p>Improved International Consultation on Incontinence Questionnaire-Overactive Bladder score</p> <p>Improved quality of life</p>
Bioabsorbable bupivacaine implant (Xaracoll) for postsurgical pain relief	Patients who undergo hysterectomy	<p>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.</p> <p>Innocoll, Inc., Ashburn, VA</p> <p>Phase II trials ongoing; several phase II trials completed; phase III trial planned</p>	<p>Postsurgical administration of intravenous and oral analgesics (opioids, nonsteroidal anti-inflammatory drugs)</p>	<p>Improved localized pain relief</p> <p>Fewer side effects (e.g., nausea, constipation, dependence) compared to systemic postsurgical pain relief modalities</p>

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Bioartificial liver system (Excorp Medical) for fulminant hepatic failure	Patients with fulminant hepatic failure (acute liver failure) awaiting a liver transplant	<p>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.</p> <p>Excorp Medical, Inc., St. Paul, MN</p> <p>Phase I/II trial ongoing; granted orphan product status by FDA</p>	Standard care for acute liver failure, including antibiotics to treat infection and lactulose to treat hepatic encephalopathy	Improved survival
Bioartificial liver system (Extracorporeal Liver Assist Device) as bridge to liver transplantation	Patients in whom acute liver failure has been diagnosed	<p>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 transplant candidate awaits donor liver.</p> <p>Vital Therapies, Inc., San Diego, CA</p> <p>Phase II/III trial completed; phase III trial ongoing</p>	Standard care for acute liver failure, including antibiotics to treat infection and lactulose to treat hepatic encephalopathy	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	<p>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 transplant candidate awaits donor liver.</p> <p>Vital Therapies, Inc., San Diego, CA</p> <p>Phase II trials completed; 1 phase II trial recently withdrawn to focus on another indication</p>	Standard care for acute liver failure, including antibiotics to treat infection and lactulose to treat hepatic encephalopathy	Improved survival for liver transplant patients awaiting a donor liver

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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	<p>Buprenorphine is an opioid that is used in current formulations for treatment of 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 cheek for buccal delivery. The technology was FDA approved for use with fentanyl and is under development for delivery of buprenorphine.</p> <p>BioDelivery Sciences International, Raleigh, NC</p> <p>Phase III trial completed; 2nd phase III trial planned; company anticipated filing new drug application in 1st half of 2012</p>	Cyclooxygenase-2 inhibitors Current buprenorphine formulations: Buprenex (injectable) Nonsteroidal anti-inflammatory drugs Opioids (oxycodone, hydrocodone, morphine)	Reduced pain Reduced risk of addiction
BreathID test to monitor liver function	Patients at risk of or in liver failure	<p>Breath test (BreathID®) intended to monitor liver function; theory is that breath test could give additional liver function assessment not available with blood tests. Office-based test.</p> <p>Exalenz Bioscience, Inc., Modi'in, Israel</p> <p>Phase III trials ongoing in Israel; approved to detect <i>Helicobacter pylori</i> infection</p>	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	<p>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); there is a need 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.</p> <p>Pacira Pharmaceuticals, Inc., Parsippany, NJ</p> <p>Oct 2011, the manufacturer announced the FDA's approval of this therapy for the treatment of postsurgical pain</p>	Conventional bupivacaine Opioids	Reduced pain on visual analog pain scale Reduced need for other pain medication

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Caspase-1 inhibitor (VX-765) for treatment of partial-onset epilepsy	Patients in whom treatment-resistant partial-onset epilepsy has been diagnosed	<p>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.</p> <p>Vertex Pharmaceuticals, Inc., Cambridge, MA</p> <p>Phase II trial completed; phase IIb trial ongoing</p>	Gamma aminobutyric acid (GABA) derivatives 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	<p>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.</p> <p>Can-Fite BioPharma, Ltd., Petah-Tikva, Israel</p> <p>Phase III trial ongoing</p>	Dry-eye medications	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 for developing cataracts	<p>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.</p> <p>Massachusetts Institute of Technology, Cambridge, MA</p> <p>Pilot trial completed</p>	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	<p>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.</p> <p>CalciMedica, La Jolla, CA</p> <p>Phase I trial ongoing</p>	<p>Topical ointments such as: Anthralin Calcineurin inhibitors Coal tar Corticosteroids</p> <p>Phototherapy</p> <p>Systemic medications: Cyclosporin Hydroxyurea Immunomodulators Methotrexate Retinoids Thioguanine</p>	<p>Improved psoriasis severity index scale scores Improved quality of life</p>
CNV2197944 for treatment of chronic neuropathic pain	Patients in whom chronic neuropathic pain has been diagnosed	<p>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.</p> <p>Convergence Pharmaceuticals, Ltd., Cambridge, UK</p> <p>Phase I trial ongoing</p>	<p>Nonsteroidal anti-inflammatory drugs Opioid analgesics</p>	<p>Reduced pain Improved quality of life</p>
Collagenase clostridium histolyticum (Xiaflex) for treatment of Peyronie's disease	Men in whom Peyronie's disease has been diagnosed	<p>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 treatment of the hand disorder Dupuytren's contracture.</p> <p>Auxilium Pharmaceuticals, Inc., Malvern, PA</p> <p>Phase III trial ongoing</p>	<p>Surgical correction Interferon local injections Verapamil local injections</p>	<p>Change in penile curvature from baseline Improved Peyronie's Disease Questionnaire (PDQ) score</p>

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	<p>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.</p> <p>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)</p>	Skin grafts Stem cell transplantation Wound débridement	Improved wound healing Decreased post-surgical blister and skin damage Improved quality of life
Concussion Management System to assess concussion and prevent second impact syndrome	Patients in whom a concussion has been diagnosed	<p>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 second 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.</p> <p>Cleveland Clinic, Cleveland, OH</p> <p>Pilot trial ongoing</p>	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 second 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	<p>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 the 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.</p> <p>Avedro, Inc., Waltham, MA</p> <p>Phase III trial completed; Conformité Européene (CE) marked</p>	<p>Corneal ring segment inserts                      Corneal transplants/penetrating keratoplasty                      Epikeratophakia                      Radial keratotomy (under investigation)</p>	<p>Improved corneal structure                      Improved vision                      Improved quality of life</p>
Cyclic pyranopterin monophosphate enzyme replacement therapy for molybdenum cofactor deficiency type A	Patients in whom molybdenum cofactor deficiency (MoCD) type A has been diagnosed	<p>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.</p> <p>Alexion Pharmaceuticals, Inc., Cheshire, CT</p> <p>Early phase trials ongoing</p>	<p>No treatments currently available</p>	<p>Improved urine sulfite levels                      Improved neurological symptoms                      Reduced mortality</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Daclizumab (Zenapax) for treatment of multiple sclerosis	Patients in whom multiple sclerosis (MS) has been diagnosed	<p>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</p> <p>Biogen Idec International GmbH, Zug, Switzerland Abbott Laboratories, Abbott Park, IL</p> <p>Phase III trials ongoing; data expected in late 2012; FDA granted fast track status</p>	Fingolimod Glatiramer Interferon beta-1a Natalizumab	Delayed disease progression Decreased demyelination Fewer relapses Improved quality of life
Davunetide for treatment of progressive supranuclear palsy	Patients in whom progressive supranuclear palsy (PSP) has been diagnosed	<p>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.</p> <p>Allon Therapeutics, Inc., Vancouver, British Columbia, Canada</p> <p>Phase II/III trial ongoing; FDA granted orphan drug status in Jan 2010</p>	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
Deferiprone (Ferriprox) for treatment of contrast-induced acute kidney injury	Patients in whom contrast-induced acute kidney injury (CI-AKI) has been diagnosed	<p>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.</p> <p>CorMedix, Inc., Bridgewater, NJ</p> <p>Phase II trial completed Jun 2011; phase III trial planned for 2012</p>	Cincor™ system (in development) Deferoxamine Hydration	Reduced occurrence and complications of CI-AKI Reduced incidence of CI-AKI in high risk patients with CKD
Dimethyl fumarate (BG-12) for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis has been diagnosed	<p>Available treatments provide unsatisfactory efficacy for many patients. Dimethyl fumarate (BG-12) 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.</p> <p>Biogen Idec International GmbH, Zug, Switzerland</p> <p>Phase III trial ongoing; received fast track status from FDA in 2008; FDA accepted new drug application for review May 2012</p>	Fingolimod Glatiramer acetate Interferon beta (IFNβ) IFNβ-1a (Avonex) 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	<p>DNA chip (microarray) diagnostic tool to detect mutations in the LL gene from a blood sample to identify patients at risk for acute pancreatitis.</p> <p>Progenika Biopharma S.A., Vizcaya, Spain Amsterdam Molecular Therapeutics Holding N.V., Amsterdam, The Netherlands</p> <p>U.S. trial status unclear; Conformité Européene (CE) marked Sept 2010</p>	Standard lipid profile laboratory test Other laboratory exams	Increased definitive diagnosis of LL deficiency Identification of patients at risk for acute pancreatitis

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Dopamine stabilizer pridopidine (ACR16, Huntexil) for treatment of Huntington's disease	Patients in whom Huntington's disease (HD) has been diagnosed	<p>There is no cure 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.</p> <p>NeuroSearch a/s, Ballerup, Denmark</p> <p>Phase III trials completed</p>	Antidepressants Antipsychotics Tetrabenazine	Improved clinical global impression of change, cognitive function, behavior, and symptoms of depression and anxiety Improved voluntary motor function
Doxepin nasal solution (Dolorac) for migraine prophylaxis	Patients in whom chronic migraine headaches (more than 180 headache days per year) have been diagnosed	<p>A nasal solution (Dolorac) formulation of the tricyclic antidepressant doxepin; tricyclic antidepressants have been used off label for some time for migraine prophylaxis.</p> <p>Winston Pharmaceuticals, Inc., Vernon Hills, IL</p> <p>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 Apr 2012</p>	Botulinum toxin type A (Botox®) injection Off-label medications for this condition: beta blockers (propranolol, atenolol, metoprolol, nadolol, timolol), tricyclic antidepressants (amitriptyline, nortriptyline, doxepin), antiepileptics (divalproex, valproic acid, topiramate)	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	<p>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.</p> <p>Chelsea Therapeutics, Inc., Charlotte, NC</p> <p>Phase III trials completed; new drug application submitted to FDA Sept 28, 2011 with a decision date set for Mar 28, 2012; 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 (CRL) requesting additional efficacy data; FDA granted orphan drug and fast track status; approved for marketing in Japan</p>	Midodrine hydrochloride (ProAmatine, Apo-Midodrine [Canada]), the only FDA-approved drug to treat orthostatic hypotension; midodrine is an alpha1-adrenoceptor agonist	Decreased orthostatic hypotension Decreased risk of falling Decreased confusion from reduced cerebral circulation

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Drug-releasing implant (Propel system) to prevent occlusion of sinuses after surgery for chronic sinusitis	Patients in whom chronic sinusitis has been diagnosed	<p>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.</p> <p>Intersect ENT, Inc., Palo Alto, CA</p> <p>Aug 2011, FDA approved under premarket approval process</p>	<p>Antibiotics Decongestants Immunotherapy Nasal corticosteroids Nonsteroidal anti-inflammatory drugs Oral or injected corticosteroids Saline nasal spray Sinus surgery</p>	<p>Reduced sinus inflammation Improved breathing Decreased headaches and facial pain Improved gustatory and olfactory senses Improved quality of life</p>
Dual orexin receptor antagonists (MK-6096 and MK-4305) for treatment of primary insomnia	Patients in whom primary insomnia has been diagnosed	<p>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.</p> <p>Merck &amp; Co., Inc., Whitehouse Station, NJ</p> <p>MK-6096: phase II trial completed MK-4305: phase III trials completed</p>	<p>Anticonvulsants Antihistamines Behavior modifications Benzodiazepines Hypnotics (Ambien®, Sonata®) Melatonin stimulants Muscle relaxants</p>	<p>Improved sleep cycle Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ear implant for treatment of Ménière's disease	Patients with persistent, severe vertigo in whom Ménière's disease has been diagnosed	<p>Intervention is an inner ear implant modeled after cochlear implant and designed to quell vertigo attacks experienced by people with Ménière'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.</p> <p>University of Washington, Seattle</p> <p>Phase III trial ongoing</p>	Medications Surgery	Cessation of vertigo
Electrical Nerve Block system for treatment of chronic amputation pain	Patients who have had an amputation who experience chronic amputation pain	<p>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.</p> <p>Neuros Medical, Inc., Willoughby, OH</p> <p>Pilot trials ongoing</p>	Acupuncture Analgesics Anticonvulsants Electrical spinal cord stimulation Intrathecal catheter-delivered drugs Stump revision/neurectomy Transcutaneous electrical nerve stimulation Tricyclic antidepressants	Reduced pain Improved quality of life

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Electromagnetic field therapy (Resonator) for treatment of fibromyalgia	Patients in whom fibromyalgia has been diagnosed	<p>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.</p> <p>Pico-Tesla Magnetic Therapies, Clearwater, FL</p> <p>Phase II trial completed</p>	<p>Duloxetine Fluoxetine Gabapentin Lorazepam Milnacipran Pregabalin Stress reduction Tricyclic antidepressants</p>	<p>Improved ability to perform daily activities Reduced symptoms Improved quality of life</p>
Enzyme replacement therapy (ENB-0040) for treatment of hypophosphatasia in infants and children	Infants and children receiving a diagnosis of hypophosphatasia	<p>Hypophosphatasia is a rare metabolic disorder caused by deficiency of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP). No other pharmacologic therapy is available currently. TNSALP is a phosphomonoesterase that plays a key role in regulation of bone mineralization. Alterations in the <i>TNSALP</i> 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.</p> <p>Alexion Pharmaceuticals, Inc., Cheshire, CT</p> <p>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</p>	<p>Cortisone Magnesium Plasma Vitamin B<sub>6</sub> Zinc</p>	<p>Restoration of bone mineralization Decreased risk of rickets and osteomalacia Improved quality of life</p>

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	<p>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.</p> <p>Synageva BioPharma, Lexington, MA</p> <p>Phase II and II/III trial ongoing; FDA granted orphan drug status</p>	Palliative treatments	<p>Improved cholesteryl ester and triglyceride levels</p> <p>Improved quality of life</p>
Eprodisate disodium (Kiacta) for treatment of amyloid A amyloidosis	Patients at risk for amyloid A amyloidosis, especially those in whom rheumatoid arthritis or chronic infection is present	<p>Eprodisate disodium (Kiacta™) is designed to interfere with the formation of amyloid A fibrils that can accumulate in organs and tissues. Orally administered capsules.</p> <p>Bellus Health, Inc. (formerly Neurochem), Laval, Quebec, Canada Celtic Therapeutics Management LLP, St. Thomas, U.S. Virgin Islands</p> <p>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</p>	<p>Standard treatment primarily targets symptomatic relief and reduction of amyloid production</p> <p>Immunosuppressive agents to reduce chronic inflammation, including: chlorambucil, cyclophosphamide, methotrexate, and biologics (tumor necrosis factor-alpha inhibitors and interleukin-1-receptor antagonists)</p> <p>Surgical excision of infected tissue and antibiotics for chronic infection</p> <p>Kidney transplantation (for kidney failure)</p> <p>Colchicine for familial Mediterranean fever</p>	<p>Reduced risk of organ failure (especially kidneys, liver, spleen)</p> <p>Reduced mortality</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Erythropoiesis-stimulating agent (peginesatide, Omontys) for treatment of anemia of chronic renal failure</p>	<p>Patients with chronic kidney disease (CKD) who are on dialysis and in whom anemia has been diagnosed</p>	<p>Anemia is a common consequence of chronic renal failure, affecting more than 90% of patients with chronic renal failure stage 5. Erythropoiesis stimulating agents 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 treatment of 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 erythropoiesis-stimulating agents. 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.</p> <p>Affymax, Inc., Palo Alto, CA, in collaboration with Takeda Pharmaceutical Co., Ltd., Osaka, Japan</p> <p>FDA approved Mar 27, 2012 with a Risk Evaluation and Mitigation Strategy for treatment of 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.”</p>	<p>Ivy erythropoietin Other ESAs Renal transplantation</p>	<p>Reduced frequency of drug administration Resolution of anemia Improved quality of life</p>

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<p>Etanercept for treatment of dermatomyositis</p>	<p>Patients in whom dermatomyositis has been diagnosed</p>	<p>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, and 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 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.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase I trials completed; FDA approved in 1998 for moderate to severe rheumatoid arthritis and other inflammatory conditions</p>	<p>Azathioprine Intravenous immunoglobulin Methotrexate Prednisone</p>	<p>Symptom resolution as measured by International Myositis Assessment Clinical Study score Halted or slowed disease progression</p>
<p>Exon-skipping agent (Eteplirsen, AVI-4658) for treatment of Duchenne muscular dystrophy</p>	<p>Patients in whom Duchenne muscular dystrophy (DMD) has been diagnosed</p>	<p>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.</p> <p>AVI BioPharma, Inc., Bothell, WA</p> <p>Phase IIb trial completed; phase III trial planned; FDA granted orphan drug status in 2007</p>	<p>Corticosteroids Beta-2 agonists Orthopedic devices Physical therapy Respiratory support devices</p>	<p>Delayed or halted muscle degeneration Reduced symptoms Increased survival Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Extended-release cysteamine bitartrate (RP103) for treatment of nephropathic cystinosis</p>	<p>Patients in whom nephropathic cystinosis has been diagnosed</p>	<p>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.</p> <p>Raptor Pharmaceutical Corp., Novato, CA</p> <p>Phase III trial completed; extension phase III trial ongoing; Mar 2012, company submitted new drug application to FDA; FDA granted orphan drug status</p>	<p>Cystagon® (immediate-release cysteamine bitartrate) Growth hormone therapy Indomethacin Renal transplantation Urinary loss supplementation</p>	<p>Improved glomerular function Reduced morbidity and mortality Improved quality of life</p>
<p>Ezogabine (Potiga) for treatment of epilepsy</p>	<p>Patients in whom epilepsy has been diagnosed</p>	<p>Ezogabine (Potiga™) is a drug with a new mechanism of action intended for treatment of 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.</p> <p>Valeant Pharmaceuticals International, Inc., Mississauga, Ontario, Canada GlaxoSmithKline, Middlesex, UK</p> <p>FDA approved Jun 2011</p>	<p>Anticonvulsant medications for partial seizures (e.g., tricyclics, gamma aminobutyric acid [GABA] derivatives, valproate, lamotrigine, levetiracetam, tiagabine)</p>	<p>Reduced frequency of partial seizures Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fentanyl iontophoretic transdermal system (lonsys) for patient-controlled delivery of pain medication	Patients who would receive opioid treatment for pain (e.g., postsurgery patients)	<p>The iontophoretic transdermal system delivers fentanyl (lonsys™) 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.</p> <p>ALZA Corp. and Janssen Pharmaceuticals, Inc., both subsidiaries of Johnson &amp; Johnson, New Brunswick, NJ Incline Therapeutics, Inc., Redwood City, CA</p> <p>Received FDA new drug application approval May 2006, but product was not launched; in Jun 2010, lonsys 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.</p>	Non-patient-controlled fentanyl patches Patient-controlled analgesic pumps	Adequate postsurgery pain management Fewer side effects because of delivery mode
Fingolimod (Gilenya) for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	<p>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.</p> <p>Novartis AG, Basel, Switzerland</p> <p>FDA approved Sept 2010</p>	Glatiramer acetate Interferon beta (IFNb) IFNb-1a (Avonex) 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
Focused ultrasound for treatment of essential tremor	Patients in whom essential tremor (ET) has been diagnosed	<p>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</p>	Antiepileptics Beta blockers Deep brain stimulation Stereotactic thalamotomy	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	<p>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.</p> <p>Pluromed, Inc., Woburn, MA</p> <p>FDA approved Oct 2011 under premarket approval process</p>	Elastic vessel loops Surgical clamps	Effective temporary blood vessel block Minimized blood loss Decreased damage to blood vessels

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Gene therapy (CD34+ cells) for childhood severe combined immunodeficiency	Children in whom severe combined immunodeficiency has been diagnosed (also known as "bubble boy disease")	<p>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.</p> <p>The multi-center study was conducted by the San Raffaele Telethon Institute for Gene Therapy, Milan, Italy</p> <p>Phase I/II trials ongoing at multiple institutions; cells have received orphan drug designation from the European Medicines Agency</p>	Bone marrow transplantation from unrelated donors or parents, which is not always possible	Improved survival Fewer infections Freedom from weekly enzyme injections Improved quality of life
Gene therapy NLX-P101 (AAV2-GAD) for treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	<p>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.</p> <p>Neurologix, Inc., Fort Lee, NJ</p> <p>Phase II trial completed</p>	Dopamine agonists Levodopa MOA-B inhibitors	Improved motor skill functions/movement control Slowed disease progression Improved quality of life

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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)	<p>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.</p> <p>Pfizer, Inc., New York NY Protalix BioTherapeutics, Inc., Carmiel, Israel</p> <p>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</p>	<p>Cerezyme enzyme replacement with intravenous recombinant glucocerebrosidase (imiglucerase) Blood transfusions Joint replacement surgery Splenectomy Bone marrow transplant (rarely done because of significant risk)</p>	<p>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</p>
Glutamate receptor antagonist (perampanel) for treatment of partial-onset epilepsy	Patients in whom partial-onset epilepsy has been diagnosed	<p>Some patients with partial-onset epilepsy do not respond to current therapy. Perampanel 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; drug also known as E2007.</p> <p>Eisai Co., Ltd., Tokyo, Japan</p> <p>Phase III trials completed; new drug application (NDA) and marketing authorization application submitted to FDA and to the European Medicines Agency, respectively, in May 2011; Jul 2011, FDA issued Refusal to File letter requesting that reformatting and reanalysis be done on submitted datasets before consideration for NDA acceptance; Dec 2011, NDA resubmitted to FDA; Mar 2011, FDA accepted resubmitted NDA</p>	<p>Gamma aminobutyric acid (GABA) derivatives Lamotrigine Levetiracetam Tiagabine Tricyclics Valproate</p>	<p>Reduced frequency of partial seizures Improved quality of life</p>

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Glycogen synthase kinase-3 enzyme inhibitor (tideglusib; Zentylor) for treatment of progressive supranuclear palsy	Patients in whom progressive supranuclear palsy (PSP) has been diagnosed	<p>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 treatment of 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.</p> <p>Noscira, S.A., Madrid, Spain</p> <p>Phase II trial ongoing; FDA granted orphan drug and fast track status; has orphan drug status in EU</p>	Anticholinergic medications Davunetide (in development)	Improved symptom control Delayed or halted disease progression Improved quality of life
Gracilis muscle transplant for treatment of facial paralysis in pediatric population	Pediatric patients in whom facial paralysis has been diagnosed	<p>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.</p> <p>Massachusetts Eye and Ear Infirmary, Boston, MA</p> <p>Pilot study completed Jul 2011</p>	Facial slings (masseter, temporalis, or anterior belly of digastric muscle) Nerve graft	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	<p>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.</p> <p>GlaxoSmithKline, Middlesex, UK, in partnership with Prosensa, Leiden, The Netherlands</p> <p>Phase III trial ongoing; FDA granted orphan drug status</p>	Symptom control using corticosteroids and 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

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Handheld intracranial scanner (InfraScanner, Model 1000) for detection of intracranial hematomas	Patients at risk of intracranial hematoma	<p>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.</p> <p>InfraScan Inc., Philadelphia, PA, in collaboration with the Office of Naval Research, Arlington, VA</p> <p>FDA approved Dec 2011</p>	<p>Automated Neuropsychological Assessment Metrics (computerized cognitive test)</p> <p>Computed tomography scans</p> <p>MRI studies</p> <p>Onsite neurophysical exam</p>	<p>Reduced morbidity</p> <p>Reduced mortality</p> <p>Improved quality of life</p>
High-intensity focused ultrasound for treatment of primary hyperparathyroidism	Patients with primary hyperparathyroidism who either decline or are not candidates for parathyroidectomy	<p>High-intensity focused ultrasound technique with TH-One under sonographic guidance is intended to ablate the gland while the patient is under conscious sedation.</p> <p>Theraclion, Paris, France</p> <p>Pilot trial completed in Bulgaria; phase I trial ongoing in France</p>	<p>Parathyroidectomy</p> <p>Percutaneous ethanol injection</p>	<p>Decreased serum parathyroid hormone levels</p> <p>Decreased serum calcium levels</p> <p>Reduced size of benign parathyroid tumors</p> <p>Reduced blurred vision, back pain, depression, fatigue</p> <p>Improved quality of life</p> <p>Adverse events</p>
Hormone stimulation drug (FG-2216) for treatment of anemia from dialysis	Patients needing dialysis who are at risk for anemia	<p>First oral drug (FG-2216) intended to stimulate production of the hormone erythropoietin in dialysis patients who are at risk for anemia; erythropoietin stimulates production of oxygen-carrying red blood cells.</p> <p>Astellas Pharma, Inc., Tokyo, Japan</p> <p>Fibrogen Inc., San Francisco, CA</p> <p>Phase II trial completed</p>	<p>Erythropoietin replacement therapy with erythropoiesis-stimulating agents</p>	<p>Resolution of anemia</p> <p>Improved quality of life</p>

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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)	<p>The only available pharmacologic option, riluzole, may slow disease progression, not stop it. 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.</p> <p>Neuralstem, Inc., Rockville, MD</p> <p>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 second dose to 3 patients in the cervical spine.</p>	<p>Riluzole (Rilutek®)</p> <p>Physical therapy and speech therapy to improve daily functioning</p> <p>Medications for symptom management (muscle cramps, constipation, fatigue, excessive salivation, excessive phlegm, pain, depression)</p>	<p>Slowing or halting progression of ALS</p> <p>Reduced symptoms</p> <p>Improved quality of life</p>
IGF-2 peptide conjugated alpha-glucosidase (BMN-701) enzyme replacement therapy for Pompe disease	Patients in whom late-onset Pompe disease has been diagnosed	<p>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.</p> <p>BioMarin Pharmaceuticals, Inc., Novato, CA</p> <p>Phase I/II and phase II trial ongoing</p>	<p>Alpha-glucosidase enzyme replacement therapies:</p> <p>Lumizyme</p> <p>Myozyme</p>	<p>Improved muscle strength, functional status, pulmonary function and/or ventilation</p> <p>Improved quality of life</p>
Implantable miniature telescope for treatment of end-stage age-related macular degeneration	Patients with end-stage age-related macular degeneration who have severe vision loss	<p>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.</p> <p>VisionCare Ophthalmic Technologies, Inc., Saratoga, CA</p> <p>FDA approved with conditions in 2010; 2 postapproval studies required; in Nov 2011, 1st patient received the new device</p>	<p>Anti-vascular endothelial growth factor injections</p> <p>Laser surgery</p> <p>Photodynamic therapy</p>	<p>Improved vision</p> <p>Improved quality of life</p>

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Inhaled apomorphine (VR040) for fluctuating, idiopathic Parkinson's disease	Patients in whom fluctuating, idiopathic Parkinson's disease has been diagnosed	<p>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.</p> <p>Vectura Group, plc, Chippenham, UK</p> <p>Phase II trials completed; European Medicines Agency granted orphan drug designation 2006; Vectura is seeking to license</p>	L-dopa with and without inhaled VR040	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	<p>About 20 million people in the U.S. are affected by dry-eye disease. There are numerous causal factors for 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 treatment of 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.</p> <p>SARcode Bioscience, Inc., Brisbane, CA</p> <p>Phase III trial ongoing</p>	<p>Artificial tears Hot compresses Lubricating ointments Proper eyelid cleaning and sanitary behavior modification Tetracycline and doxycycline Topical azithromycin Topical corticosteroids</p>	<p>Reduced occurrence and recurrence of dry eye Decreased incidence of blindness from chronic dry eye Improved quality of life</p>
Intranasal gel (Compleo TRT) for treatment of hypogonadism	Patients in whom hypogonadism has been diagnosed	<p>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.</p> <p>Trimel Pharmaceuticals Corp., Mississauga, Ontario, Canada</p> <p>Phase III trial ongoing</p>	Various formulations of testosterone	Increased testosterone levels Reduced adverse events

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Keratin gel for nerve regeneration of traumatically injured peripheral nerves	Patients who have experienced traumatic injury to peripheral nerves	<p>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.</p> <p>Wake Forest University, Winston-Salem, NC</p> <p>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</p>	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
Kidney growth factor peptide (NX-001) for prevention of delayed graft function in renal transplantation	Patients who have received a kidney transplant	<p>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.</p> <p>NephRx Corp., Kalamazoo, MI</p> <p>Phase I trial ongoing; phase II trial planned for late 2011, but not registered trial on National Clinical Trials database as of Mar 2012; FDA granted orphan drug status in 2010</p>	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	<p>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.</p> <p>AB Science S.A., Paris, France Phase II/III trial ongoing</p>	Dimethyl fumarate Fingolimod Glatiramer acetate Interferon b-1a (Avonex) Laquinimod Natalizumab	Delayed disease progression Reduced symptoms Improved quality of life

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Laquinimod for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	<p>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.</p> <p>Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel Active Biotech, Lund, Sweden</p> <p>Phase III trials completed; manufacturer expected to file new drug application in early 2012; received fast track status from FDA in 2009</p>	Fingolimod Glatiramer acetate Interferon (IFN) IFN beta-1a (Avonex) Natalizumab	Reduced brain tissue loss/atrophy Reduced frequency of relapse Slowed disease progression Improved quality of life
Laser surgery for treatment of epilepsy	Patients in whom epilepsy has been diagnosed	<p>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.</p> <p>Texas Children's Hospital, Houston, TX</p> <p>Pilot trial completed</p>	Antiseizure medications Craniotomy Deep brain stimulation	Reduction or elimination of seizures

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Lasmiditan (COL-144) for treatment of migraine headaches	Patients in whom migraine headaches have been diagnosed	<p>Lasmiditan is a small-molecule, serotonin receptor agonist that binds to the 5-HT<sup>1F</sup> receptor and is intended to have a reduced vasoconstrictive effect compared with other drugs. Oral and intravenous formulations are under study.</p> <p>CoLucid Pharmaceuticals, Inc., Research Triangle Park, NC</p> <p>Phase IIb trial completed (outside U.S.); FDA accepted investigational new drug application in Aug 2011; phase III trial planned for 2012</p>	<p>Acetaminophen plus aspirin plus caffeine Butorphanol injection Dihydroergotamine in any of several formulations Ibuprofen oral Naproxen sodium Naratriptan Prochlorperazine Rizatriptan Sumatriptan in any of several formulations Triptans</p>	<p>Quicker reduction in pain and light/noise sensitivity Reduced recurrence of symptoms Reduced side effects</p>
Levadex (MAP-0004) orally inhaled for treatment of migraine headaches	Patients in whom migraine headaches have been diagnosed	<p>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.</p> <p>MAP Pharmaceuticals, Inc., Mountain View, CA</p> <p>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</p>	<p>Acetaminophen plus aspirin plus caffeine Butorphanol injection Dihydroergotamine formulations Ibuprofen oral Naproxen sodium Naratriptan Prochlorperazine Rizatriptan Sumatriptan formulations Triptans</p>	<p>Quicker reduction in pain and light/noise sensitivity Reduced recurrence of symptoms Reduced side effects</p>

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	<p>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, 1,000 mg dosages.</p> <p>Kessler Foundation, West Orange, NJ</p> <p>Phase I trial ongoing</p>	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	<p>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.</p> <p>Neuraltus Pharmaceuticals, Inc., Palo Alto, CA</p> <p>Phase II trial ongoing; FDA granted fast track and orphan drug status Aug 2011</p>	Drugs that address symptoms but do not address biomarkers	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	<p>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).</p> <p>Georgia Institute of Technology, Atlanta</p> <p>Pilot trial and unphased trials completed</p>	<p>Comparators depend on severity of spinal cord paralysis</p> <p>Chin control wheelchair</p> <p>Head control wheelchair</p> <p>"Sip and puff" wheelchair</p> <p>Speech control wheelchair</p> <p>Tongue keyboard controller wheelchair</p>	<p>Improved wheelchair function and control</p> <p>Improved aesthetics of device</p> <p>Improved mobility</p> <p>Improved quality of life</p>
Mapracorat ophthalmic suspension for treatment of postcataract-surgery inflammation	Patients who have undergone cataract surgery	<p>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.</p> <p>Bausch &amp; Lomb, Inc., Rochester, NY</p> <p>Phase III trial ongoing; 1 phase III trial terminated</p>	<p>Antibiotics</p> <p>Corticosteroids</p> <p>Nonsteroidal anti-inflammatory drugs</p> <p>Tobradex (tobramycin 3 mg/mL, dexamethasone 1 mg/mL)</p>	<p>Reduced inflammation-related complications</p> <p>Reduced side effects</p>
Mecobalamin (E-0302) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	<p>Only 1 drug (Riluzole) is approved for treatment of ALS. Mecobalamin (E-0302) is a methylated form of vitamin B<sub>12</sub> proposed for parenteral therapy for ALS.</p> <p>Eisai Co., Ltd., Tokyo, Japan</p> <p>Phase II/III trials ongoing in Japan</p>	<p>Riluzole</p> <p>Supportive care</p>	<p>Increased survival rate</p> <p>Improved functional rating scale</p> <p>Increased safety</p> <p>Improved quality of life</p>

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	<p>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 <i>Glycyrrhizae uralensis</i> Fisch. MF-101 is administered orally, 5, 10, or 15 g, daily.</p> <p>Bionovo, Inc., Emeryville, CA</p> <p>Phase III trial ongoing</p>	<p>Antidepressants Estrogen therapy (pill or cream form) Hormone therapy Ibuprofen Neurontin® Phytoestrogens Progesterone/progestin-estrogen Raloxifene Tamoxifen Vitamin B complex Vitamin E</p>	<p>Decreased incidence of hot flashes Improved quality of life</p>
Mesenchymal stem cell transplantation for treatment of multiple sclerosis	Patients in whom multiple sclerosis (MS) has been diagnosed	<p>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.</p> <p>Cleveland Clinic, Cleveland, OH University Hospitals Seidman Cancer Center, Cleveland, OH Case Western Reserve University, Cleveland, OH</p> <p>Phase I/II trial completed; Phase II trials ongoing as well at other institutions</p>	<p>Fingolimod Glatiramer acetate Interferon beta (IFNβ) IFNβ-1a (Avonex) Laquinimod Natalizumab</p>	<p>Improved motor/cognitive function Reduced brain tissue loss/atrophy Reduced frequency of relapse Slowed rate of disease progression Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Metabotropic glutamate receptor 5 antagonist dipraglurant (ADX48621) for treatment of Parkinson's disease</p>	<p>Patients in whom Parkinson's disease (PD) has been diagnosed</p>	<p>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. While dystonia is a significant problem for PD patients, no products are specifically licensed for treatment of 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.</p> <p>Addex Pharmaceuticals, Geneva, Switzerland</p> <p>Phase IIa trial ongoing</p>	<p>Dopamine agonists Levodopa/carbidopa Mavoglurant MOA-B inhibitors, etc.</p>	<p>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</p>

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Metabotropic glutamate receptor 5 antagonist mavoglurant (AFQ056) for treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	<p>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.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Phase IIb and phase II/III trials ongoing</p>	Dipraglurant Dopamine agonists Levodopa/carbidopa MOA-B inhibitors, etc. NP002	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) for treatment of glaucoma	Patients undergoing cataract surgery who are also at risk of developing glaucoma due to uncontrolled elevated intraocular pressure (IOP)	<p>iStent is intended for implantation during cataract surgery in patients with or at risk for 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 treatment of glaucoma.</p> <p>Glaukos Corp., Laguna Hills, CA</p> <p>Phase I U.S. trial ongoing; in Aug 2010, FDA advisory panel recommended approval; under FDA review. Conformité Européene (CE) marked in select countries in Europe; approved in Canada</p>	Trabectome (device) Trabeculotomy Surgery Medications Combination of medications and surgery	Preserved vision Reduced elevated or uncontrolled IOP

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Migalastat hydrochloride (AT1001) for treatment of Fabry disease	Patients with Fabry disease who have either migalastat-responsive mutations in alpha-galactosidase A or who are receiving enzyme replacement therapy	<p>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.</p> <p>Amicus Therapeutics, Inc., Cranbury, NJ</p> <p>Phase III trial ongoing</p>	Enzyme replacement therapy Palliative treatment of secondary symptoms	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	<p>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.</p> <p>Nektar Therapeutics, San Francisco, CA</p> <p>Phase Ia trial complete; phase Ib trial ongoing</p>	Conventional mu-opioid agonists	Improved pain relief Reduced adverse effects Reduced risk of addiction Improved quality of life

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Nabiximols oromucosal spray (Sativex) for treatment of multiple sclerosis spasticity and neuropathic pain	Patients in whom multiple sclerosis (MS) has been diagnosed	<p>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.</p> <p>GW Pharmaceuticals, plc, Salisbury, UK Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan</p> <p>Phase III trial ongoing; approved in New Zealand and Canada for treatment of spasticity due to MS; approved in Canada for relief of MS-related neuropathic pain</p>	Opioids	<p>Reduced pain Reduced spasticity Improved quality of life</p>
N-acetylgalactosamine 6-sulfatase (GALNS) for treatment of Morquio syndrome	Patients in whom the genetic disorder Morquio syndrome type A has been diagnosed	<p>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.</p> <p>BioMarin Pharmaceutical, Inc., Novato, CA</p> <p>Phase III trial ongoing</p>	No current treatments are available to resolve the underlying disease.	<p>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</p>
Neural stem cell therapy (ReN001) for stroke recovery	Patients in whom a stroke has been diagnosed	<p>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.</p> <p>ReNeuron Group, Inc., Guildford, UK</p> <p>Phase I trial ongoing in UK; investigational new drug application on hold with FDA in U.S.</p>	Current rehabilitative treatment for disabled stroke survivors	Resolution of functional deficits

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Neuron transplantation (MotorGraft) for patients with spinal muscular atrophy type 1	Patients in whom spinal muscular atrophy (SMA) type I has been diagnosed	<p>A stem cell–derived motor neuron transplantation therapy, MotorGraft™ is intended for treatment of SMA type I; cells are delivered surgically into the spinal cord of these patients.</p> <p>California Stem Cell, Inc., Irvine, CA</p> <p>Phase I trial placed on clinical hold (delayed) per FDA official response to company's investigational new drug application</p>	No treatment exists	Improved function in muscles that control crawling, walking, swallowing, and breathing
Nicotinic receptor agonist NP002 for treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	<p>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.</p> <p>Neuraltus Pharmaceuticals, Inc., Palo Alto, CA</p> <p>Completed phase I/II trial</p>	Dipraglurant Dopamine agonists Levodopa/carbidopa Mavoglurant MOA-B inhibitors, etc.	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	<p>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.</p> <p>National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD</p> <p>Phase III trial ongoing</p>	Anti-bone–resorptive drugs (bisphosphonates, selective estrogen receptor modulators, estrogen, calcitonin, anti-RANKL [receptor activator of nuclear factor kappa B ligand] antibodies). 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

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<p>Nonsurgical, removable dental hearing device (SoundBite) for treatment of single-sided deafness</p>	<p>Patients in whom single-sided deafness has been diagnosed</p>	<p>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.</p> <p>Sonitus Medical, Inc., San Mateo, CA</p> <p>FDA 510(k) clearance granted 2011</p>	<p>Bone anchored implants Hearing aid devices (BTE, in-the-ear devices, canal aids)</p>	<p>Improved hearing Improved quality of life</p>
<p>NuQu injectable cell-therapy for spinal disc regeneration</p>	<p>Patients with severe chronic lower back pain that is refractory to conservative treatment</p>	<p>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.</p> <p>ISTO Technologies, Inc., St. Louis, MO</p> <p>Phase I trial ongoing</p>	<p>Artificial disc replacement Discectomy Spinal fusion</p>	<p>Reduced back pain Increased function Improved quality of life</p>

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NX-1207 for treatment of benign prostatic hyperplasia	Patients in whom benign prostatic hyperplasia (BPH) has been diagnosed	<p>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. While its exact mechanism of action is unknown, it is thought that NX-1207 has pro-apoptotic properties.</p> <p>Nymox Pharmaceutical Corp., Hasbrouck Heights, NJ</p> <p>Phase III trials ongoing</p>	<p>5-Alpha reductase inhibitors: finasteride, dutasteride Alpha blockers: terazosin, doxazosin, tamsulosin, alfuzosin, silodosin Minimally invasive surgery (laser ablation, transurethral microwave therapy) Surgery (transurethral resection of the prostate)</p>	<p>Improved International Prostate Symptom Score or improved American Urological Association Symptom Index Increased urine flow rate Improved quality of life</p>
Obeticholic acid (INT-747) for treatment of nonalcoholic steatohepatitis	Patients in whom nonalcoholic steatohepatitis (NASH) has been diagnosed	<p>Obeticholic acid (INT-747) is a farnesoid X receptor agonist derived from human bile intended for administration to decrease liver tissue scarring and fibrosis.</p> <p>Intercept Pharmaceuticals, Inc., New York, NY</p> <p>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</p>	Currently, no other treatment exists	<p>Reduced tissue scarring Slowed progression of fibrosis Improved liver function Improved quality of life Reduced need for liver transplantation</p>
Ocrelizumab for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	<p>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.</p> <p>F. Hoffman-La Roche, Ltd., Basel, Switzerland Biogen Idec International GmbH, Zug, Switzerland</p> <p>Phase III trials ongoing</p>	<p>Fingolimod Glatiramer acetate Interferon beta (IFN<math>\beta</math>) IFN<math>\beta</math>-1a (Avonex) Natalizumab</p>	<p>Decreased frequency of relapse Slowed disease progression Improved quality of life</p>

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Off-label beta blockers for treatment of serious infantile hemangiomas	Infants in whom a hemangioma has been diagnosed	<p>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.</p> <p>Hackensack University Medical Center, Hackensack, NJ, and various centers conducting trials</p> <p>Unphased trials completed; phase II and III trials ongoing</p>	Corticosteroids Laser treatment	<p>Reduced hemangiomas</p> <p>Improved functional ability</p> <p>Prevention of future complications</p> <p>Improved quality of life</p>
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	<p>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.</p> <p>BEAT-ROP cooperative (trial sponsor) Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland (manufacturer) is not pursuing a labeled indication; postmarket trial of off-label use completed</p>	Peripheral retinal ablation with lasers (e.g., xenon, argon, diode)	<p>Prevented recurrence of neovascularization arising from the retinal vessels</p> <p>Improved visual acuity</p>

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Off-label etanercept for treatment of Kawasaki disease	Patients in whom Kawasaki disease (KD) has been diagnosed	<p>KD is the most common cause of acquired heart disease in U.S. children, and many patients are refractory to current standard of care; new treatment options are needed for patients whose disease is refractory to treatment. Etanercept 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.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase II trial ongoing; FDA approved in 1998 for moderate to severe rheumatoid arthritis and other inflammatory conditions</p>	High-dose aspirin IVIG	<p>Improved survival</p> <p>Prevented increase in coronary artery diameter</p> <p>Prevented new coronary artery dilation/cardiac dysfunction</p> <p>Reduced fever</p>
Off-label rifampicin for treatment of multiple system atrophy	Patients in whom multiple system atrophy (MSA) has been diagnosed	<p>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.</p> <p>Mayo Clinic, Minneapolis, MN</p> <p>Phase III trial ongoing</p>	Blood pressure medications Impotence drugs Incontinence drugs Levodopa and carbidopa	<p>Improved symptoms based on Unified Multiple System Atrophy Rating Scale</p> <p>Reduced neurodegeneration</p> <p>Improved quality of life</p>
Off-label teriparatide (Forteo) for hard-to-heal fractures	Patients in whom unhealed bone fractures of the pelvis have been diagnosed	<p>Teriparatide (Forteo®) subcutaneous injection intended to promote fracture healing in Jones, pelvic, and shoulder fractures.</p> <p>Eli Lilly &amp; Co., Indianapolis, IN</p> <p>Unphased trial ongoing; already approved as treatment for osteoporosis</p>	Fracture healing rate without teriparatide Growth factors Electrical stimulation	<p>Faster and more complete healing time</p> <p>Improved function</p> <p>Improved mobility</p> <p>Improved quality of life</p>

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Olesoxime (TRO19622) for treatment of spinal muscular atrophy	Patients who have been given a diagnosis of spinal muscular atrophy (SMA)	<p>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.</p> <p>Trophos SA, Marseille, France</p> <p>Phase II trial ongoing</p>	<p>Assistive technology Butyrates Hydroxyurea Quinazoline495 Riluzole Valproic acid</p>	<p>Increased survival Increased progression-free survival Improved quality of life</p>
Oral calcitonin (Ostora) for prevention and treatment of postmenopausal osteoporosis	Women at risk for or in whom postmenopausal osteoporosis has been diagnosed	<p>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.</p> <p>Tarsa Therapeutics, Philadelphia, PA</p> <p>Phase III treatment trial completed; phase II prevention trial ongoing; company planned to file new drug application in 2nd half of 2012</p>	<p>Capsitonin oral calcitonin (in development) Injectable calcitonin Intranasal calcitonin</p>	<p>Slowed rate of bone breakdown Decreased bone loss Decreased numbers of hip and spine fractures Improved quality of life</p>

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	<p>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 current 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.</p> <p>AEterna Zentaris, Inc., Quebec, Quebec, Canada</p> <p>Phase III trial completed; FDA granted orphan drug status; company expects new drug application filing in 2012</p>	<p>Blood GH testing  Insulin-like growth factor level testing  Insulin tolerance testing  MRI of pituitary to detect dysfunction</p>	<p>Increased sensitivity and specificity  Improved diagnostic accuracy  Increased patient adherence with recommended diagnostic strategy  Reduced risk of adverse events from invasive tests</p>
Oral opioid antagonist (ALKS-37) for treatment of opioid-induced bowel dysfunction	Patients in whom opioid-induced bowel dysfunction has been diagnosed	<p>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.</p> <p>Alkermes, Inc., Waltham, MA</p> <p>Phase II trials ongoing</p>	<p>Injectable opioid antagonists (methylnaltrexone)  Laxatives</p>	<p>Reduced bowel dysfunction  Increased frequency of bowel movements  Adherence with opioid treatment</p>

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	<p>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.</p> <p>AstraZeneca, London, UK Nektar Therapeutics, San Francisco, CA</p> <p>Phase III trials ongoing</p>	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	<p>SCD is an autosomal recessive disorder that affects about 100,000 people in the U.S. and Europe. There is increased prevalence of disease 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).</p> <p>HemaQuest Pharmaceuticals, Inc., San Diego, CA</p> <p>Phase I/II trial completed; phase II trial ongoing; FDA granted orphan drug status</p>	Allogeneic hematopoietic stem cell transplantation Antioxidant therapy Azacitidine Decitabine butyrate Gene therapy Gardos channel inhibition Hydroxyurea Lenalidomide Nitrous oxide and vasodilators Statins	Reduced severity and duration of vaso-occlusive crises Reduced health disparities (African Americans) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Osseointegrated implants for lower-limb prostheses	Patients who have had amputation of a lower limb	<p>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.</p> <p>Specific device manufacturer(s) unclear</p> <p>In early use in Europe; FDA has not yet approved any trials</p>	Conventional prosthetic legs that attach over stump of residual lower limb	Improved gait, mobility and comfort Reduced pain Improved fit
Oxybutynin intravaginally (FP 1097) for treatment of urinary urge incontinence	Women in whom urinary urge incontinence has been diagnosed	<p>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.</p> <p>FemmePharma Global Healthcare, Inc., Wayne, PA</p> <p>Phase II trials completed; phase III trial planned for 2011, but currently not registered on National Clinical Trials database; FDA has agreed to grant FP 1097 505(b)(1) filing status (lower evidence requirement)</p>	Systemic anticholinergic drugs: darifenacin, fesoterodine fumarate, oxybutynin, solifenacin, tolterodine	Reduced micturition and incontinence episodes Reduced systemic side effects (dry mouth, constipation, blurry vision, confusion)
Pasireotide (SOM230) for treatment of acute radiation syndrome	Patients in whom acute radiation syndrome (ARS) has been diagnosed	<p>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. While few treatments exist for irradiated bone marrow, none exist for irradiated GI organs. Additionally, there are no FDA-approved treatments for use as medical radiation countermeasures for the prevention or treatment of ARS. Pasireotide is a cyclohexapeptide engineered to bind to multiple somatostatin receptor subtypes to mimic the actions of natural somatostatin. For ARS, pasireotide is intended to reduce pancreatic secretions known to invade the irradiated intestinal wall and induce an inflammatory response.</p> <p>Novartis AG, Basel, Switzerland (manufacturer) University of Arkansas for Medical Sciences, Little Rock (investigator)</p> <p>Clinical trial phase not reported</p>	Antibiotics Hematopoiesis-stimulating agents Stem cell therapy Various pharmacotherapies under development	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	<p>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.</p> <p>BioMarin Pharma, Inc., Novato, CA</p> <p>Phase II trials ongoing; FDA granted orphan drug status</p>	Kuvan (tetrahydrobiopterin or BH4)	<p>Decreased phenylalanine levels</p> <p>Fewer diet restrictions</p> <p>Improved quality of life</p> <p>Injection site inflammation is most common adverse event (43%)</p>
Personalized T-cell immunotherapy (Tovaxin) for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	<p>There is no cure for MS. Current treatments do not sustain long-term remission, and some have severe secondary effects. 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.</p> <p>Opexa Therapeutics, Inc., The Woodlands, TX</p> <p>Phase IIb trial completed</p>	<p>Interferon beta (IFNβ)-1a (Avonex®, CinnoVex™, ReciGen® and Rebif®)</p> <p>IFNβ-1b (Betaseron®)</p> <p>Glatiramer acetate (Copaxone®)</p> <p>Mitoxantrone</p> <p>Natalizumab (Tysabri®)</p>	<p>Decreased annualized relapse rate</p> <p>Improvement in disability score</p> <p>Improved safety</p> <p>Improved long-term management of disease</p>
PET/MRI integrated imaging system (Biograph mMR) for diagnosis of neurologic conditions	Patients who require morphologic, functional, and metabolic imaging exams for neurologic indications	<p>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.</p> <p>Siemens Healthcare, Malvern, PA</p> <p>FDA 510(k) clearance granted Jun 2011</p>	Stand-alone PET and MRI exams	<p>More efficient imaging for patient</p> <p>Improved diagnosis from combined morphologic, functional, and metabolic imaging</p> <p>Improved treatment planning</p>

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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	<p>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.</p> <p>Respocardia, Inc., Minneapolis, MN</p> <p>Phase II trial ongoing</p>	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)	<p>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 as drowsiness and respiratory distress.</p> <p>Icagen, Inc., Durham, NC, in collaboration with Pfizer, Inc., New York, NY</p> <p>Phase I trial ongoing</p>	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])	<p>PHN affects a significant proportion of adults older than age 65 who have a bout of shingles, and severe PHN can require hospitalization; current treatments for PHN have variable efficacy in different patients and often require trial and error to achieve optimal relief. 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.</p> <p>Aestus Therapeutics, Inc., North Brunswick, NJ</p> <p>Phase II trial completed</p>	Lidocaine skin patches Tricyclic antidepressants: Amitriptyline Nortriptyline Anticonvulsants: Gabapentin Pregabalin Opioids: Morphine Oxycodone Tramadol	Reduced pain on visual analog scale Improved quality of life

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Preladenant for treatment of moderate to severe Parkinson's disease	Patients in whom moderate to severe Parkinson's disease (PD) has been diagnosed	<p>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.</p> <p>Merck &amp; Co., Inc. (Schering-Plough), Whitehouse Station, NJ</p> <p>Phase III trials ongoing</p>	Levodopa and carbidopa Rasagiline (Azilect) as monotherapy or adjunct therapy in advanced cases	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	<p>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).</p> <p>Research commissioned and funded by U.S. Defense Advanced Research Projects Agency, Arlington, VA; U.S. Department of Defense, Washington, DC, and U.S. Department of Veterans Affairs, Washington, DC, conducting clinical testing. Several U.S. and international research partners participating</p> <p>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</p>	Conventional prosthetic arms	Significant restoration of limb function compared with current prosthetic devices
PTH(1-84) for treatment of hypo-parathyroidism	Patients in whom hypo-parathyroidism has been diagnosed	<p>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; PTH(1-84) is hormone replacement therapy intended to provide long-term control of serum calcium and urinary calcium excretion.</p> <p>Columbia University, New York, NY</p> <p>Phase III trial completed; phase III trials ongoing</p>	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
PYM50028 (Cogane) for treatment of Parkinson's disease	Patients in whom early-stage Parkinson's disease has been diagnosed	<p>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.</p> <p>Phytopharm, plc, Huntingdon, UK</p> <p>Phase II trial ongoing</p>	Deep brain stimulation Levodopa	Improved motor skill function and reduction in symptoms Improved quality of life
Real-time functional magnetic resonance imaging with cognitive training to treat chronic pain	Patients in whom chronic pain has been diagnosed	<p>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.</p> <p>Omneuron, Inc., Menlo Park, CA National Institute of Neurological Disorders and Stroke, Bethesda, MD</p> <p>Phase II trial ongoing</p>	Standard therapies with and without fMRI Combination therapies Management with tricyclic antidepressants, anticonvulsants, or opioid analgesics Physical therapy Spinal cord stimulation Transcutaneous electrical nerve stimulation	Ability to perform activities of daily living Decreased pain Return to work Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Reciprocating gait orthoses (ReWalk and eLegs systems) for mobility after spinal cord injury	Patients with spinal cord injury resulting in paraplegia and need for wheelchair use	<p>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 eLegs system incorporates technology similar to that in the ReWalk system.</p> <p>Argo Medical Technologies, Ltd., Yokneam Illit, Israel (ReWalk system) Ekso Bionics, Berkeley, CA (eLegs system)</p> <p>The ReWalk-I (institutional use) system is FDA-listed for institutional use only. The company expected to register the ReWalk-P system for personal use with FDA by the end of 2011 and make it available to patients in mid-2012. The eLegs system is available for institutional use only.</p>	Wheelchairs	Improved mobility Improved independence Improved quality of life
Recombinant human interleukin-12 (HemaMax) for treatment of acute radiation syndrome	Patients in whom acute radiation syndrome (ARS) has been diagnosed	<p>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.</p> <p>Neumedicines, Inc., Pasadena, CA</p> <p>Phase I trial ongoing</p>	Antibiotics Hematopoiesis-stimulating agents Stem cell therapy Various pharmacotherapies under development	Decreased secondary complications (i.e., hematopoietic syndrome) Decreased mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>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.</p> <p>ThromboGenics NV, Heverlee, Belgium</p> <p>Phase III trials completed; company filed biologics license application Dec 2011</p>	Pegaptanib sodium (Macugen®) injection Surgery	Preserved vision Reduced complications associated with surgical treatment Improved quality of life
Recombinant porcine factor VIII (OBI-1) for treatment of acquired hemophilia	Individuals with acquired hemophilia A who develop immune reaction to human Factor VIII	<p>About 15% to 30% of patients with acquired hemophilia develop immune reaction to recombinant human 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.</p> <p>Inspiration Biopharmaceuticals, Inc., Laguna Niguel, CA</p> <p>Phase II/III and phase III trial ongoing</p>	Human Factor VIIa	Adequate control of bleeding episodes
RenalGuard for prevention of contrast-induced nephropathy	Patients at risk for contrast-induced nephropathy (CIN)	<p>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.</p> <p>PLC Systems, Inc., Milford, MA</p> <p>Pivotal trial completed</p>	Cincor™ system (in development) Deferiprone (in development) Deferoxamine Hydration	Reduced occurrence and complications of CIN Reduced incidence of CIN in high risk patients with CKD Improved quality of life

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Retargeted endopeptidase (AGN-214868) for treatment of overactive bladder and urinary incontinence	Patients in whom overactive bladder leading to urinary incontinence has been diagnosed	<p>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.</p> <p>Syntaxin Ltd., Oxford, UK, in collaboration with Allergan, Inc., Irvine, CA</p> <p>Phase II trial ongoing</p>	<p>Behavioral therapy in combination with bladder relaxing drugs (e.g., darifenacin, oxybutynin, oxybutynin skin patches, solifenacin, tolterodine, trospium)</p> <p>Onabotulinum toxin A</p> <p>Sacral nerve stimulation</p> <p>Surgical treatment (bladder enlargement, cystectomy)</p>	<p>Decrease in urge to urinate</p> <p>Decrease in urination episodes per week</p> <p>Improved International Consultation on Incontinence Questionnaire-Overactive Bladder score</p> <p>Improved quality of life</p>
Retargeted endopeptidase (AGN-214868) for treatment of postherpetic neuralgia	Patients in whom postherpetic neuralgia has been diagnosed	<p>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.</p> <p>Syntaxin Ltd., Oxford, UK, in collaboration with Allergan, Inc., Irvine, CA</p> <p>Phase II trial ongoing</p>	<p>Anticonvulsants (gabapentin, pregabalin)</p> <p>Lidocaine skin patches</p> <p>Opioids (tramadol, oxycodone, morphine)</p> <p>Tricyclic antidepressants (nortriptyline, amitriptyline)</p>	<p>Reduced pain score on visual analog pain scale</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Retinal prosthesis system (Argus II) for treatment of retinitis pigmentosa	Patients with retinitis pigmentosa (RP) and a functioning optic nerve	<p>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.</p> <p>Second Sight, Inc., Sylmar, CA</p> <p>Phase II trial ongoing under FDA investigational device exemption status, Conformité Européene (CE) marked in 2011</p>	<p>Other retinal prostheses in development: On the retina: Intelligent Implants, Bonn, Germany Under the retina: Optobionics, Chicago, IL Retinal Implant (Germany) subretinal location of implant and no glasses Gene therapy delivered to retinal cells</p>	<p>Improved visual acuity Improved quality of life and independence</p>
Rituximab (Rituxan) for treatment of Wegener's granulomatosis and microscopic polyangiitis	Patients in whom Wegener's granulomatosis has been diagnosed	<p>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 the treatment of 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.</p> <p>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland</p> <p>FDA approved Apr 2011 for this indication</p>	<p>Azathioprine (Imuran®) Cyclophosphamide (Cytoxan®) Methotrexate Prednisone</p>	<p>Disease remission</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Robotic navigation aid (Guide Vest) to assist visually impaired persons</p>	<p>Patients with visual impairment</p>	<p>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.</p> <p>University of Southern California Keck School of Medicine's Doheny Eye Institute, Los Angeles</p> <p>Pilot study completed at Braille Institute</p>	<p>Long canes Remote Infrared Audible Signage (RIAS) "Sighted" wheelchair Spectacles with stereoscopic cameras (under study)</p>	<p>Decreased risk of falls and injury Improved mobility Increased independence</p>
<p>Sclerostin neutralizing monoclonal antibody (AMG 785) for treatment of postmenopausal osteoporosis</p>	<p>Patients in whom postmenopausal osteoporosis (PMO) has been diagnosed</p>	<p>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.</p> <p>Amgen, Inc., Thousand Oaks, CA</p> <p>Phase II trial ongoing</p>	<p>AvB3 integrin antagonists Bisphosphonates Calcitonin Cathepsin K inhibitors Denosumab Estrogen therapy Glucagon-like peptide 2 Osteoprotegerin Parathyroid hormone Selective estrogen receptor modulators Strontium ranelate</p>	<p>Higher bone density Reduced fracture rate Improved quality of life Increased survival</p>

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	<p>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.</p> <p>Anacor Pharmaceuticals, Inc., Palo Alto, CA</p> <p>Phase II trials completed</p>	<p>Topical ointments: Corticosteroids Calcineurin inhibitors Salicylic acid Coal tar Phototherapy Systemic medications: Retinoids Methotrexate Cyclosporin Hydroxyurea Immunomodulators Thioguanine</p>	<p>Improved psoriasis area severity index scale Improved quality of life</p>
SMT C1100 for treatment of Duchenne muscular dystrophy	Patients in whom Duchenne muscular dystrophy (DMD) has been diagnosed	<p>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.</p> <p>Summit, plc, Oxfordshire, UK</p> <p>Phase I trial ongoing; FDA granted orphan drug status</p>	<p>ACE-031 Beta-2 agonists Corticosteroids Eteplirsen GSK-2402968 Orthopedic devices Physical therapy Respiratory support devices</p>	<p>Decreased muscle degeneration Decreased need for supportive devices Improved symptoms Reduced mortality Improved quality of life</p>
SOLX gold shunt for treatment-refractory glaucoma	Patients in whom treatment-refractory glaucoma has been diagnosed	<p>There is no cure for glaucoma and untreated or if 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.</p> <p>SOLX, Inc., Waltham, MA</p> <p>Phase III trials ongoing; approved in Canada and parts of Europe</p>	<p>Ahmed glaucoma valve sheet valve Baerveldt implant Glaucoma drainage device Krupin implant slit valve Laser surgery Medications to reduce IOP Molteno implant Trabectome (device) - Trabeculotomy</p>	<p>Reduced IOP Preserved vision</p>

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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	<p>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.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Phase III trial ongoing</p>	Ketoconazole Metyrapone Mitotane Radiation therapy Surgical resection	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	<p>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.</p> <p>Bruin Biometrics, LLC, Los Angeles, CA</p> <p>Pilot trial completed</p>	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	<p>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.</p> <p>Retina Implant AG, Reutlingen, Germany</p> <p>Pilot trial completed; early unphased clinical trial ongoing</p>	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 and plans to resubmit the NDA in early 2012	Currently available oral drugs: Nonsteroidal anti-inflammatory drugs (oral) Combination analgesics containing caffeine Isometheptene combinations Migraine-specific drugs (i.e., triptans [natriptan, rizatriptan, sumatriptan, zolmitriptan], dihydroergotamine) Combination drug therapy (e.g., aspirin plus acetaminophen plus caffeine) Ergotamine	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 intended to block new synthesis of pyrimidines and reduce T- and B-cell proliferation. It has been given in trials as once-daily, oral teriflunomide monotherapy, 7 or 14 mg.  Sanofi, Paris, France  Phase III trials ongoing	Glatiramer acetate (Copaxone) Interferon beta (IFNβ) (Betaseron) IFNβ-1a (Avonex) Fingolimod (Gilenya) Natalizumab	Longer remission time Reduced relapse rate Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Terlipressin for reversal of hepatorenal syndrome type 1	Patients in whom hepatorenal syndrome (HRS) type 1 has been diagnosed	<p>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.</p> <p>Ikaria Holdings, Inc., Clinton, NJ</p> <p>Phase III and II/III trials ongoing</p>	Standard care with and without terlipressin Liver transplantation (i.e., the treatment for HRS type 1 and underlying end-stage cirrhosis; however, because of long waiting lists, many patients die before transplantation)	Confirmed HRS reversal Increased survival to time of transplantation Transplant-free survival up to 90 days
Thermal pulsation system (LipiFlow) for treatment of meibomian gland dysfunction	Patients in whom meibomian gland dysfunction (MGD) has been diagnosed	<p>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 (48° 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.</p> <p>TearScience, Inc., Morrisville, NC</p> <p>Received FDA 510(k) clearance Jul 2011</p>	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	<p>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 of AKI. 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.</p> <p>Thrasos, Inc., Montreal, Quebec, Canada</p> <p>Phase I trial ongoing</p>	Cincor™ system (in development) Deferoxamine Deferiprone (in development) 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	<p>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.</p> <p>Oceana Therapeutics, Inc., Edison, NJ</p> <p>FDA approved Apr 2011</p>	Antidiarrhea drugs Bowel training mechanisms Dietary changes Enemas/laxatives Sacral nerve stimulation Surgeries (sphincter repair, sphincter replacement, sphincteroplasty, colostomy, rectal prolapse correction)	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 XEN402 for treatment of postherpetic neuralgia	Patients in whom postherpetic neuralgia has been diagnosed	<p>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.</p> <p>Xenon Pharmaceuticals, Inc., Burnaby, British Columbia, Canada</p> <p>Phase IIa trial completed, Phase IIb trial ongoing</p>	<p>Anticonvulsants (Gabapentin [Neurontin], pregabalin [Lyrica®]) Lidocaine skin patches Opioid painkillers (Tramadol [Ultram®, Ryzolt®], oxycodone [Percocet] or morphine) Tricyclic antidepressants</p>	<p>Reduced or eliminated pain Reduced time to pain reduction Shorter recovery time</p>
TrkA kinase inhibitor (CT327) for treatment of psoriasis	Patients in whom mild to moderate psoriasis vulgaris has been diagnosed	<p>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.</p> <p>Creabilis SA, Luxembourg City, Luxembourg</p> <p>Phase II trial completed</p>	<p>Topical ointments: Corticosteroids Calcineurin inhibitors Salicylic acid Coal tar Phototherapy Systemic medications: Retinoids Methotrexate Cyclosporin Hydroxyurea Immunomodulators Thioguanine</p>	<p>Improved psoriasis area severity index scale Improved quality of life</p>
Troponin activator (CK-2017357) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	<p>The average life expectancy of a patient with ALS is about 3–5 years, and only 10% of patients survive for more than 10 years. Only 1 treatment option exists, and it has limited efficacy. 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.</p> <p>Cytokinetics, Inc., South San Francisco, CA</p> <p>Phase II trials completed; FDA granted orphan drug status</p>	Riluzole	<p>Improved patient/investigator global assessment of symptoms Improved pulmonary function Reduced muscle fatigue</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Troponin activator (CK-2017357) for treatment of myasthenia gravis	Patients in whom generalized myasthenia gravis (MG) has been diagnosed	<p>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.</p> <p>Cytokinetics, Inc., South San Francisco, CA</p> <p>Phase II trial ongoing; FDA granted orphan drug status</p>	<p>Cholinesterase inhibitors Emergency plasmapheresis or intravenous immunoglobulin Immunosuppressant drugs Thymectomy</p>	<p>Improved muscle function Delayed onset and reduced magnitude of muscle fatigue Reduced need for therapeutic thymectomy (nonthymoma) Fewer side effects</p>
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)	<p>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.</p> <p>NeoTract, Inc., Pleasanton, CA</p> <p>Phase III and IV trials ongoing</p>	<p>Alpha blockers 5-Alpha reductase inhibitors Minimally invasive surgical treatment (e.g., laser ablation, transurethral needle ablation, transurethral microwave therapy) Surgical treatments (e.g., transurethral resection of prostate, transurethral microwave therapy, open prostatectomy)</p>	<p>Improved International Prostate Symptom Score (IPSS) Increased urine flow rate Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vagus nerve stimulation for treatment of fibromyalgia	Patients in whom treatment refractory fibromyalgia has been diagnosed	<p>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.</p> <p>Under study at the University of Medicine and Dentistry of New Jersey's New Jersey Medical School, Newark, and Pain and Fatigue Study Center, Beth Israel Medical Center, New York, NY</p> <p>Various manufacturers make VNS systems</p> <p>Phase I/II trial completed</p>	<p>Duloxetine Fluoxetine Gabapentin Lorazepam Milnacipran Pregabalin Stress reduction Tricyclic antidepressants</p>	<p>Minimal clinically important difference (pain, overall wellness, and physical function)</p>
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	<p>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.</p> <p>Regeneron Pharmaceuticals, Inc., Tarrytown, NY</p> <p>Phase III trials completed; FDA approved Nov 2011</p>	<p>Ranibizumab (Lucentis®)</p>	<p>Improved visual acuity Improved treatment adherence because of reduced number of eye injections</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
VEN-309 (iferanserin) for treatment of symptomatic internal hemorrhoids	Patients in whom internal symptomatic hemorrhoids have been diagnosed	<p>According to the National Institute of Diabetes and Digestive and Kidney Diseases, an estimated 12.5 million adults in the U.S. have symptomatic hemorrhoids; internal hemorrhoids can cause bleeding, pain, or pruritus with topical therapies such as witch hazel, hydrocortisone cream, and topical anesthetics used to treat these symptoms. These agents are not disease-modifying (i.e., they do not treat the actual pathogenesis). Surgical intervention may also be used in the treatment of therapy. VEN-309 has highly selective, antagonistic properties against peripheral 5-HT<sub>2A</sub> (serotonin family) receptors involved in clotting and the contraction of arteries and veins, leading to hemorrhoid formation. Through this mechanism of action, VEN-309 is said to improve the flow of blood out of the dilated veins that comprise the hemorrhoid, thereby reducing bleeding, itchiness, and pain. VEN-309 is administered topically intra-anally, twice a day, at 0.5% ointment (containing 10 mg VEN-309).</p> <p>Ventrus Biosciences, Inc., New York, NY</p> <p>Phase III trial ongoing; expected primary completion Apr 2012</p>	Cryotherapy Surgical interventions Topical treatments (for symptoms)	Halted progression of hemorrhoids Reduced bleeding Reduced itchiness and pain associated with internal hemorrhoids Improved quality of life
Vesicular monoamine transporter type 2 inhibitor (NBI-98854) for treatment of tardive dyskinesia	Patients with schizophrenia who have been given a diagnosis of tardive dyskinesia	<p>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.</p> <p>Neurocrine Biosciences, Inc., San Diego, CA</p> <p>Phase II trials completed; FDA granted fast track status Jan 2012</p>	Benzodiazepines Cogentin® Omega-3 fatty acids Parkinson's medications (Mirapex®, etc.) Tarvil® Tetrabenazine	Reduced abnormal involuntary movements

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Video game therapy for stroke rehabilitation	Patients who are recovering from mild to moderate ischemic or hemorrhagic strokes	<p>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.</p> <p>Heart and Stroke Foundation, Ottawa, Ontario, Canada Ontario Stroke System, Toronto, Ontario, Canada</p> <p>Phase I trial completed</p>	<p>Standard physical therapy Standard occupational therapy Robot-assisted rehabilitative therapy</p>	<p>Improved motor function Improved strength Improved quality of life</p>
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	<p>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.</p> <p>Ceregene, Inc., San Diego, CA</p> <p>Phase I/II trial ongoing; phase II trial completed</p>	<p>No treatments currently exist, just symptom relief (levodopa, dopamine agonists, MOA-B inhibitors, etc.)</p>	<p>Reduced symptoms Increased motor skill functions Slowed disease progression Continued effect of treatment over time Improved quality of life</p>
Wearable artificial kidney (WAKs) for end-stage kidney failure	Patients with advanced kidney failure	<p>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.</p> <p>AWAK Technologies, Inc., Burbank, CA</p> <p>Clinical trials scheduled to start the end of 2011, but no registered trials on National Clinical Trials database or updates as of May 2012</p>	<p>Conventional home dialysis systems</p>	<p>Adequate filtration of toxins from kidneys Improved mobility Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>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.</p> <p>Medtronic, Inc., Minneapolis, MN</p> <p>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</p>	Intraurethral suppository of alprostadil PDE-5 inhibitors Vacuum pump Various surgical implants	Improved erectile function Improved quality of life

**Table 9. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 107 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	<p>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 <i>N</i> gene of the RSV genome, a gene required for replication of RSV; ALN-RSV01 is intended to silence the <i>N</i> gene, thereby reducing the virus' ability to reproduce.</p> <p>Alnylam Pharmaceuticals, Cambridge, MA</p> <p>Phase II trial ongoing</p>	Hypertonic saline Salbutamol Supportive care (e.g., oxygen support, hydration, etc.)	Reduced infection rate Improved lung function Reduced progression of bronchiolitis obliterans syndrome Shorter hospital stay for treating RSV infection

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 filed in 2009	Anthrax vaccine Antibiotics Valortim	Protection against inhalation anthrax Rapid resolution of symptoms
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™)	Rapid resolution of symptoms Increased survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Attachment inhibitor BMS-663068 for treatment of HIV	Patients in whom HIV infection has been diagnosed	<p>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.</p> <p>Bristol-Myers Squibb, New York, NY</p> <p>Phase II trial ongoing</p>	<p>Antiretroviral therapy            Enfuvirtide            Ibalizumab            Maraviroc            Personalized vaccination            Pro 140            Therapeutic vaccination (investigational)</p>	<p>Decreased viral load            Slower development of resistance            Reduced morbidity            Reduced mortality</p>
Autologous dendritic cell vaccine for treatment of HIV infection	Patients in whom chronic HIV infection has been diagnosed	<p>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.</p> <p>Baylor College of Medicine, Houston, TX</p> <p>Phase I/II trial ongoing</p>	<p>AGS-004            Antiretroviral therapy (ART)            Off-the-shelf therapeutic vaccines in development</p>	<p>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</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous dendritic cell vaccine (AGS-004) for treatment of HIV infection	Patients in whom HIV infection has been diagnosed	<p>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.</p> <p>Argos Therapeutics, Inc., Durham, NC</p> <p>Phase II trial ongoing</p>	Antiretroviral therapy	<p>Improved CD4+ T-cell counts</p> <p>Improved CD8+ T-cell responses</p> <p>Sustained control of viral load after cessation of therapy</p> <p>Time to viral load reduction</p> <p>Reduced morbidity</p> <p>Improved quality of life</p>
Autologous encapsulated fecal matter to rehabilitate gastrointestinal flora after <i>Clostridium difficile</i> infection	Patients at risk for <i>Clostridium difficile</i> infection (CDI)	<p>Recurrent CDI is responsible for significant morbidity, mortality, and costs. Recurrent CDI is resistant to treatment and 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.</p> <p>Medilink North West, Manchester, UK</p>	Allogeneic fecal microbiota therapy Fidaxomicin Metronidazole Vancomycin	<p>Faster time to resolution of CDI-related diarrhea</p> <p>Reduced CDI recurrence and morbidity</p> <p>Shorter hospitalization time</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>AVI-6002 for treatment of Ebola virus exposure</p>	<p>Patients who have been exposed to Ebola virus</p>	<p>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.</p> <p>AVI BioPharma, Inc., Bothell, WA</p> <p>Phase I trial completed; manufacturer to file for approval through the animal efficacy rule after completing studies in healthy human subjects</p>	<p>Supportive care</p>	<p>Increased symptom resolution Reduced mortality</p>
<p>AVI-6003 for treatment of Marburg virus</p>	<p>Patients who have been exposed to Marburg virus</p>	<p>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.</p> <p>AVI BioPharma, Inc., Bothell, WA, with support from the U.S. Army Medical Research Institute for Infectious Diseases, Frederick, MD</p> <p>Phase I trial ongoing; manufacturer to file for approval through the animal efficacy rule after completing studies in healthy human subjects</p>	<p>Supportive care</p>	<p>Improved symptom resolution Reduced mortality</p>

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	<p>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 <i>Pseudomonas aeruginosa</i>, <i>Acinetobacter</i> spp., <i>Klebsiella</i> spp. and <i>Enterobacter</i> 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 the treatment of hospital-acquired pneumonia (including ventilator-associated pneumonia), complicated intra-abdominal infections, or complicated urinary tract infections.</p> <p>Basilea Pharmaceutica, Ltd., Basel, Switzerland</p> <p>Phase I trial ongoing</p>	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	<p>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 to 6.0 mg/kg of body weight, weekly, for 8 or 12 weeks in clinical trials as a monotherapy and combination therapy with ribavirin.</p> <p>Peregrine Pharmaceuticals, Inc., Tustin, CA</p> <p>Phase I/II trial completed</p>	Boceprevir Combination therapy NS5B polymerase inhibitors (in phase II trials) Pegylated interferon/ribavirin combination 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

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Bedaquiline (TMC207) for treatment of drug-resistant tuberculosis	Patients in whom drug-resistant tuberculosis (TB) is inspected	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	Ethionamide (Trecator) Kanamycin Ofloxacin (Floxin) Pyrazinamide	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, 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, 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 Pegylated interferon/ribavirin combination PSI-7977 Telaprevir VX-222	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

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<p>BIT225 (viroporin inhibitor) for treatment of chronic hepatitis C virus infection</p>	<p>Patients in whom chronic hepatitis C infection (HCV) has been diagnosed</p>	<p>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.</p> <p>Biotron Ltd., Sydney, Australia</p> <p>Phase II trial complete</p>	<p>Boceprevir IFN/RBV Polymerase inhibitors (in clinical development) Other protease inhibitors (in clinical development) Telaprevir</p>	<p>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</p>
<p>BMS-914143 (pegylated interferon lambda) for treatment of chronic hepatitis C virus infection</p>	<p>Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed</p>	<p>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.</p> <p>Bristol-Myers Squibb, New York, NY</p> <p>Phase II trials ongoing</p>	<p>IFNa-2a IFN-free HCV drug combinations Pegylated interferon/ribavirin combination</p>	<p>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</p>

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BTA798 for treatment of human rhinovirus infection	Patients who are immunocompromised or have respiratory complications such as asthma or chronic obstructive pulmonary disease (COPD)	<p>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.</p> <p>Biota Holdings, Ltd., Notting Hill, Victoria, Australia</p> <p>Phase II trial ongoing</p>	Supportive care	<p>Reduced exacerbations and hospitalization for asthma and COPD from rhinovirus infection</p> <p>Improved quality of life</p>
Capsaicin 8% patch (Qutenza) for treatment of HIV-associated peripheral neuropathy	Patients in whom HIV-associated peripheral neuropathy (HIV-PN) has been diagnosed	<p>HIV-PN is the most common neurological complication of HIV infection. No treatments are available for HIV-PN, which may be caused by injury to sensory neurons by HIV, inflammation, or antiretroviral therapy. Capsaicin 8% patch (Qutenza®) is a localized dermal delivery system containing prescription strength capsaicin. Capsaicin is an agonist for the transient receptor potential vanilloid 1 receptor (TRPV1), which is an ion-channel receptor complex expressed on nociceptive nerve fibers in the skin. Capsaicin is purported to initially enhance stimulation of the TRPV1-expressing cutaneous nociceptors that may be associated with pain, followed by pain relief hypothesized by the manufacturer to be mediated by a reduction in TRPV1-expressing nociceptive nerve endings. Administered by a health care practitioner.</p> <p>NeurogesX, Inc., San Mateo, CA</p> <p>Phase III trials completed; supplemental new drug application submitted, FDA declined to approve application and requested at least 1 additional study.</p>	<p>Amitriptyline (Elavil)</p> <p>Carbamazepine (Tegretol®)</p> <p>Duloxetine (Cymbalta®)</p> <p>Nonsteroidal anti-inflammatory drugs</p> <p>Pregabalin (Lyrica®)</p>	Pain relief measured using the numeric pain rating scale
CB-183,315 for treatment of recurrent <i>Clostridium difficile</i> infection	Patients in whom recurrent <i>Clostridium difficile</i> infection (CDI) has been diagnosed	<p>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.</p> <p>Cubist Pharmaceuticals, Inc., Lexington, MA</p> <p>Phase II trial completed</p>	<p>Fidaxomicin</p> <p>Metronidazole</p> <p>Vancomycin</p>	<p>Reduced CDI recurrence rate</p> <p>Shorter hospitalization time</p> <p>Faster time to resolution of diarrhea</p>

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<p><i>Clostridium difficile</i> vaccine (ACAM-CDIFF) for prevention of infection in patients expecting treatment in a health care facility</p>	<p>At-risk individuals, including adults facing imminent hospitalization or current or impending residence in a long-term care or rehabilitation facility</p>	<p><i>Clostridium difficile</i> is a common hospital-acquired infection the can lead to significant morbidity, mortality, lengthened hospital stays and cost methods to prevent <i>C. difficile</i> infection are needed. <i>C. difficile</i> vaccine (ACAM-CDIFF™) consists of a toxoid from the bacterium intended to induce protective antibody responses.</p> <p>Sanofi, Paris, France</p> <p>Phase II trials ongoing</p>	<p>Hospital infection control programs</p>	<p>Reduced <i>C. difficile</i> infection rates                      Reduced use of antibacterial drugs                      Reduced hospitalization time                      Reduced isolation</p>
<p>CMX001 for prevention of cytomegalovirus infection after hematopoietic stem cell transplant</p>	<p>Patients who recently received a hematopoietic stem cell transplant (HSCT)</p>	<p>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 the treatment of 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.</p> <p>Chimerix, Inc., Durham, NC</p> <p>Phase II trial completed; FDA granted fast track status</p>	<p>Cidofovir (off label)</p>	<p>Reduced morbidity from adenovirus infection                      Reduced mortality from adenovirus infection</p>

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Collaborative care model (HITIDES) for treatment of depression secondary to HIV	Patients in whom depression secondary to HIV has been diagnosed	<p>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).</p> <p>Veterans Affairs Medical Centers</p> <p>Trial completed</p>	Usual HIV care without depression care team	<p>Depression improvement</p> <p>Improved care implementation process</p> <p>Improved quality of care</p> <p>Improved health status</p> <p>Decreased HIV symptom severity</p> <p>Improved HIV medication adherence</p> <p>Improved antidepressant adherence</p> <p>Improved patient satisfaction</p> <p>Improved health-related quality of life</p>
Copper surfaces in the intensive care unit for prevention of hospital-acquired infections	Patients admitted to an intensive care unit (ICU)	<p>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.</p> <p>International Copper Association</p> <p>Commercially available; studies at hospitals ongoing</p>	Terminal cleaning of standard surfaces	<p>Reduced infection rates</p> <p>Reduced bacteria isolated from surfaces</p> <p>Reduced morbidity and mortality from HAIs</p>

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Crofelemer for treatment of HIV-1-associated diarrhea	Patients on HIV antiretroviral therapy with chronic diarrhea	<p>About 40% of patients in the U.S. with HIV-1 have chronic diarrhea, which can reduce adherence to antiretroviral regimens. Effective anti-diarrheals 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.</p> <p>Salix Pharmaceuticals, Ltd., Raleigh NC Napo Pharmaceuticals, Inc., San Francisco, CA</p> <p>Phase III trial ongoing; FDA granted fast track status; new drug application submitted to FDA for treatment of HIV-associated diarrhea; decision date is Jun 5, 2012</p>	Absorbents containing attapulgite or polycarbophil Antibiotics Diphenoxylate Loperamide	Reduced number of watery bowel movements Relief of diarrhea
Cyclophilin inhibitor alisporivir for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>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.</p> <p>Debiopharm, S.A., Lausanne, Switzerland Novartis AG, Basel, Switzerland</p> <p>Phase III trials ongoing; FDA granted fast track status</p>	Boceprevir Pegylated interferon/ribavirin combination SCY-635 (in development) 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

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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	<p>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).</p> <p>Pharmasset, Inc., Princeton, NJ F. Hoffmann-La Roche Ltd., Basel, Switzerland</p> <p>Phase II trials ongoing</p>	IFN/RBV	<p>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</p>
DAS181 (Fludase) for treatment and prevention of influenza-like illness	Patients at high risk for influenza-like illness (ILI)	<p>Resistance to current neuraminidase inhibitors may leave patients at risk for 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; DAS181 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.</p> <p>NexBio, Inc., San Diego, CA</p> <p>Phase II trials ongoing</p>	Laninamivir (in phase III trials) Oseltamivir Peramivir Zanamivir	<p>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</p>
Disinfection of high-touch surfaces with peracetic acid disinfectant to prevent transmission of hospital-acquired infections	Patients at risk for developing a health care-acquired infection (HAI)	<p>HAIs are the 4th leading cause of death in the U.S. after heart disease, stroke, and cancer. About 1 of every 20 hospitalized U.S. patient 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 <i>Clostridium difficile</i> and methicillin-resistant <i>Staphylococcus aureus</i> more than standard terminal-cleaning procedures using bleach.</p> <p>Cleveland VA Medical Center, Cleveland, OH</p>	Antimicrobial copper touch surfaces Terminal cleaning procedures using bleach and cleaning of visibly soiled surfaces as necessary Ultraviolet light	<p>Reduced infection rates Reduced bacteria isolated from surfaces Reduced morbidity and mortality</p>

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DNA vaccine (INO-3510) for prevention of H1N1 and H5N1 influenza	Patients at risk for H1N1 and H5N1 influenza	<p>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.</p> <p>Inovio Pharmaceuticals, Inc., Blue Bell, PA</p> <p>Phase I trial ongoing</p>	<p>Pandemic influenza vaccines Seasonal inactivated flu vaccines Seasonal live flu vaccines</p>	<p>Protection against influenza Reduced morbidity and mortality</p>
Duct tape Red Box safe zone for prevention of transmission of hospital infections and improve care	Patients with infections requiring isolation	<p>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.</p> <p>Trinity Medical Center, Rock Island and Moline, IL, and Bettendorf and Muscatine, IA</p>	Standard infection control procedures	<p>Improved frequency of communication Improved patient experience/satisfaction Reduced staff hours/costs spent gowning</p>

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Extracorporeal membrane oxygenation for treatment of serious influenza infections	Patients in whom serious influenza infection has been diagnosed	<p>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.</p> <p>Far Eastern Memorial Hospital, Taipei, Taiwan, and National Taiwan University Hospital, Taipei</p> <p>Could be implemented readily</p>	Ventilation support Treatment of comorbidities	Reduced morbidity Reduced mortality
Fecal microbiota transplantation for treatment of recurrent <i>Clostridium difficile</i> infection	Patients with recurrent <i>Clostridium difficile</i> 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	Antibiotics Probiotics	Reduced diarrhea Reduced dehydration Reduced reinfection
Fidaxomicin (Dificid) for treatment of <i>Clostridium difficile</i> infection	Patients in whom <i>Clostridium difficile</i> infection (CDI) has been diagnosed	<p>Because of antibiotic resistance, new antibacterials that can improve clinical cure rates and reduce 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.</p> <p>Optimer Pharmaceuticals, Inc., San Diego, CA</p> <p>FDA approved May 27, 2011</p>	Metronidazole (off label) Oral vancomycin	Increased clinical cure rates Reduced CDI recurrence

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Hemopurifier blood filter for pandemics and bioterrorism	Patients affected by pandemic disease or bioterrorism agents	<p>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.</p> <p>Aethlon Medical, Inc., San Diego, CA</p> <p>In initial clinical trials; commercialization planned for India</p>	Standard public health measures for containing and treating pandemic disease and/or biologic weapon threats	Reduced severity of pandemic disease
Hemopurifier blood filter for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C infection has been diagnosed	<p>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.</p> <p>Aethlon Medical, Inc., San Diego</p> <p>In initial trials; commercialization planned for India</p>	Standard drug therapy	<p>Reduced viral load</p> <p>Improved efficacy of drug therapy</p> <p>Resolution of chronic infection</p> <p>Improved quality of life</p>
Hemopurifier blood filter for treatment of HIV infection	Patients in whom HIV infection has been diagnosed	<p>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.</p> <p>Aethlon Medical, Inc., San Diego, CA</p> <p>In initial clinical trials; commercialization planned for India</p>	Standard antiviral therapy for HIV	<p>Reduced viral load</p> <p>Improved efficacy of drug therapy</p> <p>Improved symptoms</p> <p>Improved quality of life</p>

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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	<p>Current HIV-infection diagnostics require 15–30 minutes for preliminary results, which must be later 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 which 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 1 visit, INSTI may increase the capacity of a health care facility to provide HIV testing to more patients and promote prompt treatment.</p> <p>BioLytical™ Laboratories, Inc., Richmond, British Columbia, Canada</p> <p>FDA approved Dec 2010 under premarket approval application for detection of antibodies to HIV-1 in whole blood, finger stick blood, or plasma specimens</p>	<p>OraQuick Advance®  Uni-Gold  Recombigen®  Clearview®  Complete HIV 1/2  and Clearview®  HIV 1/2 Stat-Pak  Reveal™ HIV</p>	<p>Improved HIV counseling  Improved HIV detection  Improved treatment outcomes  Increased rates of HIV testing</p>
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	<p>The number 1 cause of childhood hospitalization both in the U.S. and around the world is RSV infection. There are no approved vaccines to prevent it. The vaccine is being developed as an intranasal vaccine for RSV.</p> <p>NanoBio Corporation, Ann Arbor, MI</p> <p>Phase I trial planned</p>	<p>Intubation with mechanical ventilation  Oxygen  Suctioning of mucus from the airways</p>	<p>Improved adherence with vaccination (no needles)  Reduced incidence of bronchiolitis and pneumonia  Reduced hospitalizations  Reduced mortality</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Linking hepatitis C screening to screening colonoscopy to increase hepatitis C virus detection</p>	<p>Patients for whom colorectal screening is recommended (aged 50–65 years)</p>	<p>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.</p> <p>Texas A&amp;M College of Medicine</p> <p>Pilot study conducted</p>	<p>Current screening practices at other health care settings</p>	<p>Improved HCV detection rates Earlier treatment Slowed or halted disease progression Prevention of end-stage liver disease and HCV transmission</p>
<p>Live attenuated rabies virus vaccine for treatment and prevention of rabies</p>	<p>Patients at risk for rabies or who are suspected to be infected with rabies</p>	<p>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.</p> <p>Thomas Jefferson University, Philadelphia, PA</p> <p>Pilot trial ongoing</p>	<p>Prophylactic rabies vaccine Rabies immune globulin</p>	<p>Improved survival</p>

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Modified vaccinia virus Ankara vector-encoding influenza nucleoprotein and matrix protein 1 for prevention of influenza	Patients at risk for influenza	<p>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.</p> <p>Jenner Institute (a partnership between Oxford University and the Institute for Animal Health), Oxford, UK</p> <p>Phase I trial completed against the H3N2/Wisconsin influenza strain</p>	Seasonal influenza vaccines	<p>Prevention of influenza infections                      Reduced hospitalizations                      Reduced length of hospitalization                      Reduced mortality</p>
Monoclonal antibody entry inhibitor (ibalizumab) for treatment of HIV infection	Patients in whom HIV infection has been diagnosed	<p>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.</p> <p>TaiMed Biologics, Inc., Taipei, Taiwan</p> <p>Phase II trial ongoing</p>	<p>Antiretroviral therapy                      Enfuvirtide                      Maraviroc                      Personalized vaccination                      Pro 140                      Therapeutic vaccination (investigational)</p>	<p>Decreased viral load                      Slower development of resistance                      Reduced morbidity                      Reduced mortality</p>

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	<p>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.</p> <p>Romark Laboratories, L.C., Tampa, FL; Intercell AG, Vienna, Austria</p> <p>Phase II trials completed</p>	Boceprevir Daclatasvir Pegylated interferon ribavirin combination Telaprevir GS-7977	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	<p>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 administered orally, 300 mg, twice a day.</p> <p>Romark Laboratories, L.C., Tampa, FL</p> <p>Phase II/III trial completed</p>	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	<p>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.</p> <p>Romark Laboratories, L.C., Tampa, FL</p> <p>Phase II trial completed</p>	Oseltamivir (Tamiflu®; for influenza) Supportive care Zanamivir (Relenza®; for influenza)	Reduced duration of symptoms Reduced morbidity Viral resolution

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Nitroimidazole (PA-824) for treatment of pulmonary tuberculosis	Patients in whom multidrug-resistant/drug susceptible tuberculosis has been diagnosed	<p>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.</p> <p>Novartis AG, Basel, Switzerland Bayer AG, Leverkusen, Germany</p> <p>Phase II trials ongoing</p>	Isoniazid Rifampicin	<p>Shorter duration of therapy Simpler dosing Improved adherence Safer method of action Lower cost of overall treatment</p>
NS5A inhibitor (daclatasvir, BMS-790052) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C infection (HCV) has been diagnosed	<p>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.</p> <p>Bristol-Myers Squibb, New York, NY</p> <p>Phase III trials ongoing</p>	Boceprevir Pegylated interferon/ribavirin combination PSI-7977 Telaprevir VX-222	<p>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</p>
NS5A inhibitor (PPI-461) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>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 NS5A 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.</p> <p>Presidio Pharmaceuticals, Inc., San Francisco, CA</p> <p>Phase I trial completed</p>	Daclatasvir	<p>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</p>

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Nucleoside polymerase inhibitor (TMC649128) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>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.</p> <p>Medivir AB, Huddinge, Sweden</p> <p>Phase I trial completed</p>	Boceprevir Nucleoside polymerase inhibitors Pegylated interferon/ribavirin combination 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
Off-label neurokinin-1 receptor antagonist aprepitant (Emend) for treatment of HIV infection	Patients in whom HIV infection has been diagnosed	<p>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 treatment of 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.</p> <p>Merck &amp; Co., Inc., Whitehouse Station, NJ (manufacturer) University of Pennsylvania, Philadelphia, and National Institute of Mental Health, Bethesda, MD (trial sponsors)</p> <p>Phase I trial ongoing for HIV-1 treatment; FDA approved in 2003 for prevention of acute and delayed CINV and prevention of postoperative nausea and vomiting</p>	Antiretroviral therapy Baviximab Therapeutic vaccines	Delayed onset of AIDS Increased T-cell counts Reduced cognitive impairment Reduced viral load

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Oligonucleotide (miravirsen) for treatment of chronic hepatitis C infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>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.</p> <p>Santaris Pharma a/s, Hørsholm, Denmark</p> <p>Phase II trial completed</p>	Boceprevir NS5B polymerase inhibitors Pegylated interferon/ribavirin combination Telaprevir	<p>Rapid virologic response (HCV RNA undetectable at week 4)</p> <p>Sustained virologic response (HCV RNA undetectable after 24 weeks of followup)</p> <p>Reduced need for liver transplantation</p> <p>Reduced symptoms</p>
OraQuick Rapid HCV Antibody Test using an oral swab specimen for detection of hepatitis C virus infection	Patients with unknown hepatitis C virus (HCV) infection status	<p>The current OraQuick® HCV Rapid Antibody Test requires blood from a finger prick, deterring some patients from being tested and some care settings from performing the test; a testing method using an oral swab may remove barriers for many patients with unknown HCV status to be tested in community health centers and primary care practices. OraQuick HCV Rapid Antibody Test is being validated for use with an oral swab sample that would contain antibodies to HCV, which can be detected by the kit; the OraQuick HCV Rapid Antibody Test uses an indirect lateral flow immunoassay method to detect antibodies to synthetic peptides and recombinant antigens from the core, NS3, and NS4 regions of the HCV genome, immobilized as a single test line on the assay strip.</p> <p>OraSure Technologies, Inc., Bethlehem, PA</p> <p>FDA approved OraQuick HCV Rapid Antibody Test that uses a finger stick under premarket approval process Jun 2010</p>	OraQuick HCV Rapid Antibody test using venipuncture Other HCV tests	<p>Increased rate of HCV detection</p> <p>Earlier treatment of HCV infection</p> <p>Reduced transmission</p> <p>Reduced morbidity</p> <p>Reduced mortality</p>

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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	<p>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.</p> <p>Windsor Regional Hospital, Windsor, Ontario, Canada</p>	<p>Antimicrobial copper touch surfaces Peracetic acid Terminal cleaning procedures using bleach and cleaning of visibly soiled surfaces as necessary Ultraviolet light</p>	<p>Reduced bacteria isolated from surfaces Reduced infection rates Reduced morbidity and mortality</p>
Ozone and hydrogen peroxide-based sterilization system (AsepticSure) to reduce health care-acquired infections	Patients at risk for health care-acquired infections (HAIs)	<p>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.</p> <p>Medizone International, Inc., Sausalito, CA</p> <p>Beta testing in U.S. hospitals planned</p>	<p>Antimicrobial copper touch surfaces Peracetic acid Terminal cleaning procedures using bleach and cleaning of visibly soiled surfaces as necessary Xenon/UV light</p>	<p>Reduced bacteria isolated from surfaces Reduced infection rates Reduced morbidity and mortality</p>
Patient-centered signage to improve hand washing among health care workers	Patients attending health care facilities	<p>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.</p> <p>University of North Carolina at Chapel Hill</p>	<p>Standard hand-washing practices Radiofrequency identification hand-washing systems</p>	<p>Reduced costs associated with health care-acquired infections (HAIs) Reduced HAI incidence Reduced HAI morbidity and mortality</p>

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Peramivir for treatment of influenza	Patients in whom H1N1 influenza has been diagnosed or is suspected	<p>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.</p> <p>BioCryst Pharmaceuticals, Inc., Research Triangle Park, NC</p> <p>Phase III trial ongoing; approved for emergency use in patients with confirmed or suspected H1N1 influenza</p>	Laninamivir (in phase III trials) Oseltamivir Zanamivir	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	<p>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, which 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: evaluation of 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; individual appointments with pharmacists to discuss medication therapy; adherence packaging beyond any provided by manufacturer (e.g., personalized blister packs for all ART medications); identification of peer advocates to assist in medication adherence; and weekly telephone call or home visit after initiation of therapy.</p> <p>School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego</p>	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

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Plant-derived virus-like particle vaccine for prevention of H5N1 avian influenza	Patients at risk for avian influenza	<p>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 <i>Nicotiana benthamiana</i>, 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.</p> <p>Medicago, Inc., Quebec, Quebec, Canada Phase II trial ongoing</p>	<p>INO-3510 Nitazoxanide Novavax VLP vaccine Oseltamivir Peramivir Seasonal influenza vaccines Zanamivir</p>	<p>Faster production of pandemic vaccine Reduced incidence of influenza Lower morbidity and mortality Vaccine option for people allergic to eggs</p>
PMX-30063 for treatment of acute bacterial skin infections	Patients in whom acute bacterial skin and skin structure infection has been diagnosed	<p>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 <i>Staphylococcus aureus</i> in human blood samples in vitro. Administered intravenously.</p> <p>PolyMedix, Inc., Radnor, PA Phase II trial ongoing</p>	<p>Linezolid Vancomycin</p>	<p>Complete clinical response Complete microbiologic response Infection resolution/cure</p>

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<p>Point-of-care testing systems for methicillin-resistant <i>Staphylococcus aureus</i> screening</p>	<p>Patients who may be infected by methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)</p>	<p>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.</p> <p>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</p> <p>Early trials ongoing. Devices and test kits expected to be cleared through 510(k) pathway with no requirement for clinical evidence of efficacy</p>	<p>MRSA culture                      Conventional 1st-generation polymerase chain reaction (PCR) assay                      Second-generation quantitative PCR</p>	<p>Reduced transmission of MRSA                      Increased sensitivity and specificity of MRSA detection                      Increased speed of MRSA detection</p>
<p>Polymerase inhibitor (BMS-791325) for treatment of chronic hepatitis C virus infection</p>	<p>Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed</p>	<p>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.</p> <p>Bristol-Myers Squibb, New York, NY</p> <p>Phase IIb trials ongoing</p>	<p>Boceprevir                      IFN/RBV                      NS5B inhibitors (in phase II trials)                      Telaprevir</p>	<p>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</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>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.</p> <p>Gilead Sciences, Inc., Foster City, CA</p> <p>Phase IIb trials ongoing</p>	Boceprevir Nonnucleoside polymerase inhibitors Nucleoside polymerase inhibitors Pegylated interferon/ribavirin combination 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 (INX-189) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>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. INX-189 is an orally administered prodrug and 2'-C-methylguanosine analog. It is purported to inhibit the HCV NS5B protease 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 INX-189's potential for once-daily dosing.</p> <p>Inhibitex, Inc., Alpharetta, GA (as of Jan 2012, Bristol-Myers Squibb, New York, NY, intends to acquire Inhibitex)</p> <p>Phase I/II trials ongoing; FDA granted fast track status</p>	Boceprevir IFN/RBV NS5B polymerase inhibitors (in phase II trials) 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
Polymerase inhibitor (PSI-7977) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>Uridine nucleotide analog polymerase inhibitor (PSI-7977) of HCV is expected to be used in conjunction with standard-of-care pegylated interferon plus ribavirin (IFN/RBV) and, possibly, in conjunction with PSI-938. Administered orally.</p> <p>Pharmasset, Inc., Princeton, NJ</p> <p>Phase III trial ongoing; received FDA fast track status</p>	IFN/RBV	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	<p>Polymerase inhibitor (VX-222) acts on HCV; likely to be used in combination with telaprevir and ribavirin.</p> <p>Vertex Pharmaceuticals, Inc., Cambridge, MA</p> <p>Phase II trials ongoing</p>	<p>Boceprevir Pegylated interferon/ribavirin combination Telaprevir</p>	<p>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</p>
Preventive vaccine Pennvax-B (VGX-3300) for HIV infection	Patients at high risk for chronic HIV-1 infection	<p>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 Celectra 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.</p> <p>Inovio Pharmaceuticals, Inc., Blue Bell, PA ChronTech Pharma AB, Huddinge, Sweden</p> <p>Phase I trial ongoing</p>	<p>Pre-exposure prophylaxis (tenofovir/emtricitabine) Prime-boost vaccination with DNA and modified vaccinia virus Ankara Vaginal gels dapivirine, tenofovir</p>	<p>Lower incidence of HIV-1 infection Improved B- and T-cell responses to HIV antigens</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Prime-boost vaccine with DNA and modified vaccinia virus Ankara for prevention of HIV infection	Persons who are at risk for HIV infection	<p>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.</p> <p>GeoVax Labs, Inc., Smyrna, GA</p> <p>Phase I trial ongoing</p>	<p>Dapivirine gel Pre-exposure prophylaxis with antiretroviral Personalized vaccination Therapeutic vaccination</p>	<p>Improved antibody and T-cell responses Decreased incidence of infection</p>
Private intensive care rooms to reduce hospital-acquired infections	Patients admitted to an intensive care unit (ICU)	<p>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.</p> <p>McGill University Health Centre, Montreal, Quebec, Canada</p> <p>Early adoption ongoing</p>	<p>Antimicrobial copper touch surfaces Portable pulsed xenon ultraviolet light added to terminal cleaning Standard infection control practices Terminal cleaning with peracetic acid</p>	<p>Reduced health care-acquired infection rates Increased overall survival</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pro 140 monoclonal antibody for treatment of HIV infection	Patients chronically infected with HIV	<p>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.</p> <p>Progenics Pharmaceuticals, Inc., Tarrytown, NY</p> <p>Phase II trial ongoing</p>	<p>Antiretroviral therapy Personalized vaccination Therapeutic vaccination (investigational)</p>	<p>Decreased viral load Decreased morbidity Increased survival</p>
Prophylactic vaccine recombinant vesicular stomatitis virus expressing HIV-1 gag protein (VSV <sub>IN</sub> HIV-1 gag) for HIV-1	Patients at risk for HIV-1 infection	<p>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<sub>IN</sub> 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.</p> <p>Profectus BioSciences, Inc., Baltimore, MD</p> <p>Phase I trial ongoing</p>	<p>Pre-exposure prophylaxis (tenofovir/emtricitabine) Prime-boost vaccination with DNA and modified vaccinia virus Ankara Vaginal gels dapivirine, tenofovir</p>	<p>Lower incidence of HIV-1 infection Improved T-cell responses to Gag</p>

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	<p>Current standard of care for HCV infection (pegylated interferon plus ribavirin [IFN/RBV]) 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. ABT-450/r is an HCV protease inhibitor.</p> <p>Abbott Laboratories, Abbott Park, IL</p> <p>Phase II trials ongoing</p>	Boceprevir IFN/RBV Telaprevir	<p>Rapid virologic response (HCV RNA undetectable at week 4)</p> <p>Slowed or halted disease progression (fibrosis and cirrhosis)</p> <p>Sustained virologic response (defined as undetectable virus at 24 weeks)</p> <p>Decreased need for liver transplant</p> <p>Improved quality of life</p>
Protease inhibitor (ACH-1625) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>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. ACH-1625 is a NS3 protease inhibitor intended to block the activity of HCV protease, preventing the cleavage and maturation of functional viral particles; ACH-1625 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.</p> <p>Achillion Pharmaceuticals, Inc., New Haven, CT</p> <p>Phase II trial ongoing; FDA granted fast track status for the treatment of chronic HCV</p>	Boceprevir IFN/RBV Telaprevir	<p>Rapid virologic response (HCV RNA undetectable at week 4)</p> <p>Slowed or halted disease progression (fibrosis and cirrhosis)</p> <p>Sustained virologic response (defined as undetectable virus at 24 weeks)</p> <p>Decreased need for liver transplant</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Protease inhibitor asunaprevir (BMS-650032) for treatment of chronic hepatitis C virus infection	Patients in whom chronic infection with hepatitis C virus (HCV) has been diagnosed	<p>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).</p> <p>Bristol-Myers Squibb, New York, NY</p> <p>Phase II trials ongoing</p>	Boceprevir IFN/RBV Telaprevir	<p>Rapid virologic response (HCV RNA undetectable at week 4)</p> <p>Slowed or halted disease progression (fibrosis and cirrhosis)</p> <p>Sustained virologic response (defined as undetectable virus at 24 weeks)</p> <p>Decreased need for liver transplant</p> <p>Improved quality of life</p>
Protease inhibitor (boceprevir, Victrelis) for treatment of hepatitis C virus infection	Patients in whom hepatitis C virus (HCV) infection has been diagnosed	<p>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 standard-of-care pegylated interferon plus ribavirin (IFN/RBV).</p> <p>Merck &amp; Co., Inc., Whitehouse Station, NJ</p> <p>FDA approved May 2011</p>	IFN/RBV Telaprevir	<p>Rapid virologic response (HCV RNA undetectable at week 4)</p> <p>Slowed or halted disease progression (fibrosis and cirrhosis)</p> <p>Sustained virologic response (defined as undetectable virus at 24 weeks)</p> <p>Decreased need for liver transplant</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Protease inhibitor (danoprevir, RO5190591) for treatment of chronic hepatitis C virus infection	People chronically infected with hepatitis C virus (HCV) infection	<p>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 other agents.</p> <p>F. Hoffmann-La Roche Ltd., Basel, Switzerland</p> <p>Phase II trials ongoing</p>	Ribavirin IFN/RBV	<p>Rapid virologic response (HCV RNA undetectable at week 4)</p> <p>Slowed or halted disease progression (fibrosis and cirrhosis)</p> <p>Sustained virologic response (defined as undetectable virus at 24 weeks)</p> <p>Decreased need for liver transplant</p> <p>Improved quality of life</p>
Protease inhibitor (GS-9256) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>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. 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).</p> <p>Gilead Sciences, Inc., Foster City, CA</p> <p>Phase IIb trials ongoing</p>	Boceprevir IFN/RBV Telaprevir	<p>Early virologic response</p> <p>Reduced need for liver transplant</p> <p>Slowed or halted disease progression</p> <p>Sustained virologic response (HCV RNA undetectable after 24 weeks of followup)</p> <p>Improved quality of life</p>
Protease inhibitor (MK-5172) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>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. 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).</p> <p>Merck &amp; Co., Inc., Whitehouse Station, NJ</p> <p>Phase II trials ongoing</p>	Boceprevir IFN/RBV Telaprevir	<p>Early virologic response</p> <p>Reduced need for liver transplant</p> <p>Slowed or halted disease progression</p> <p>Sustained virologic response (HCV RNA undetectable after 24 weeks of followup)</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Protease inhibitor (simeprevir, TMC435) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>Current standard of care is ineffective in as many as half of patients with chronic HCV infection, so new, more effective treatment is 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.</p> <p>Tibotec BVBA, Beerse, Belgium</p> <p>Phase III trials ongoing; FDA fast track status</p>	Boceprevir IFN/RBV Telaprevir	<p>Rapid virologic response (HCV RNA undetectable at week 4)</p> <p>Slowed or halted disease progression (fibrosis and cirrhosis)</p> <p>Sustained virologic response (defined as undetectable virus at 24 weeks)</p> <p>Decreased need for liver transplant</p> <p>Improved quality of life</p>
Protease inhibitor (telaprevir, Incivek) for treatment of hepatitis C virus infection	Patients in whom hepatitis C virus (HCV) infection has been diagnosed	<p>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. 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 pegylated interferon plus ribavirin (IFN/RBV).</p> <p>Vertex Pharmaceuticals, Inc., Cambridge, MA</p> <p>FDA approved May 2011</p>	IFN/RBV Boceprevir	<p>Rapid virologic response (HCV RNA undetectable at week 4)</p> <p>Slowed or halted disease progression (fibrosis and cirrhosis)</p> <p>Sustained virologic response (defined as undetectable virus at 24 weeks)</p> <p>Decreased need for liver transplant</p> <p>Improved quality of life</p>

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Protease inhibitor (vaniprevir, MK7009) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>Current standard of care for HCV infection (pegylated interferon plus ribavirin [IFN/RBV]) 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. Vaniprevir (MK7009) is a next-generation HCV protease inhibitor.</p> <p>Merck &amp; Co., Inc., Whitehouse Station, NJ</p> <p>Phase III trials ongoing</p>	Boceprevir IFN/RBV Telaprevir	<p>Rapid virologic response (HCV RNA undetectable at week 4)</p> <p>Slowed or halted disease progression (fibrosis and cirrhosis)</p> <p>Sustained virologic response (defined as undetectable virus at 24 weeks)</p> <p>Decreased need for liver transplant</p> <p>Improved quality of life</p>
Rapid molecular detection test (Xpert MTB/RIF) for <i>Mycobacterium tuberculosis</i> infection with rifampin resistance	Patients suspected of having <i>Mycobacterium tuberculosis</i> infection	<p>Automated molecular test (Xpert® MTB/RIF) for <i>M. tuberculosis</i> infection that also simultaneously tests for resistance to rifampin.</p> <p>Cepheid, Sunnyvale, CA</p> <p>Expected to become available in the U.S. in 2012 or 2013; Conformité Européene (CE) marked</p>	Microscopy Tuberculin skin test (Mantoux test) Ziehl-Neelsen microscopy	<p>Less training time</p> <p>Rapid detection</p> <p>Improved treatment</p> <p>Better control of antibacterial resistance</p>
Recombinant fusion protein–derived vaccine (RSV-F) for preventing respiratory syncytial virus	Children at risk for respiratory syncytial virus (RSV) infection	<p>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.</p> <p>Administered at days 0 and 30.</p> <p>Novavax, Inc., Rockville, MD</p> <p>Phase I trial completed</p>	Hypertonic saline Salbutamol Supportive care (e.g., oxygen support, hydration)	<p>Improved lung function</p> <p>Reduced infection rate</p> <p>Reduced progression of bronchiolitis obliterans syndrome</p> <p>Fewer hospitalizations</p> <p>Shorter hospital stays</p>

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Recombinant interleukin-7 (CYT107) for immune reconstitution in treatment of HIV infection	HIV immune nonresponding patients 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 trial ongoing	Standard HIV therapy HAART therapy	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	Bavituximab Boceprevir GS-7977 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
RHB-104 for treatment of Crohn's disease due to <i>Mycobacterium avium paratuberculosis</i> infection	Patients with Crohn's disease that shows evidence of <i>Mycobacterium avium paratuberculosis</i> 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 <i>M. avium paratuberculosis</i> , 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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Routine anal Pap smear screening at HIV clinics to prevent anal cancer	Patients in whom HIV infection has been diagnosed	<p>Patients with HIV have a higher risk of developing anal cancer, yet there are no national or international guidelines 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.</p> <p>University of Miami Miller School of Medicine, Miami, FL</p>	Anal Pap screening or anoscopy by other physician during regular intervals (after 50 years of age)	<p>Earlier detection of suspicious polyps</p> <p>Reduced anal cancer incidence in patients with HIV</p> <p>Reduced anal cancer mortality in patients with HIV</p>
RTS,S for prevention of malaria caused by <i>Plasmodium falciparum</i>	Patients living in or traveling to areas endemic for malaria	<p>Almost half of the world population is at risk for malaria. Current treatments to the <i>Plasmodium falciparum</i> 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 <i>P. falciparum</i> 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.</p> <p>GlaxoSmithKline, Middlesex, UK PATH Malaria Vaccine Initiative, Washington, DC</p> <p>Phase III trials completed; phase II/III trial ongoing</p>	Chloroquine phosphate Mosquito nets	<p>Reduced incidence of malaria infection</p> <p>Increased overall survival</p>

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SB-728 for treatment of HIV infection	Patients in whom chronic HIV infection has been diagnosed	<p>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.</p> <p>Sangamo BioSciences, Inc., Richmond, CA</p> <p>Phase I/II trials ongoing</p>	ART CYT-107 Pro 140	<p>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</p>
SCY-635 for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>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).</p> <p>SCYNEXIS, Inc., Durham, NC</p> <p>Phase II trial ongoing</p>	Bavituximab Boceprevir Direct acting antivirals Pegylated IFN alpha-2a or lambda/ribavirin Telaprevir Combination therapy	<p>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</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Setrobuvir (ANA598; nonnucleoside NS5B polymerase inhibitor) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>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.</p> <p>Anadys Pharmaceuticals, Inc., San Diego, CA</p> <p>Phase II trial ongoing; FDA granted fast track status</p>	Boceprevir IFN/RBV NS5B inhibitors (in phase II trials) Telaprevir	<p>Rapid virologic response (HCV RNA undetectable at week 4)</p> <p>Slowed or halted disease progression (fibrosis and cirrhosis)</p> <p>Sustained virologic response (defined as undetectable virus at 24 weeks)</p> <p>Decreased need for liver transplant</p> <p>Improved quality of life</p>
Taribavirin hydrochloride (AVS-000206) for treatment of chronic hepatitis C virus infection	Patients in whom hepatitis C virus (HCV) infection has been diagnosed	<p>Effective treatment is needed for treatment resistant HCV infection. Taribavirin, a liver-targeted prodrug of ribavirin, is an antiviral designed to block the enzyme inosine monophosphate dehydrogenase (IMPDH) to inhibit the proliferation of certain cell types.</p> <p>Valeant Pharmaceuticals, Inc., Mississauga, Ontario, Canada</p> <p>Phase III trials completed</p>	Pegylated interferon/ribavirin combination Protease inhibitors (in clinical development) Polymerase inhibitors (in clinical development) TBI-301 (preclinical IMPDH)	<p>Slowed or halted disease progression (fibrosis and cirrhosis)</p> <p>Sustained virologic response (defined as undetectable virus at 24 weeks)</p> <p>Decreased need for liver transplant</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Tenofovir and emtricitabine (Truvada) for prevention of HIV infection</p>	<p>People at risk for HIV infection</p>	<p>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.</p> <p>Gilead Sciences, Inc., Foster City, CA</p> <p>Phase II-IV trials ongoing; The FDA panel voted in favor of approving Truvada for PrEP in three at-risk segments: 19-3 in favor for HIV-uninfected men who have sex with men (MSM); 19-2-1 in favor for HIV-uninfected partners in serodiscordant couples; 12-8-2 in favor for other individuals at risk of acquiring HIV. FDA decision date is Jun 15, 2012; the drug is already marketed for HIV treatment; prevention would be a new indication.</p>	<p>Condoms Harm reduction campaigns Safe needle exchange programs</p>	<p>Reduced transmission and incidence of HIV</p>
<p>Therapeutic vaccine (DermaVir) for HIV infection</p>	<p>Patients in whom chronic HIV infection has been diagnosed</p>	<p>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.</p> <p>Genetic Immunity, LLC, McLean, VA</p> <p>Phase II trials ongoing</p>	<p>Highly active antiretroviral therapy ( HAART) Personalized vaccination Therapeutic vaccination</p>	<p>T cell precursors with high proliferative capacity Reduced viral load Reduction of medication regimen Reduced HIV-related morbidity</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>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 <i>Saccharomyces cerevisiae</i>; 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.</p> <p>GlobelImmune, Inc., Louisville, CO</p> <p>Phase IIb trial ongoing</p>	Interferon alpha-2a Protease inhibitors (in phase III development) Ribavirin	<p>Slowed or halted disease progression (fibrosis and cirrhosis)</p> <p>Sustained virologic response (defined as undetectable virus at 24 weeks)</p> <p>Decreased need for liver transplant</p> <p>Improved quality of life</p>
Therapeutic vaccine (HerpV) for treatment of genital herpes infection	Patients infected with herpes simplex virus 2 (HSV-2)	<p>One in 6 people from age 14–49 years are infected with HSV-2, greatly affecting quality of life; additionally, there is some evidence to suggest that resistance to existing herpes treatments is increasing. HerpV is a recombinant, off-the-shelf, therapeutic vaccine for the treatment of 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.</p> <p>Agenus, Inc., Lexington, MA</p> <p>Phase II trial planned</p>	Acyclovir Valacyclovir	<p>Reduced duration of outbreaks</p> <p>Reduced frequency of outbreaks</p> <p>Reduced transmission of HSV-2</p>
Therapeutic vaccine (V5) for tuberculosis	Patients in whom tuberculosis (TB) has been diagnosed	<p>Therapeutic vaccine (V5) intended for use as adjunctive TB immunotherapy in combination with standard drugs. Oral pill.</p> <p>Immunitor USA, Inc., College Park, MD</p> <p>Phase II trial completed</p>	Ethambutol Isoniazid Pyrazinamide Rifampicin	<p>Improved treatment adherence</p> <p>Resolution of active TB</p> <p>Reduced treatment failures</p> <p>Reduced antibacterial resistance</p> <p>Reduced spread of TB infection</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
TKM-Ebola for treatment of Ebola infection	Patients infected with Ebola virus	<p>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.</p> <p>Tekmira Pharmaceuticals Corp., Burnaby, British Columbia, Canada</p> <p>Phase I trial ongoing</p>	AVI-6002	<p>Increased symptom resolution</p> <p>Reduced mortality</p>
Universal vaccine (N8295) for prevention of influenza	Patients at risk for influenza	<p>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.</p> <p>Dynavax Technologies Corp., Berkeley, CA</p> <p>Phase I trials completed</p>	<p>INO-3510</p> <p>Nitazoxanide</p> <p>Novavax VLP vaccine</p> <p>Oseltamivir</p> <p>Peramivir</p> <p>Seasonal influenza vaccines</p> <p>Zanamivir</p>	<p>Reduced incidence of influenza</p> <p>Reduced morbidity and mortality</p>
Vacc-4x for treatment of chronic HIV-1 infection	Patients in whom chronic HIV-1 infection has been diagnosed	<p>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.</p> <p>Bionor Pharma ASA, Oslo, Norway</p> <p>Phase I/II trial ongoing</p>	<p>Highly active antiretroviral therapy</p> <p>Personalized vaccination</p> <p>Therapeutic vaccination</p>	<p>Reduced viral load</p> <p>Reduced medication regimen</p> <p>Reduced morbidity and mortality</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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 for influenza infection or complications	Influenza is one 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 <i>Salmonella typhimurium</i> 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	Quadrivalent influenza vaccine (in development) Trivalent influenza vaccine Virus-like particle vaccine (in development)	Decreased transmission rates of viral influenza Improved immunogenicity in older patients Lower morbidity and mortality from influenza
Virus-like particle seasonal flu vaccine for prevention of viral 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 flu vaccine formulations	Faster production and distribution of vaccine Reduced incidence of viral influenza Vaccination option for people who are allergic to eggs

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Virus-like particle vaccine for prevention of Norovirus infection	Patients at risk for Norovirus infection	<p>Norovirus is the most common cause of acute gastroenteritis in the U.S. There is currently no 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.</p> <p>LigoCyte Pharmaceuticals, Inc., Bozeman, MT</p> <p>Phase I trial ongoing</p>	Supportive care	Reduced frequency of gastroenteritis
VP 20621 for treatment of recurrent <i>Clostridium difficile</i> infection	Patients in whom recurrent <i>Clostridium difficile</i> infection (CDI) has been diagnosed	<p>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 <i>C. difficile</i> 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.</p> <p>ViroPharma, Inc., Exton, PA</p> <p>Phase II trial ongoing</p>	Fecal transplant Fidaxomicin Metronidazole Vancomycin Vaccination (Sanofi)	<p>Reduced hospitalization time</p> <p>Reduced presence of toxin-producing <i>C. difficile</i> in stool</p> <p>Reduced use of additional antibacterial drugs</p>
VPM1002 vaccine for prevention of tuberculosis infection	People at risk for tuberculosis (TB) infection	<p>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 <i>Mycobacterium bovis</i> Bacillus Calmette-Guérin (BCG) strain TB vaccine that has been modified to express the altered <i>a</i> gene from the <i>Listeria</i> bacterium. This allows the vaccine to escape the phagosome, gain access to the cytosol of the antigen-presenting cell, and potentially improve immunogenicity.</p> <p>Vakzine Projekt Management GmbH, Hannover, Germany</p> <p>Phase II trial ongoing</p>	Antibacterial therapy Current BCG vaccine	<p>Protection against multidrug-resistant TB</p> <p>Reduced infection rates</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
XF-73 for prevention of postsurgical infections due to <i>Staphylococcus aureus</i>	Patients undergoing surgery who may be at risk for infection	<p>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 <i>Staphylococcus aureus</i>, the number 1 global cause of hospital-acquired bacterial infections. XF-73 has also shown activity against drug-resistant strains of methicillin-resistant <i>S. aureus</i> (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 for developing serious postsurgical infections.</p> <p>Destiny Pharma, Ltd., Brighton, UK, in collaboration with National Institute of Allergy and Infectious Disease, Bethesda, MD</p> <p>Phase I trials completed</p>	Daptomycin Fluoroquinolones Fusidic acid Minocycline Vancomycin	Reduction in bacterial infections

**Table 10. AHRQ Priority Condition: 10 Obesity: 16 Interventions**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Controlled-release phentermine-topiramate (Qnexa) for treatment of obesity	Obese patients or overweight patients with type 2 diabetes mellitus or other comorbidities	<p>Only 1 long-term weight loss drug is currently on the market in the U.S., and this drug results in 5% weight loss in only 50% of patients. 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); Qnexa is a controlled-release pill that is intended to be taken once daily.</p> <p>Vivus, Inc., Mountain View, CA</p> <p>Feb 2012, FDA Endocrinologic and Metabolic Drugs Advisory Committee voted 20-2 recommending approval; FDA decision date was originally set for Apr 17, 2012, but delayed to Jul 17, 2012.</p>	Orlistat Other antiobesity drugs in development	Excess weight loss Decreased rate of obesity-related 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
Endoluminal sleeve (EndoBarrier) for preoperative weight loss or treatment for obesity	Adults with body mass index (BMI) >35 kg/m <sup>2</sup> who need to lose weight before bariatric surgery	<p>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.</p> <p>GI Dynamics, Inc., Lexington, MA Medtronic, Inc., Minneapolis, MN</p> <p>U.S. pilot trial completed; several trials completed in Europe, South America; marketed in Europe</p>	<p>Antiobesity drugs Dietary, exercise changes Intragastric balloon</p>	<p>Preoperative weight loss Improved patient safety Reduced side effects Reduced morbidity</p>
FGFR4 antagonist (ISIS-FGFR4Rx) for treatment of obesity	Adults with body mass index (BMI) ≥30 kg/m <sup>2</sup>	<p>Currently, only 1 weight loss drug is available for treatment of obesity in the U.S., and FDA approval of other drugs in development has been delayed due to concerns over long-term safety. The available drug results in about 5% weight loss in only about 50% of patients. 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.</p> <p>ISIS Pharmaceuticals, Inc., a unit of Johnson &amp; Johnson, New Brunswick, NJ</p> <p>Phase I trial ongoing</p>	<p>Antiobesity drugs Dietary, exercise changes</p>	<p>Total weight loss Excess total weight loss</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Food-based polymer (Attiva) for treatment of obesity	Adults with body mass index (BMI) $\geq 30$ kg/m <sup>2</sup>	<p>Currently, only 1 FDA-approved drug is available for treatment of obesity. 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.</p> <p>Gelesis, Inc., Boston, MA</p> <p>Pilot study completed; company pursuing FDA 510(k) clearance</p>	Lifestyle changes Weight loss drugs on the market and under development Bariatric surgery	Total weight loss Excess weight loss Decline in obesity-associated comorbidities (e.g., prediabetes, high blood pressure)
Gastric pacemaker (Abiliti) for treatment of obesity	Adults with body mass index (BMI) $\geq 40$ or $\geq 35$ kg/m <sup>2</sup> with comorbidity	<p>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.</p> <p>IntraPace, Inc., Mountain View, CA</p> <p>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</p>	Gastric banding surgery Gastric bypass surgery Intragastric balloon Sleeve gastrectomy surgery	Percentage excess weight loss Percentage total weight loss Decreased obesity-associated comorbidities (e.g., prediabetes, high blood pressure) Improved quality of life
Lorcaserin (APD-356) for treatment of obesity	Adults with body mass index (BMI) 30–45 kg/m <sup>2</sup>	<p>Lorcaserin (APD-356) is in a new class of selective serotonin 2C receptor agonists that are taken daily.</p> <p>Arena Pharmaceuticals, Inc., San Diego, CA</p> <p>Three phase III trials completed; new drug application (NDA) submitted Dec 2009; FDA rejected NDA Oct 2010; Jan 2012, the company has resubmitted and FDA has accepted NDA; FDA decision date Jun 27, 2012</p>	Dietary modification Exercise Other diet drugs	Weight loss Decreased comorbidities 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
Melanin concentrating hormone 1 antagonist (ALB-127158[a]) for treatment of obesity	Overweight adults	<p>Only 1 long-term weight-loss drug is currently on the market in the U.S., and this drug results in 5% weight loss in only 50% of patients. 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.</p> <p>AMRI, Albany, NY</p> <p>Phase I trial completed</p>	Orlistat Antiobesity drugs in development: Contrave®, Qnexa®	Excess weight loss Total weight loss Reduced obesity-related comorbidities (e.g., cardiovascular, diabetes)
Melanocortin receptor partial agonist (AZD2820) for treatment of obesity	Adults with body mass index (BMI) >18 to <30 kg/m <sup>2</sup> who weigh at least 50 kg (110 lb) and no more than 100 kg (220 lb)	<p>The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Currently, only 1 FDA-approved drug is available for treatment of obesity and FDA approval of other drugs in development has been rejected because of concerns over long-term safety. AZD2820 is a peptide melanocortin receptor partial agonist that purportedly acts by stimulating the melanocortin-3 and melanocortin-4 receptors that have been implicated in regulating food intake, body weight, and energy homeostasis. AZD2820 will be administered as a subcutaneous injection in abdomen or thigh.</p> <p>AstraZeneca, London, UK, in partnership with Palatin Technologies, Inc., Cranbury, NJ</p> <p>Phase Ia trial completed; phase Ib trial ongoing</p>	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
Methionine aminopeptidase 2 inhibitor (ZGN-433) for treatment of obesity	Adults with body mass index (BMI) ≥32 to ≤45 kg/m <sup>2</sup> with or without comorbidities	<p>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).</p> <p>Zafgen, Inc., Cambridge, MA</p> <p>Phase IIa trials planned for 1st half of 2012</p>	Bariatric surgery Dietary and exercise changes Orlistat (Alli®, Xenical®)	Weight loss Decreased comorbidities Fewer adverse events Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Naltrexone and bupropion extended-release (Contrave SR) for treatment of obesity	Adults with body mass index (BMI) 30–45 kg/m <sup>2</sup> or 27–45 kg/m <sup>2</sup> with comorbidities	<p>Naltrexone and bupropion extended release (Contrave SR®) is taken orally once a day.</p> <p>Orexigen Therapeutics, Inc., La Jolla, CA</p> <p>Completed COR-I trial; FDA rejected new drug application Feb 2011; requested additional trial on cardiovascular effects; manufacturer met with FDA's Office of New Drugs in Sept 2011 to discuss pathway to regulatory approval; cardiovascular outcomes trial required by FDA is not scheduled to begin until the 1st half of 2012; the manufacturer anticipates submitting results and having the drug become eligible for approval in 2014</p>	Dietary and exercise changes Other weight-loss drugs	Weight loss Adverse events Improved quality of life
Neuropeptide Y antagonist (velneperit) for treatment of obesity	Adults with body mass index (BMI) ≥30 kg/m <sup>2</sup>	<p>Only 1 weight loss drug is currently on the market in the U.S. and this drug results in about 5% weight loss in only about 50% of patients. 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.</p> <p>Shionogi &amp; Co., Ltd., Osaka, Japan</p> <p>Phase IIb trial completed Jan 2009; trial investigating use with orlistat halted after endpoints not reached; company intends to resume investigation in U.S. as single therapy</p>	Dietary and exercise changes Weight-loss drugs on the market and under development	Total weight loss Excess weight loss Decline in obesity-associated comorbidities (e.g., prediabetes, high blood pressure)
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 <sup>2</sup> )	<p>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.</p> <p>University of Minnesota, Minneapolis</p> <p>Pilot trial completed</p>	Bariatric surgery Dietary and behavior modifications Orlistat	Total weight loss Excess weight loss Reduced glycosylated hemoglobin levels 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
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 <sup>2</sup> and minor comorbidity or BMI of 30–33 kg/m <sup>2</sup> with or without comorbidity	<p>The World Health Organization estimates that more than 1.5 billion adults are overweight, and 500 million are considered obese. Currently, only 1 FDA-approved drug is available for obesity treatment, and 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.</p> <p>Scientific Intake Ltd. Co., Atlanta, GA</p> <p>Pilot study completed</p>	<p>Antiobesity devices (e.g., gastroelectric stimulation devices, expanding polymer devices within stomach)</p> <p>Antiobesity drugs (approved and in development)</p> <p>Lifestyle and behavior modification</p> <p>Surgical intervention</p>	<p>Weight loss</p> <p>Decreased obesity-associated comorbidities (e.g., prediabetes, high blood pressure)</p> <p>Improved quality of life</p>
PRX00933 (5-HT <sub>2C</sub> serotonin receptor agonist) for treatment of obesity	Patients in whom obesity has been diagnosed	<p>Only 1 long-term weight management drug is currently on the market, and it is not effective for many patients. PRX00933 is one in a new class of antiobesity drugs in development; it is an agonist of the 5-HT<sub>2C</sub> serotonin receptor, which is involved in appetite control; preclinical studies have demonstrated that stimulation of the 5-HT<sub>2C</sub> receptor results in appetite suppression.</p> <p>Proximagen Group, plc, London, UK</p> <p>Phase II trial completed</p>	<p>Orlistat</p> <p>Lorcaserin (in late phase development)</p> <p>Contrave® (combination naltrexone/bupropion in late phase development)</p>	<p>Percentage excess weight loss</p> <p>Reduced rate of obesity-associated comorbidities (e.g., prediabetes, high blood pressure)</p> <p>Improved quality of life</p>
Restorative obesity surgery (endoluminal ROSE) for postgastric-bypass weight regain	Patients who have undergone gastric bypass, but regained weight and stretched the stomach pouch or stoma	<p>Restorative obesity surgery (endoluminal ROSE) is intended to restore the stomach or stoma to the original postsurgical size; procedure is minimally invasive and incisionless because it is performed through the mouth.</p> <p>Van Den Bossche and Elemental Healthcare, Ltd., UK</p> <p>Pilot study ongoing</p>	Bariatric revision surgeries	<p>Reduction in stoma</p> <p>Weight loss</p> <p>Quicker recovery than open revision surgery</p> <p>No scarring</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vagus nerve blocking (Maestro system VBLOC) for treatment of obesity	Adults with body mass index (BMI) of $\geq 40$ to $\leq 45$ kg/m <sup>2</sup> or $\geq 35$ kg/m <sup>2</sup> with comorbidities	<p>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.</p> <p>EnteroMedics, Inc., St. Paul, MN</p> <p>Pivotal ReCharge trial ongoing; phase III EMPOWER™ trial ongoing, expected completion in 2013</p>	Minimally invasive bariatric procedures Anti-obesity drugs Similar marketed devices (in EU)	Amount of weight loss Duration of weight loss Resolution of comorbidity (cardiovascular, diabetes)

**Table 11. AHRQ Priority Condition: 11 Peptic Ulcer Disease and Dyspepsia: 18 Interventions**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
A3309 oral agent to treat chronic idiopathic constipation	Patients with chronic idiopathic constipation	<p>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.</p> <p>Albireo, Gothenburg, Sweden</p> <p>Phase II trials completed</p>	Laxatives Enemas	Relief of constipation Fewer side effects

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Acetylcholinesterase inhibitor (acotiamide) for treatment of functional dyspepsia	Patients in whom functional dyspepsia (FD) has been diagnosed	<p>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 the treatment of 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.</p> <p>Zeria Pharmaceutical Co., Ltd., Tokyo, Japan, in collaboration with Astellas Pharma, Inc., Tokyo, Japan</p> <p>Phase III trial completed in Japan; phase II trial completed in U.S.; submitted application for marketing authorization in Japan Sept 2010</p>	<p>Antacids Antibiotics Antispasmodic agents Behavioral therapy Gas remedies H<sub>2</sub> receptor blockers Low-dose antidepressants Prokinetic agents Proton pump inhibitors</p>	<p>Postprandial fullness Early satiety Decreased upper abdominal bloating Improved rate of gastric emptying Improved gastric accommodation Improved quality of life</p>
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	<p>Patients with Crohn's disease frequently suffer damage to their bowels and require surgery; no regenerative therapies are currently approved for Crohn's disease. 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.</p> <p>Osiris Therapeutics, Inc., Columbia, MD</p> <p>Phase III trials ongoing; FDA granted fast track status</p>	<p>Autologous bone marrow-derived mesenchymal stromal cells Teduglutide</p>	<p>Increased disease remission Improved disease symptoms Improved quality of life</p>

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	<p>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 tissue matching or need for immunosuppressive drugs. Administered by injection.</p> <p>Athersys, Inc., Cleveland, OH Pfizer, Inc., New York, NY</p> <p>Phase II trial ongoing</p>	<p>5-Aminosalicylates Antimicrobial therapy Corticosteroids Immunosuppressive agents Monoclonal antibodies Sulfasalazine</p>	<p>Reduced relapse rates Healing of colon Reduced UC-related complications Improved quality of life</p>
Fecal microbiota transplantation for treatment of ulcerative colitis	Patients in whom ulcerative colitis (UC) has been diagnosed	<p>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 there is no 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.</p> <p>Phase II trial ongoing; procedure may be adopted by gastroenterologists who are using the procedure for treatment of recurrent <i>Clostridium difficile</i> infection</p>	<p>Anti-inflammatory drugs Immunosuppressive drugs Biologic therapy Colectomy Over-the-counter nonsteroidal anti-inflammatory drugs and herbal medications</p>	<p>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</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
GSK1605786 (Traficet-EN) for treatment of Crohn's disease	Patients who have been given a diagnosis of moderate to severe Crohn's disease	<p>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.</p> <p>GlaxoSmithKline, Middlesex, UK</p> <p>Phase III trials ongoing</p>	<p>Immunomodulators (azathioprine, etc.)            Monoclonal antibodies (natalizumab, infliximab, etc.)            Corticosteroids (prednisone, etc.)            Antibiotics (for acute flares)            Aminosalicylates (mesalazine)            Low-dose naltrexone            Helminthic therapy</p>	<p>Delayed or avoided surgery            Improved quality of life            Reduced flare-ups            Reduced side effects            Remission            Symptom improvement</p>
Helminthic therapy (pig whipworm) for treatment-resistant ulcerative colitis	Patients in whom treatment-resistant ulcerative colitis has been diagnosed	<p>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.</p> <p>University of California, San Francisco</p> <p>One trial ongoing at NYU School of Medicine; 2 trials completed; 1 for ulcerative colitis and 1 for Crohn's disease</p>	<p>Anti-inflammatory drugs            Biologic therapy targeting specific components of the immune response            Colectomy            Immunosuppressive drugs            Over-the-counter drugs and herbal medications</p>	<p>Increased safety            Reduced flare symptoms            Maintained remission            Reduced or postponed need for surgery            Improved quality of life</p>

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)	<p>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; 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.</p> <p>Royal Philips Electronics, Eindhoven, the Netherlands</p> <p>Prototype developed in 2008, redesigned and renamed in 2009; platform would be used by other companies to develop specific medications delivered by IntelliCap</p>	No direct comparators	<p>Reduced medication side effects</p> <p>Improved efficacy due to local delivery of drugs</p>
JAK 3 kinase inhibitor (tofacitinib) for treatment of ulcerative colitis	Patients in whom ulcerative colitis (UC) has been diagnosed	<p>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.</p> <p>Pfizer, Inc., New York, NY</p> <p>Phase II trials completed</p>	<p>5-Aminosalicylates</p> <p>Antimicrobial therapy</p> <p>Corticosteroids</p> <p>Immunosuppressive agents</p> <p>Monoclonal antibodies</p> <p>Sulfasalazine</p>	<p>Improved clinical response</p> <p>Reduced flare symptoms</p> <p>Reduced or postponed need for surgery</p> <p>Improved quality of life</p>
Linaclotide for treatment of irritable bowel syndrome with constipation	Patients in whom irritable bowel syndrome (IBS) with constipation has been diagnosed	<p>Linaclotide is a peptide agonist of guanylate cyclase 2C located on the luminal surface of the intestine. In preclinical models, linaclotide is purported to reduce visceral hypersensitivity, increased fluid secretion, and accelerate intestinal transit. Linaclotide is taken orally once daily.</p> <p>Ironwood Pharmaceuticals, Cambridge, MA</p> <p>Phase III trials completed; new drug application filed for the treatment of IBS; decision date Jun 2012</p>	<p>Antispasmodic drugs</p> <p>Laxatives</p> <p>Serotonin agonists</p> <p>Tricyclic antidepressants</p>	<p>Reduced abdominal pain and constipation symptoms</p> <p>Long-term relief</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Magnetically guided capsule endoscopy for diagnosis of gastrointestinal disorders	Patients appropriate for gastrointestinal (GI) endoscopic examinations	<p>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.</p> <p>Siemens Healthcare, Munich, Germany Olympus Medical Systems, Center Valley, PA</p> <p>Unphased trial ongoing</p>	Endoscope procedure Pill Cam	<p>Increased sensitivity and specificity Positive and negative predictive values Improved diagnostic accuracy Impact on clinical decision making for managing symptoms</p>
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)	<p>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.</p> <p>Furiex Pharmaceuticals, Morrisville, NC</p> <p>Phase III trials planned; received fast track status from FDA Jan 2011</p>	Antispasmodic drugs Opioids Serotonin agonists Tricyclic antidepressants	<p>Reduced abdominal pain and bloating symptoms Long-term relief</p>
PerOral endoscopic myotomy for treatment of esophageal achalasia	Patients in whom esophageal achalasia has been diagnosed	<p>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 treatment of 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.</p> <p>Northwestern Memorial Hospital, Chicago, IL</p> <p>Phase IV trial ongoing</p>	Heller myotomy	<p>Improved Esophageal Function Tests (upper endoscopy, barium swallow, esophageal manometry, pH test) scores Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Plecanatide (SP-304) for treatment of chronic idiopathic constipation	Patients in whom chronic idiopathic constipation has been diagnosed	<p>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.</p> <p>Synergy Pharmaceuticals, Inc., New York, NY</p> <p>Phase II/III trial ongoing</p>	Linaclotide 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	<p>Rifaximin (Xifaxan®) is a nonabsorbable oral antibiotic currently approved for treatment of traveler's diarrhea.</p> <p>Salix Pharmaceuticals, Inc., Morrisville, NC</p> <p>Phase III trial ongoing; company received complete response letter from FDA Mar 2011, received advice from FDA advisory committee</p>	Antispasmodic drugs Opioids Serotonin agonists Tricyclic antidepressants	Reduced abdominal pain and bloating symptoms Long term relief
Teduglutide (Gattex) for treatment of short bowel syndrome	Patients in whom short bowel syndrome (SBS) has been diagnosed	<p>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.</p> <p>NPS Pharmaceuticals, Bedminster, NJ</p> <p>Phase III trials ongoing; new drug application submitted to FDA Dec 2011 for treatment of SBS; FDA approval date May 2012</p>	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
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)	<p>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.</p> <p>Neovacs S.A., Paris, France</p> <p>Phase II trial ongoing</p>	<p>Aminosalicylates (mesalazine)</p> <p>Antibiotics (for acute flares)</p> <p>Corticosteroids (prednisone, etc.)</p> <p>Low-dose naltrexone</p> <p>Helminthic therapy</p> <p>Immunomodulators (azathioprine, etc.)</p> <p>Monoclonal antibodies (natalizumab, infliximab, etc.)</p>	<p>Delayed or avoided surgery</p> <p>Improved quality of life</p> <p>Reduced flareups</p> <p>Reduced side effects</p> <p>Remission</p> <p>Symptom improvement</p>
Vedolizumab for treatment of moderate to severe ulcerative colitis	Patients in whom moderate to severe ulcerative colitis (UC) has been diagnosed	<p>Vedolizumab is an infused monoclonal antibody; current treatments for UC have limited effectiveness; the only cure is surgery. This may provide an alternative treatment.</p> <p>Millennium Pharmaceuticals, a unit of Takeda Pharmaceutical Co., Ltd., Osaka, Japan</p> <p>Phase III trials ongoing</p>	<p>Anti-inflammatory drugs</p> <p>Biologic therapy targeting specific components of the immune response</p> <p>Colectomy</p> <p>Immunosuppression drugs</p> <p>Over-the-counter drugs and herbal medications</p>	<p>Reduced flare symptoms</p> <p>Maintained remission</p> <p>Reduced or postponed need for surgery</p> <p>Improved quality of life</p>

**Table 12. AHRQ Priority Condition: 12 Pregnancy, Including Preterm Birth: 19 Interventions**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Blood test for predicting spontaneous preterm birth	Pregnant women	<p>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 for 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.</p> <p>Sera Prognostics, Salt Lake City, UT</p> <p>Clinical trial ongoing; company states it is developing a commercial assay</p>	<p>Home uterine activity monitoring</p> <p>Salivary estriol testing</p> <p>Fetal fibronectin</p> <p>Detection of bacterial vaginosis</p> <p>Assessment of cervical length</p>	<p>Earlier intervention for women at risk of preterm birth</p> <p>Reduced incidence of preterm birth</p> <p>Reduced neonatal complications</p> <p>Reduced use of neonatal intensive care services</p>
Cell phone bi-directional communication educational program (Text4Baby) for pregnant women and new mothers	Pregnant women, new mothers, and perinatal case managers and providers	<p>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.</p> <p>National Healthy Babies, Healthy Mothers Coalition, Alexandria, VA</p> <p>Nov 2011 University of California, San Diego, presented Text4Baby data at American Public Health Association Conference in Washington, DC</p>	<p>No intervention</p> <p>Traditional case management (face - to-face)</p> <p>Telephone contact</p> <p>Health education services</p> <p>Home visits</p>	<p>Increased awareness of appropriate prenatal and infant care</p> <p>Adherence with recommended prenatal and infant care</p> <p>Reduction in missed appointments</p> <p>Reduced preterm births</p> <p>Reduced infant morbidity and mortality (e.g., low birth weight due to smoking)</p>
Cell-free fetal DNA test (MaterniT21 PLUS) for prenatal screening for trisomies 13, 18, and 21	Pregnant mothers at risk for trisomy 21 mutation	<p>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.</p> <p>Sequenom, Inc., San Diego, CA</p> <p>Late phase clinical trials completed; as of Oct 2011, lab-developed test has been made available to physicians in the U.S.; Sequenom plans to submit premarket approval application to FDA in late 2012 with hope for approval in 2013</p>	<p>Amniocentesis</p> <p>Blood serum markers for trisomy 21</p> <p>Chorionic villus sampling</p> <p>Ultrasound detection of fetal abnormalities</p>	<p>Increased sensitivity and specificity</p> <p>Improved predictive values</p> <p>Avoidance of invasive procedures</p> <p>Earlier diagnosis for earlier decision making</p>

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) for prevention of 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 initiated according to company, but not registered as of Apr 2012	Physical adhesion barriers Sprayed adhesion barriers	Fewer postsurgical adhesions compared with conventional treatments Less pain from adhesions
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 initiated according to company, but not registered as of Apr 2012	Other pharmacologic treatments for endometriosis	Improved treatment of endometriosis, potential avoidance of surgical treatment.
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 (RISUG). 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 per 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 Undecanoate (under phase development in China)	Long-acting male contraception

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Daily text messaging to encourage oral contraceptive continuation	Patients using an oral contraceptive pill (OCP)	<p>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 1-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.</p> <p>Columbia University Medical Center Department of Obstetrics and Gynecology, New York, NY</p> <p>Pilot trial completed</p>	Routine care Various forms of patient education (i.e., hard copy, Internet)	Increased OCP continuation Decreased risk of pregnancy
Donor human milk program for very-low-birthweight infants	Very-low-birthweight infants (less than 1,501 g weight at birth)	<p>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.</p> <p>University of Iowa, Iowa City</p> <p>Phase III trial ongoing</p>	Formula	Reduced health care costs Normal Bayley Scales of Infant Development, III (at 18 to 22 months of age)
Electronic early physiologic response test (PhysiScore) to predict risk of illness in preterm infants	Preterm infants	<p>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.</p> <p>Stanford University School of Medicine, Stanford, CA</p> <p>Pilot phase trial ongoing</p>	Apgar score	Increased sensitivity Improved predictive value for risk of life-threatening events Avoided invasive testing Improved health outcomes Decreased long-term disabilities

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Endoglin urine screening test for screening for preeclampsia in pregnancy	Pregnant women at risk of preeclampsia	<p>Urine test intended to detect endoglin, a cell surface glycoprotein that has been shown to be elevated in pregnant women who develop preeclampsia.</p> <p>Miraculins, Inc., Winnipeg, Manitoba, Canada Inverness Medical Professional Diagnostics, Princeton, NJ</p> <p>Assay development and optimization ongoing</p>	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
Fetal programming for prevention of metabolic disorders	Pregnant women	<p>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.</p> <p>University of Edinburgh, Scotland, UK</p> <p>Pilot trial ongoing</p>	<p>Nutritional programs alone for pregnant women</p> <p>Prenatal vitamins alone</p> <p>Routine prenatal care (examination/monitoring of fetal development)</p>	<p>Improved health in newborns</p> <p>Decreased risk for development of metabolic disorders</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Gonadotropin-releasing hormone antagonist (Elagolix) for treatment of endometriosis</p>	<p>Patients in whom endometriosis has been diagnosed</p>	<p>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.</p> <p>Neurocrine Biosciences, Inc., San Diego, CA</p> <p>Phase II trial completed; company is seeking special protocol assessment, working with FDA to design a phase III trial; company expects to commence phase III trial in 1st half 2012</p>	<p>Leuprolide (Lupron) and goserelin (Zoladex—peptides, depot injection Nafarelin acetate (Synarel)—nasal spray 2 times daily Hormonal contraceptives Danazol Pain medications Medroxy-progesterone (Depo-Provera) Removal endometrial growths, scar tissue and adhesions Hysterectomy</p>	<p>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)</p>
<p>In utero surgery to repair myelomeningocele (spina bifida)</p>	<p>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</p>	<p>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.</p> <p>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</p> <p>Late-phase trial ceased early due to high efficacy of procedure</p>	<p>Postnatal closure of the spina bifida defect (does not restore function to the already damaged nerves)</p>	<p>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</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>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.</p> <p>Yale University, New Haven, CT</p> <p>Phase II trial ongoing</p>	Standard care without NAC Standard care plus NAC	Reduced early onset neonatal sepsis Prevention of neonatal death
Nurse home visits for reducing second pregnancies in high-risk mothers	Low-income, high-risk mothers	<p>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.</p> <p>Children's Hospital of Philadelphia, Philadelphia, PA Pennsylvania Department of Public Welfare</p> <p>Pilot trial completed</p>	Lay women home visitation programs (e.g., Resource Mothers, Promotoras) Family planning clinics Healthy Start (Health Resources & Services Administration)	Improved health outcomes for mother and child Improved planning of subsequent pregnancies
Oral androgen (dimethandrolone undecanoate) for male contraception	Male patients pursuing contraception	<p>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.</p> <p>Los Angeles Biomedical Research Institute, Los Angeles, CA, in collaboration with the National Institutes of Health, Bethesda, MD, and University of Washington, Seattle</p> <p>Phase I trial ongoing</p>	Combination hormone implant (under development) Condoms Reverse inhibition of sperm under guidance copolymer (under development in India) Vasectomy	Long-acting male contraception Decreased risk of unplanned pregnancy Changes in use of condoms

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Ulipristal acetate (CDB-2914) for treatment of uterine fibroids and excessive uterine bleeding</p>	<p>Premenopausal women in whom symptomatic uterine fibroids have been diagnosed</p>	<p>Ulipristal acetate (CDB-2914; EllaOne®) is a selective P receptor modulator with antiprogestin effects. Given orally, 10 or 20 mg, once daily.</p> <p>Laboratoire HRA Pharma, SA, Paris, France</p> <p>Phase IIb and phase III trials ongoing</p>	<p>Cryomyolysis noninvasive surgery ExAblate Gonadotropin-releasing hormone agonists Hysterectomy Uterine artery embolization</p>	<p>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</p>
<p>Vaginal progesterone gel (Prochieve) to prevent preterm birth in women with a short cervix</p>	<p>Pregnant women in whom a sonographic short cervix (10–20 mm) has been diagnosed</p>	<p>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.</p> <p>Watson Pharmaceuticals, Parsippany, NJ</p> <p>FDA advisory panel voted Jan 20, 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 for this new drug application</p>	<p>Hospital admission for bed rest At-home bed rest Tocolytic therapy Steroid administration Cervical cerclage: invasive (tracheloplasty) or placement of stitches in the cervix to hold it closed Vaginal pessary: noninvasive (removable device placed into the vagina designed to support areas of pelvic organ prolapse)</p>	<p>Sustained pregnancy to full-term Reduced preterm (delivery at &lt;3 weeks before term) birth rate Fewer admissions to neonatal intensive care unit Reduced neonatal morbidity Reduced perinatal mortality Shorter length of neonatal stay</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vending machine dispensing emergency oral contraceptives (Plan B One Step) for pregnancy prevention	Women at risk of pregnancy	<p>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.</p> <p>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.</p> <p>Shippensburg University, Shippensburg, PA</p> <p>Not yet subject to FDA approval</p>	Over-the-counter emergency contraceptives	<p>Decreased risk of pregnancy</p> <p>Increased emergency contraceptive use</p> <p>Increased risk of adverse events associated with emergency contraception</p>

**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	<p>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.</p> <p>Arena Pharmaceuticals, Inc., San Diego, CA</p> <p>Phase I trial completed; phase Ib trial planned</p>	<p>Currently available: Phosphodiesterase type 5 inhibitors, prostanoids, endothelin receptor antagonists, and calcium channel blockers, atrial septostomy, lung transplant, heart-lung transplant</p> <p>Investigational: Selexipag (ACT-293987) non-prostanoid prostacyclin receptor agonist Macitentan (endothelin receptor antagonist)</p>	<p>Reduced mortality</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
ASM8 for treatment-resistant asthma	Patients with severe asthma that has not responded to current standard of care	<p>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.</p> <p>Pharmaxis, Sydney, Australia</p> <p>Phase II trial planned</p>	<p>Inhaled corticosteroids Leukotriene modifiers Long-acting beta agonists Theophylline Short-acting beta agonist Ipratropium (Atrovent)</p> <p>Treatment for allergy-induced asthma: Allergy shots Omalizumab (Xolair) Antihistamines and decongestants</p>	<p>Reduced symptoms Fewer days lost from work or school Prevent permanent narrowing of the bronchial tubes Reduced number of emergency room visits and hospitalizations Prevent/delay side effects from long-term use of some asthma medications</p>
Ataluren for treatment of nonsense mutation cystic fibrosis	Patients in whom cystic fibrosis (CF) due to a nonsense mutation (nmCF) has been diagnosed	<p>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.</p> <p>PTC Therapeutics, Inc., South Plainfield, NJ</p> <p>Phase III trials ongoing; FDA granted orphan drug status</p>	<p>Bronchodilators (albuterol or salmeterol) DNase (such as Pulmozyme®) Mucolytics (acetylcysteine) Hypertonic saline</p>	<p>Improved lung function as measured by forced expiratory volume in 1 second Reduced daily therapy needed in adults</p>
BIBF-1120 (intedanib) to preserve lung function in idiopathic pulmonary fibrosis	Patients in whom idiopathic pulmonary fibrosis (IPF) has been diagnosed	<p>BIBF-1120 (intedanib) is an inhibitor of tumor angiogenesis; under study for treatment of IPF and slowing of disease progression and symptoms.</p> <p>Boehringer Ingelheim GmbH, Ingelheim, Germany</p> <p>Phase III trials ongoing</p>	<p>Bosentan Corticosteroids Pirfenidone</p>	<p>Improved lung function measured by forced vital capacity Improved quality of life Improved ability to perform activities of daily living Slowed disease progression</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
BIO-11006 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	Corticosteroids Ipratropium bromide	Decreased cough frequency Decreased inflammation Decreased sputum production Improved pulmonary function
Endobronchial valve system (Zephyr) for treatment of heterogeneous emphysema	Patients in whom heterogeneous emphysema has been diagnosed	Endobronchial valve system (Zephyr®) is intended to allow air to escape from a pulmonary lobe but not enter it to try to reduce lobar volume improve lung function.  Pulmonx Inc. (formerly Emphasys), Redwood City, CA  Phase III trial ongoing	Lung volume-reduction surgery Physical therapy	Improved lung function Improved activities of daily living Improved quality of life
Ex vivo lung perfusion assessment with Steen solution to increase viable donor lungs	Patients awaiting lung transplant	Donor lungs that might otherwise not be usable were subjected to ex vivo lung perfusion (mechanical ventilation with controlled perfusion flows and pressures in the pulmonary vasculature) plus Steen Solution™ restorative solution for 4 hours in an effort to recondition donor lungs and make them suitable for transplantation.  Vitrolife AB, Göteborg, Sweden  Phase II trial ongoing	Blood-based lung perfusion systems (do not enable lung repair/reconditioning)	Increased number of donor lungs Increased number of successful lung transplantations

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	<p>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.</p> <p>Asthmapolis, Madison, WI</p> <p>Trial completed (no phase); anticipated date to market, fall 2011</p>	Self-recorded logs (hand-written, mobile, Web)	<p>Reduced need for recording logs for patients with asthma                      Enhanced detection of triggers for asthma                      Reduced health disparities                      Improved quality of life</p>
Heparin (VR-496) dry inhaled powder for treatment of cystic fibrosis	Patients in whom cystic fibrosis (CF) has been diagnosed	<p>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.</p> <p>Vectura Group, Wiltshire, UK</p> <p>Phase II trial completed; FDA granted orphan drug status</p>	<p>Hypertonic saline (to clear mucus)                      Mucolytics: Pulmozyme                      TOBI: tobramycin solution for inhalation antibiotic treatment                      Physical therapy for mucolysis                      Investigational: Ataluren, Denufosol, ivacaftor, VX-809</p>	<p>Reduced chest infections                      Reduced anti-inflammatory activity                      Improved mucolysis</p>
Human monoclonal antibody (FG-3019) for treatment of idiopathic pulmonary fibrosis	Patients in whom idiopathic pulmonary fibrosis (IPF) has been diagnosed	<p>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.</p> <p>FibroGen, Inc., San Francisco, CA</p> <p>Phase II trial ongoing</p>	<p>Corticosteroid (prednisone)                      Immunosuppressant (azathioprine, cyclophosphamide)                      Oxygen therapy                      Pulmonary rehabilitation                      Lifestyle changes (smoking, diet, exercise)                      Lung transplantation</p>	<p>Improved lung function                      Improved survival</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Imatinib (Gleevec) for treatment of pulmonary arterial hypertension	Patients in whom pulmonary arterial hypertension (PAH) has been diagnosed	<p>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.</p> <p>Novartis AG, Basel, Switzerland</p> <p>Phase III trials ongoing</p>	<p>Anticoagulants Bosentan Calcium channel blockers Epoprostenol Nitric oxide inhalation Sildenafil Treprostinil</p>	<p>Improved exercise capacity Reduced mortality Reduced hospitalization</p>
Inhaled amikacin (Arikace) for treatment of nontuberculous <i>Mycobacteria</i> infection	Patients in whom pulmonary nontuberculous mycobacterial (NTM) lung infection has been diagnosed	<p>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.</p> <p>Insmed, Inc., Richmond, VA</p> <p>Phase II trial planned; FDA placed a clinical hold on phase III studies while carcinogenicity is being assessed; FDA granted orphan drug status</p>	<p>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</p>	<p>Resolved abnormalities as seen on computed tomographic scan Higher rate of culture conversion to negative Improved 6-minute walk distance and improved oxygen saturation Time to “rescue” antimycobacterial drugs</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>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 to treatment as 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.</p> <p>Pharmaxis, Ltd., Frenchs Forest, Australia</p> <p>Phase III trial completed</p>	Antibiotics Chest mucus clearance therapy	Improved lung function Reduced pulmonary exacerbations Reduced antibiotic use Improved quality of life
Interleukin-5 antagonist (mepolizumab, Bosatria) for treatment of eosinophilic asthma	Patients in whom eosinophilic asthma has been diagnosed	<p>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.</p> <p>GlaxoSmithKline, Middlesex, UK</p> <p>Phase III trial ongoing</p>	Masitinib Omalizumab Oral corticosteroids Reslizumab	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
Interleukin-5 antagonist (reslizumab, Cinquil) for treatment of eosinophilic asthma	Patients in whom eosinophilic asthma has been diagnosed	<p>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.</p> <p>Cephalon, Inc., acquired by Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, in Oct 2011</p> <p>Phase III trials ongoing</p>	Masitinib Mepolizumab Omalizumab Oral corticosteroids	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 with cystic fibrosis (CF) who have the G551D-CFTR gene mutation (10% to 15% of patients with CF)	<p>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. Given orally.</p> <p>Vertex Pharmaceuticals, Inc., Cambridge, MA</p> <p>Phase III trial ongoing; FDA approved on Jan 31, 2012 for cystic fibrosis patients age 6 years and older with the G551D mutation</p>	Currently, no treatment exists to treat the cause of the gene mutation	Reduced lung damage Improved lung function Slowed disease progression
KIT tyrosine kinase inhibitor masitinib for treatment of severe asthma	Patients in whom severe persistent asthma has been diagnosed	<p>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.</p> <p>AB Science S.A., Paris, France</p> <p>Phase III trial ongoing</p>	Omalizumab Oral corticosteroids	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
<p>KL4 synthetic lung surfactant (Aerosurf and Surfaxin [lucinactant]) for prevention of neonatal respiratory distress syndrome</p>	<p>Very-low- and low-birthweight premature infants at risk for respiratory distress syndrome</p>	<p>KL4 surfactant is a synthetic peptide-containing surfactant intended to closely mimic the essential attributes of human lung surfactant; 2 forms in development. One (Aerosurf®), a combination drug/device is administered in conjunction with noninvasive nasal continuous positive airway pressure (nCPAP); other (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.</p> <p>Discovery Laboratories, Inc., Warrington, PA</p> <p>Phase III for lucinactant (Surfaxin) completed; Sept 2, 2011, company submitted Complete Response to FDA's 2009 complete response letter; FDA approved Mar 2012 for prevention of respiratory distress syndrome (RDS). Phase IIa trial for aerosolized Aerosurf formulation completed.</p>	<p>Animal-derived surfactants delivered by endotracheal intubation with or without mechanical ventilation</p>	<p>Improved survival Reduced pulmonary complications Reduced intubation and mechanical ventilation Prevention of risks associated with intubation and mechanical ventilation</p>
<p>Lebrikizumab for treatment of moderate to severe uncontrolled asthma</p>	<p>Patients in whom moderate to severe uncontrolled asthma has been diagnosed</p>	<p>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.</p> <p>Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland</p> <p>Phase III trials ongoing</p>	<p>Glucocorticoids Long-acting beta agonists</p>	<p>Improved change in quality of life and symptom scores Improved forced expiratory volume in 1 second Improved peak flow Reduced rate of asthma exacerbations Reduced rescue medication use</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Lung volume reduction coil (RePneu) for treatment of emphysema</p>	<p>Patients in whom upper and/or lower lobe heterogeneous emphysema and/or multiple emphysematous lobes with focal tissue defects has been diagnosed</p>	<p>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.</p> <p>PneumRx, Inc., Mountain View, CA</p> <p>Pivotal phase II/III trials ongoing; Conformité Européene (CE) marked Oct 2010</p>	<p>Antibiotics Bronchodilators Corticosteroids Oxygen Pulmonary rehabilitation program Surgery: LVR surgery, bullectomy, lung transplantation</p>	<p>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)</p>
<p>Milrinone lactate for treatment of persistent pulmonary hypertension of the newborn</p>	<p>Newborns (up to 10 days) in whom persistent pulmonary hypertension of the newborn (PPHN) has been diagnosed</p>	<p>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 patients with acute decompensated heart failure (HF).</p> <p>Children's Hospital of Philadelphia, Philadelphia, PA, and Bedford Laboratories, Bedford, OH (maker of generic milrinone), are collaborating</p> <p>Pilot study of 18 newborns ongoing; to be followed by a randomized controlled trial; milrinone is indicated for the short-term intravenous treatment of patients with acute decompensated HF</p>	<p>Assisted ventilation Extracorporeal membrane oxygenation High frequency oscillatory ventilation NO Oxygen</p>	<p>Improved oxygenation index Decreased signs of pulmonary hypertension Improved safety profile</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label azithromycin for prevention of chronic obstructive pulmonary disease exacerbations	Patients in whom chronic obstructive pulmonary disease (COPD) has been diagnosed	<p>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.</p> <p>University of Colorado Denver Health Sciences Center</p> <p>Phase III trials ongoing; FDA approved in 1992 for treatment of community-acquired respiratory infections and skin infections</p>	<p>Glucocorticoids                      Long-acting anticholinergic agents                      Long-acting beta2-agonists                      Phosphodiesterase type 4 inhibitors</p>	<p>Reduced cost due to exacerbations                      Reduced incidence of exacerbations                      Increased survival                      Improved quality of life</p>
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	<p>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 the treatment of 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.</p> <p>National Institute of Allergy and Infectious Diseases, Bethesda, MD, is trial sponsor</p> <p>Phase II trial ongoing</p>	<p>Vasodilator therapy                      Prostacyclin (e.g., epoprostenol) - vasodilator                      Sildenafil                      Combined therapy: epoprostenol and sildenafil</p>	<p>Improved pulmonary vascular resistance                      Improved exercise capacity                      Increased oxygen saturation                      Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oral sustained-release prostacyclin (treprostinil UT-15C) for treatment of pulmonary arterial hypertension	Patients in whom pulmonary arterial hypertension (PAH) has been diagnosed	<p>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.</p> <p>United Therapeutics Corp., Silver Spring, MD</p> <p>Phase III trials ongoing</p>	Phosphodiesterase type 5 inhibitors, prostanoids, endothelin receptor antagonists, and calcium channel blockers, atrial septostomy, lung transplant, heart-lung transplant. antagonist)	<p>Reduced mortality</p> <p>Improved quality of life</p>
Oral vaccine (HI-164OV) for treatment of chronic obstructive pulmonary disease	Patients in whom chronic obstructive pulmonary disease (COPD) has been diagnosed	<p>Immunotherapy (HI-164OV) using <i>Haemophilus influenzae</i>; intended to treat moderate to severe exacerbations (those that would require corticosteroid therapy) of COPD. Taken orally.</p> <p>Probiomics Limited, Gordon, NSW, Australia</p> <p>Phase IIb trial completed</p>	Corticosteroid therapy	<p>Reduced duration of episodes</p> <p>Fewer hospitalizations for exacerbations</p> <p>Reduced number and severity of exacerbations</p>
Pirfenidone for treatment of idiopathic pulmonary fibrosis	Patients in whom idiopathic pulmonary fibrosis (IPF) has been diagnosed	<p>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.</p> <p>InterMune, Inc., Brisbane, CA</p> <p>Phase III trials ongoing; FDA granted fast track and orphan drug status</p>	Corticosteroids Intedanib Pirfenidone	<p>Improved ability to perform activities of daily living</p> <p>Improved lung function measured by forced vital capacity</p> <p>Slowed disease progression</p> <p>Improved quality of life</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>PL-3994 for treatment of acute exacerbations of asthma</p>	<p>Patients with asthma who experience acute exacerbations</p>	<p>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.</p> <p>Palatin Technologies, Inc., Cranbury, NJ</p> <p>Phase II trial ongoing</p>	<p>Short-acting beta-agonists, anticholinergics (severe exacerbations), and systemic corticosteroids                      Albuterol inhalation (AccuNeb®, ProAir HFA®, Proventil®, Proventil® HFA, Ventolin HFA)                      Formoterol (Foradil® Aerolizer, Perforomist® inhalant solution)                      Levalbuterol (Xopenex®, Xopenex®-HFA)                      Salmeterol (Serevent®)</p>	<p>Increased forced expiratory volume in 1 second                      Improved forced vital capacity</p>
<p>Portable inhaled nitric oxide device (Nitrosyl) for treatment of pulmonary diseases</p>	<p>Patients in whom pulmonary hypertension secondary to idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension has been diagnosed</p>	<p>No medications are currently approved for treatment of 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.</p> <p>GeNO, LLC, Cocoa, FL</p> <p>Phase II trials ongoing</p>	<p>Lung transplantation                      Prescription therapies                      Pulmonary rehabilitation                      Supplemental oxygen</p>	<p>Reduced morbidity and mortality</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Riociguat (BAY63-2521) for treatment of pulmonary arterial hypertension</p>	<p>Patients in whom pulmonary arterial hypertension (PAH) has been diagnosed</p>	<p>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.</p> <p>Bayer AG, Leverkusen, Germany</p> <p>Phase III trial ongoing</p>	<p>Currently available: Phosphodiesterase type 5 inhibitors, prostanoids, endothelin receptor antagonists, calcium channel blockers, and atrial septostomy, lung transplant, and heart-lung transplant</p> <p>Investigational: Selexipag (ACT-293987) nonprostanoid prostacyclin receptor agonist Macitentan (endothelin receptor antagonist) APD811 (oral prostacyclin) Oral sustained-release prostacyclin (treprostinil UT-15C)</p>	<p>Improved cardiac output Improved exercise capacity Reduced pulmonary arterial pressure Reduced morbidity and hospitalization Reduced mortality</p>
<p>Roflumilast (Daliresp) for treatment of chronic obstructive pulmonary disease</p>	<p>Patients in whom severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis and a history of exacerbations have been diagnosed</p>	<p>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.</p> <p>Forest Laboratories, Inc., New York, NY</p> <p>FDA approved Jan 2011</p>	<p>Inhaled bronchodilators Inhaled corticosteroids</p>	<p>Increased forced expiratory volume in 1 second Reduced exacerbation rate</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Selective prostacyclin (PGI <sub>2</sub> ) receptor agonist (selexipag) for treatment of pulmonary arterial hypertension	Patients in whom pulmonary arterial hypertension (PAH) has been diagnosed	<p>PAH has no cure and can result in heart failure and death. Selexipag (ACT-293987) is a 1st-in-class, selective prostacyclin (PGI<sub>2</sub>) 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.</p> <p>Actelion Pharmaceuticals, Ltd., Allschwil, Switzerland</p> <p>Phase III trials ongoing</p>	<p>Phosphodiesterase type 5 inhibitors, prostanoids, endothelin receptor antagonists, and calcium channel blockers, atrial septostomy, lung transplant, heart-lung transplant</p> <p>Epoprostenol (Flolan®)</p> <p>Treprostinil (Remodulin®)</p> <p>Iloprost (Ventavis®)</p> <p>Treprostinil inhaled (Tyvaso®)</p> <p>Bosentan (Tracleer®)</p> <p>Ambrisentan (Letairis®)</p> <p>Sildenafil (Revatio®)</p> <p>Tadalafil (Adcirca®)</p> <p>Calcium channel blockers (not for all patients)</p> <p>Investigational:</p> <p>APD811 (selective agonist of the prostacyclin receptor)</p> <p>Macitentan (endothelin receptor antagonist)</p>	<p>Reduced pulmonary vascular resistance</p> <p>Improved 6-minute walk distance</p> <p>Reduced PAH-related morbidity</p> <p>Improved survival</p>
Surface-enhanced Raman spectroscopy for rapid diagnosis of <i>Mycoplasma pneumoniae</i> infection	Adults, older children, and young adults suspected of having <i>Mycoplasma pneumoniae</i> infection	<p>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.</p> <p>University of Georgia, Athens</p> <p>Pilot trial planned</p>	<p>Existing tests for possible <i>M. pneumoniae</i> infection</p> <p>Serology and nucleic acid amplification tests</p>	<p>Early diagnosis</p> <p>Avoided unnecessary antibiotic treatment</p> <p>Reduced transmission</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
TC-6987 oral neuronal nicotinic receptor alpha-7 modulator for treatment of asthma	Patients in whom persistent mild to moderate asthma has been diagnosed	<p>While 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.</p> <p>Targacept, Inc., Winston Salem, NC</p> <p>Phase II trial ongoing</p>	Mast cell stabilizers (e.g., cromolyn) Inhaled corticosteroids Omalizumab	Improved forced vital capacity Increased forced expiratory volume Improved quality of life
Temperature controlled laminar air-flow device (Protexo) for treatment of atopic asthma	Patients in whom atopic asthma has been diagnosed	<p>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.</p> <p>Airsonett AB, Ängelholm, Sweden</p> <p>Phase III trials completed</p>	Air purifiers Antiallergen 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
Tissue-engineered donor trachea for trachea replacement	Patients who need replacement of irreversibly damaged respiratory tract	<p>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.</p> <p>Paolo Macchiarini and colleagues, Barcelona, Spain Ministerio de Sanidad y Consumo, Madrid, Spain</p> <p>First transplant reported in late 2010</p>	None	Restored trachea Restored respiratory function/capacity Increased or restored lung capacity 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- <i>CFTR</i> gene mutation	VX-809 is considered a corrector of the cystic fibrosis transmembrane regulator ( <i>CFTR</i> ) 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 Gene therapies (viral vector or liposome delivery of normal <i>CFTR</i> ) Transplantation (lungs) Chest physiotherapy Bilevel positive airway pressure ventilators	Improved lung function Increased survival Improved quality of life

**Table 14. AHRQ Priority Condition: 14 Substance Abuse: 16 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 (efficacious, but restricted to licensed specialty clinics, requires frequent clinic visits, has risk of mortality associated with overdose) Sublingually (under the tongue) 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	Antabuse® Beta blockers TA-CD vaccine Tiagabine Topiramate	Reduced reward associated with cocaine use Prevented relapse Long-term abstinence Improved health outcomes associated with abstinence

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Handheld, portable fingerprinting device for detection of substances of abuse	Individuals suspected of illicit drug use	<p>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 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).</p> <p>Intelligent Fingerprinting, Ltd., Norwich, UK</p> <p>Launch planned for 2012</p>	<p>Other body fluid testing (urine, saliva, blood) Field sobriety tests</p>	<p>Improved detection of illicit substances Reduced invasiveness of drug testing Reduced turnaround time for drug testing Reduced biohazard risk Reduced risk for cross reactivity Improved health outcomes</p>
Interactive text message program (Text2Quit) for smoking cessation	Patients attempting smoking cessation	<p>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 12, "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.</p> <p>Voxiva, Inc., and the George Washington University School of Public Health, both of Washington, DC</p> <p>Initial trials completed; program launched Jun 2011</p>	<p>One-way text messaging smoking cessation plans (not diffused) Hardcopy patient education Internet-based patient education Patient support groups</p>	<p>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</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Naltrexone extended-release (Vivitrol®) for treatment of opioid dependence	Patients in whom opioid dependence has been diagnosed	<p>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.</p> <p>Alkermes, Waltham, MA</p> <p>FDA approved in Oct 2010 for prevention of relapse to opioid dependence following opioid detoxification</p>	Current oral or sublingual pharmacotherapies (buprenorphine, clonidine, levomethadyl acetate, methadone, naltrexone)	Decreased pleasure derived from opioid use Lower relapse rates Improved long-term health outcomes Improved quality of life
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	<p>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.</p> <p>Merck &amp; Co., Inc., Whitehouse Station, NJ (manufacturer) National Institute on Alcohol Abuse and Alcoholism (investigator)</p> <p>Phase II trial ongoing</p>	Antabuse® Campral® Naltrexone No therapies indicated specifically for alcoholism secondary to PTSD disorder	Abstinence from alcohol use Prevented relapse Improved long-term health outcomes associated with prevention of relapse

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label aripiprazole (Abilify) for treatment of alcohol dependence	Patients in whom alcohol dependence has been diagnosed	<p>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 treatment of 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.</p> <p>Bristol-Myers Squibb, New York, NY, and Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan (manufacturers) Medical University of South Carolina, Charleston (investigator)</p> <p>Phase III trial ongoing</p>	Acamprosate Disulfiram Naltrexone	Reduced alcohol consumption Improved morbidity Decreased mortality Improved quality of life
Off-label cycloserine for treatment of cocaine dependence	Patients in whom cocaine dependency has been diagnosed	<p>Cycloserine is a broad spectrum antibiotic used for treatment of tuberculosis; psychotropic responses to it are related to the action of the D-enantiomer of the compound, which is a partial agonist of neuronal N-methyl-D-aspartate (NMDA) receptor for glutamate; calcium flux through the receptors is thought to play a role in synaptic plasticity, the cellular mechanism for learning and memory; cycloserine is intended to facilitate extinction of response to drug-related cues. Administered orally.</p> <p>Elan Corp., plc, Dublin, Ireland (manufacturer) Medical University of South Carolina, Charleston; National Institute on Drug Abuse, Bethesda, MD; University of Arkansas, Fayetteville (investigators)</p> <p>Phase II trials ongoing</p>	Antabuse (off label) Beta blockers (off label) Gamma-vinyl gamma aminobutyric acid (GABA; antiepileptic, not approved in U.S. because of visual field defects) TA-CD Vaccine (off label) Tiagabine (off label) Topiramate (off label)	Reduced association with cocaine cues Reduced self-administration of cocaine Prevented relapse Long-term abstinence Improved health outcomes associated with abstinence

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	<p>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.</p> <p>Medtronic, Inc., Minneapolis, MN (manufacturer) University of Cologne, Cologne, Germany (investigator)</p> <p>Several small pilot studies completed internationally</p>	Pharmacotherapy Psychotherapy	<p>Reduced craving for alcohol Reduced alcohol consumption Reduced morbidity Reduced mortality Improved quality of life</p>
Off-label mifepristone (Mifeprex) for treatment of cocaine dependence	Patients in whom cocaine dependence has been diagnosed	<p>No agents are approved for treatment of 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.</p> <p>New York State Psychiatric Institute, New York, NY The Scripps Research Institute, La Jolla, CA</p> <p>Phase II/III trial ongoing</p>	Antabuse Beta blockers Tiagabine Topiramate	<p>Reduced stress sensitivity Increased cocaine abstinence Improved health outcomes</p>

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	<p>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.</p> <p>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)</p> <p>Phase III trial completed</p>	Acamprosate Disulfiram Naltrexone	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	<p>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 the treatment of 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 5HT 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.</p> <p>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.)</p> <p>Phase II and phase III trials ongoing</p>	Acamprosate Disulfiram Naltrexone	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	<p>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.</p> <p>AstraZeneca, London, UK (manufacturer) University of Pennsylvania, Philadelphia (investigator)</p> <p>Phase III trial completed</p>	Acamprosate Disulfiram Naltrexone	Reduced craving for alcohol Reduced alcohol consumption Reduced morbidity Reduced mortality Improved quality of life
Synthetic vaccine (SEL-068) for treatment of nicotine dependence	Patients in whom nicotine dependence has been diagnosed	<p>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.</p> <p>Selecta Biosciences, Watertown, MA</p> <p>Phase I trial ongoing</p>	Acupuncture "Cold-turkey" quitting Hypnosis Nicotine replacement aids Oral pharmacotherapy (Zyban®, Chantix®) Other vaccines in development	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
Vaccine (Nic002) for treatment of nicotine addiction	Patients in whom nicotine dependence has been diagnosed	<p>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 the treatment of 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.</p> <p>Cytos Biotechnology, AG, Schlieren, Switzerland, in collaboration with Novartis AG, Basel, Switzerland</p> <p>Phase II trial ongoing in collaboration with Duke University, Durham, NC, and Wake Forest University, Winston-Salem, NC; filing anticipated after 2015</p>	<p>“Cold-turkey” quitting Oral pharmacotherapy (Zyban®, Chantix®) Nicotine replacement aids Acupuncture Hypnosis NicVax (in development)</p>	<p>Smoking cessation Decreased relapse rates Long-term abstinence</p>
Vaccine (TA-CD) for treatment of cocaine dependence	Patients in whom cocaine dependency has been diagnosed	<p>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.</p> <p>Celtic Pharma Management L.P., Hamilton, Bermuda</p> <p>Phase II trial ongoing</p>	<p>Antabuse (off label) Beta blockers (off label) Gamma-vinyl gamma aminobutyric acid (GABA; antiepileptic not approved in U.S. because of visual field defects) Tiagabine (off label) Topiramate (off label)</p>	<p>Reduced self-administration of cocaine Prevented relapse Long-term abstinence from cocaine Improved health outcomes associated with abstinence from cocaine</p>

**Table 15. AHRQ Priority Condition: 15 Cross-Cutting: 14 Interventions**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Automated pharmacy kiosk (MedCentre) for dispensing medications	Patients in need of commonly prescribed pharmacotherapies	<p>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 sub-optimal. PharmaTrust MedCentre™ is a free-standing, automated medication dispensing and management system with 4 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; 340 common (many generic) medications are stored inside the machine, which 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.</p> <p>PharmaTrust Corp. subsidiary of PCAS Patient Care Automation Services, Inc., Oakville, Ontario, Canada</p> <p>Released in Canada and UK; opening marketing to U.S.</p>	Retail pharmacy Mail-order pharmacy	Improved access to prescription medication Increased patient adherence with medications Increased patient volume in retail pharmacies
Barbershop-based medical screening and health education programs	Patrons of community barbershops	<p>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.</p> <p>BBHOP: Diabetic Amputation Prevention Foundation, Inglewood, CA Barbershop Health Network, Worcester, MA</p> <p>Pilot program completed</p>	Clinic-based health screenings	Improved health outcomes Improved access to care Reduced health disparities

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Intelligent pills for chronic conditions requiring long-term drug therapy	Patients in whom long-term drug therapy is needed for various chronic conditions	<p>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.</p> <p>Proteus Biomedical, Inc., Redwood City, CA</p> <p>Trial registered (no phase listed), but not yet open for recruitment; external data recorder component FDA 510(k) cleared; Conformité Européene (CE) marked</p>	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
Interactive kiosks (Ideal Life) for remote monitoring of patient health data	Patients in need of remote monitoring of health care data	<p>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.</p> <p>Ideal Life, Inc., Toronto, Ontario, Canada, and Sprint Corp., Overland Park, KS</p> <p>FDA approved for over-the-counter sales; Health Insurance Portability and Accountability Act (privacy) compliant</p>	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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Medical homes network (South Side Healthcare Collaborative) to link emergency department patients to community care</p>	<p>Patients who do not currently have a primary care medical home (PCMH)</p>	<p>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.</p> <p>University of Chicago Medical Center, Chicago, IL</p> <p>Pilot trial completed</p>	<p>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)</p>	<p>Appropriate primary care use Increased mental health, dental, substance abuse care utilization Improved health prevention and promotion Improved patient health outcomes Reduced ED utilization for nonemergency conditions</p>
<p>Motivational interviewing in the pharmacy setting to improve patient medication adherence</p>	<p>Patients who are at risk of nonadherence or nonadherence with prescribed medication regimen(s)</p>	<p>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.</p> <p>University of Missouri, Columbia; University of Pittsburgh School of Medicine, Pittsburgh, PA; Highmark Blue Cross Blue Shield, Pittsburgh, PA; Rite-Aid Pharmacies, Harrisburg, PA</p> <p>Trials completed</p>	<p>Current pharmacist-patient communication curriculum Medication review by pharmacist Nonpharmacy based adherence programs (e.g., reminder services)</p>	<p>Increased patient motivation to adhere to regimen Improved medication adherence Reduced costs of medical care from treating noncompliant patients</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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
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
Patient group appointments with physicians for management of chronic conditions	Patients in whom chronic conditions have been diagnosed	Many physicians find it difficult to incorporate patient education and other followup care into their daily appointments with single patients; also, followup appointments for chronic conditions are characterized by limitations, such as long wait times and patients who are less than optimally engaged. Scheduling group appointments is an approach in which several patients with the same chronic condition (e.g., diabetes, Parkinson's disease) share an extended appointment (1.5 hours) for followup visits. Patients receive a few minutes each for private discussion with the doctor, then a clinician shares information relevant to all patients and takes questions; this is not intended to replace annual in-depth physicals. Physicians can bill for individual patient appointments as long as certain criteria are met, such as the visit includes one-on-one time and education.  University of Rochester, Rochester, NY; Veterans Affairs Medical Centers (NC and VA)  Trial completed	Individual appointments	Increased number of patients seen Reduced waiting times for appointments Improved patient engagement Increase patient education Improved adherence with therapy/disease management

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
<p>Postdischarge clinics to provide transition care after hospital stay</p>	<p>Patients who have been recently discharged from the hospital and require followup care, but who do not have access to timely primary care</p>	<p>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 for 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 (though times vary from clinic to clinic) until the patient can get care from a primary care physician.</p> <p>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</p> <p>Several clinics have been launched in the U.S.</p>	<p>Outpatient followup care (e.g., with primary care physician)</p>	<p>Improved patient outcomes Reduced hospital readmissions</p>
<p>Primary care house calls by paramedics</p>	<p>Patients in need of primary care appointments who have barriers to obtaining primary care</p>	<p>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.</p> <p>Pilot programs ongoing in several states, including Colorado, Texas, and Minnesota</p>	<p>No care due to lack of access House calls by physicians Care in a clinical setting</p>	<p>Improved access to care Lower morbidity Improved health outcomes Increased survival Improved patient satisfaction</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
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	<p>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.</p> <p>University of Utah and the Utah Telehealth Network, Salt Lake City</p> <p>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</p>	Check-up appointments onsite at health facilities	<p>Improved access to medical care</p> <p>Reduced health care disparities</p> <p>Decreased hospitalizations</p> <p>Decreased visits to emergency departments</p> <p>Improved health outcomes</p>
Self-service kiosks to automate triage and treatment in the emergency department	Noncritical patients visiting an emergency department (ED)	<p>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.</p> <p>NCR Corp., Duluth, GA; PharmaTrust, Oakville, Ontario, Canada; StayHealthy, Monrovia, CA</p> <p>Launched in Canada Sept 2010</p>	Standard, non-automated ED triage and treatment	<p>Reduced ED wait times</p> <p>Reduced ED overcrowding</p> <p>Improved health outcomes</p> <p>Improved patient satisfaction</p> <p>Reduced costs of ED visits for minor conditions</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Senior-specific emergency departments for treatment of elderly patients	Senior or elderly patients who visit an emergency department ED	<p>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 for 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).</p> <p>Senior-specific EDs have been opened in Colorado, Missouri, New Jersey, New York, and Texas</p> <p>First senior-specific ED launched in 2008</p>	General EDs	Improved health outcomes for seniors Improved quality of life

## **Section 2. Interventions Added Since Last Update: 0 Interventions**

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

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

**Table 17. AHRQ Priority Condition: 02 Cancer: 0 Interventions**

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

**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: 0 Interventions**

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

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

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

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

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

**Table 23. AHRQ Priority Condition: 08 Functional Limitations and Disability: 0 Interventions**

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

**Table 24. 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 25. AHRQ Priority Condition: 10 Obesity: 0 Interventions**

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

**Table 26. AHRQ Priority Condition: 11 Peptic Ulcer Disease and Dyspepsia: 0 Interventions**

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

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

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

**Table 28. AHRQ Priority Condition: 13 Pulmonary Disease, Asthma: 0 Interventions**

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

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

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

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

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

## **Section 3. Interventions Tracked but Archived Since Last Update: 68 Interventions**

Table 31. AHRQ Priority Condition: 02 Cancer: 9 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Aflibercept (Zaltrap) for treatment of metastatic castration-resistant prostate cancer	Patients with metastatic castration-resistant prostate cancer who are undergoing 1st-line cytotoxic chemotherapy	<p>Current 2nd-line and adjunctive treatments for advanced prostate cancer 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. The drug is being tested as an adjunct to standard 2nd-line chemotherapy with docetaxel for advanced prostate cancer.</p> <p>Collaboration between Regeneron Pharmaceuticals, Inc., Tarrytown, NY, and Sanofi, Paris, France</p> <p>Phase III trial</p>	Abiraterone Docetaxel with prednisone Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life	Phase III trial did not show improvement in overall survival with addition of aflibercept.
<i>BRCA1</i> testing to personalize chemotherapy for advanced gastric cancer	Patients with gastric cancer who may receive chemotherapy with 5-fluorouracil (5-FU), oxaliplatin, and docetaxel	<p>Tumors bearing <i>BRCA1</i> mutations are not responsive to taxane treatments (e.g., docetaxel). Therefore, patients identified as having a <i>BRCA1</i> mutation might respond to a simplified regimen of 5-FU and oxaliplatin as well as they would respond to the standard regimen incorporating docetaxel. Personalizing the chemotherapy regimen could potentially reduce side effects associated with docetaxel in eligible patients.</p> <p>Phase II/III trials ongoing in China</p> <p><i>BRCA1</i> testing is widely available, but has not been widely used in the U.S. for personalizing chemotherapy regimens for gastric cancer</p>	Chemotherapy regimen without <i>BRCA1</i> testing to inform course of treatment	Reduced side effects from therapy (e.g., anemia, fluid retention, peripheral neuropathy, nausea, diarrhea, mouth sores, hair loss, fatigue/weakness, changes to the fingernails/toenails) Improved quality of life	No further development apparent in past 2 years

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Bruton tyrosine kinase inhibitor (AVL-292) for treatment of B-cell malignancies	Patients with treatment-resistant B-cell malignancy (e.g., non-Hodgkin's lymphoma, B-cell chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia)	<p>Patients in whom a treatment-resistant B-cell malignancy has been diagnosed have a poor prognosis and few treatment options. Many B-cell malignancies are dependent on B-cell receptor (BCR) signaling for survival. AVL-292 is a novel kinase inhibitor that is specific for the Bruton's tyrosine kinase, which is a signaling kinase essential for transduction of the BCR signaling pathway.</p> <p>Avila Therapeutics, Bedford, MA</p> <p>Phase I trial</p>	Various cytotoxic chemotherapy regimens combined with various immunotherapeutic drugs	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>	Company purchased by Celgene Corp., Summit, NJ . Drug does not appear in Celgene's pipeline.
DCC-2036 for treatment of Philadelphia chromosome–positive chronic myelogenous leukemia and acute lymphoblastic leukemia	Patients in whom Philadelphia chromosome–positive chronic myelogenous leukemia (CML) or negative acute lymphoblastic leukemia (ALL) has been diagnosed	<p>Inhibitors of the BCR[break-point cluster]-ABL[Abelson]1 fusion protein kinase have demonstrated efficacy in treating Philadelphia chromosome–positive CML and ALL; however, many patients develop resistance to the available kinase inhibitors because of mutation of the BCR-ABL kinase. Therefore, novel kinase inhibitors that are able to inhibit resistant isoforms of BCR-ABL are needed. DCC-2036 is an orally administered ABL kinase inhibitor that functions via a fundamentally different mechanism from currently available ABL kinase inhibitors. Rather than blocking adenosine triphosphate binding to the kinase, DCC-2036 inhibits the transition of the kinase from an inactive to active conformation. Because it acts at a different site on the kinase, DCC-2036 might inhibit kinase isoforms that are resistant to current inhibitors.</p> <p>Deciphera Pharmaceuticals, LLC, Lawrence, KS</p> <p>Phase I/II trial</p>	<p>Placebo</p> <p>There are no standard pharmacologic treatments for patients with CML/ALL who have developed resistance to imatinib, nilotinib, and dasatinib. Some patients may be eligible for hematopoietic stem cell transfer.</p>	<p>Increased overall survival</p> <p>Increased progression-free survival</p> <p>Improved quality of life</p>	Focus seems to have switched from BCR-ABL inhibitor to Tie-2 inhibitor. This compound looks like future studies will be for solid tumors.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
GM-CT-01 (Davanat) for treatment of advanced colorectal cancer	Patients in whom advanced colorectal cancer (CRC) has been diagnosed	<p>When CRC is detected early, it can be effectively treated; however, advanced stages of CRC are associated with a poor prognosis and require improved treatment options. GM-CT-01 (Davanat®) is a polysaccharide polymer (galactose and mannose) designed to target and inhibit galectin receptors found on the surface of tumor cells. Galectins promote tumor cell survival, angiogenesis, metastasis, and immune evasion. Davanat is administered with standard chemotherapeutic regimens and is intended to improve the safety, efficacy, and delivery of these agents.</p> <p>Galectin Therapeutics, Inc., Newton, MA</p> <p>Phase II trials completed</p>	5-Fluorouracil Bevacizumab Cetuximab Irinotecan Leucovorin Personalized vaccination Reolysin (in development)	Increased overall survival Increased progression-free survival Improved quality of life	Development appears to have halted; no new information for 2 years.
Mitochondrial metabolism inhibitor (elesclomol) for treatment of ovarian cancer	Patients in whom platinum-resistant ovarian cancer has been diagnosed	<p>Patients with platinum-resistant ovarian cancer have a poor prognosis with current treatment options. Elesclomol is a novel agent intended to induce apoptosis and is purported to act by transporting copper into the cell where it is reduced from copper(II) to copper(I) in the mitochondria. This causes a series of redox reactions that perturb mitochondrial energy production and lead to apoptosis. Elesclomol is administered by intravenous infusion, and in current clinical trials it is being administered in combination with the cytotoxic agent paclitaxel.</p> <p>Synta Pharmaceuticals Corp., Lexington, MA</p> <p>Phase II trial</p>	Docetaxel Etoposide Gemcitabine Liposomal doxorubicin Paclitaxel Topotecan	Increased overall survival Increased progression-free survival Improved quality of life	Trial suspended in April 2012 (Gynecologic Oncology Group funded by the National Cancer Institute).
Perifosine (KRX-0401) for treatment of refractory advanced colorectal cancer	Patients in whom advanced chemotherapy-resistant colorectal cancer has been diagnosed	<p>Perifosine (KRX-0401) is an anticancer agent that inhibits Akt activation in the phosphoinositide 3-kinase pathway and affects other key signal transduction pathways, including c-Jun amino-terminal kinase (JNK). Agent is intended as monotherapy and in combination with novel therapies; it is taken orally.</p> <p>Keryx Biopharmaceuticals, Inc., New York, NY</p> <p>Phase III trial ongoing under FDA special protocol assessment</p>	Surgery Chemotherapy	Increased overall survival Increased progression-free survival Improved quality of life	Did not meet endpoint; development discontinued.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Saracatinib (AZD0530) for treatment of platinum-resistant ovarian cancer	Patients in whom platinum-resistant ovarian cancer has been diagnosed	<p>Saracatinib (AZD0530) is a 5-, 7-substituted anilinoquinazoline with anti-invasive and antitumor activities is a dual-specific inhibitor of Src and Abl, which are protein tyrosine kinases affecting cell motility, migration, adhesion, invasion, proliferation, differentiation, and survival. Drug is taken orally.</p> <p>AstraZeneca</p> <p>Phase II/III trial</p>	Surgery Chemotherapy	Increased overall survival Increased progression-free survival Improved quality of life	AstraZeneca discontinued development based on lack of efficacy observed in a phase II trial.
Vosaroxin for treatment of platinum-resistant ovarian cancer	Patients in whom platinum-resistant ovarian cancer has been diagnosed	<p>Ovarian cancer usually has a poor prognosis because of the lack of effective early detection/screening tools and clear disease symptoms, resulting frequently in diagnosis at late stages at which currently available chemotherapy regimens are largely ineffective. 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 is given as an intravenous infusion.</p> <p>Sunesis Pharmaceuticals, Inc., South San Francisco, CA</p> <p>Phase II trial complete</p>	Radiation Chemotherapy	Increased overall survival Increased progression-free survival Improved quality of life	Trial completed in 2010, but no movement since. Focus appears to be on AML indication.

**Table 32. AHRQ Priority Condition: 03 Cardiovascular Disease: 21 Interventions**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Angiotensin II-targeted vaccine (CYT006-AngQb) for treatment of hypertension	Patients in whom hypertension has been diagnosed	This vaccine (CYT006-AngQb) is intended to produce a sustained decrease in blood pressure.  Cytos Biotechnology, AG, Schlieren, Switzerland  Phase II trials completed; development stalled as company pays Convertible Bond due in Feb 2012	Oral antihypertensive medications	Normal level blood pressure	No development apparent for past 2 years.
Bioabsorbable polymer-coated stent (Synergy) for treatment of coronary artery disease	Patients with coronary artery disease who are eligible for stenting	Stent (Synergy™) coated with bioabsorbable polymer and implanted in the occluded coronary vessel; coating resorbs into the body, leaving behind a bare-metal stent intended to maintain patency of coronary artery.  Boston Scientific Corp., Boston, MA  Phase I trial completed	Drug-eluting stents Drug-eluting balloons Coronary artery bypass graft surgery Cutting balloons Cryoplasty	Angina relief Earlier discontinuation of antiplatelet therapy Faster vessel healing Reduced restenosis Reduced thrombosis	Experts commenting on this technology did not see potential for high impact.
Bioengineered sirolimus-eluting stent (Combo) for treatment of coronary artery disease	Patients with coronary artery disease who are eligible for stenting	The Combo™ stent features antibodies immobilized on the stent that capture circulating endothelial progenitor cells, which in turn quickly form an endothelial layer over and between the stent struts. This is intended to protect against thrombus and minimize restenosis. The company terms it “endothelial progenitor cell capture technology” and asserts that it promotes accelerated natural healing of vessel walls after implantation and could reduce need for anticoagulation therapy.  OrbusNeich, Wanchai, Hong Kong  Phase II trial ongoing	Other drug-eluting stents	Angina relief Earlier discontinuation of antiplatelet therapy Faster vessel healing Reduced restenosis Reduced thrombosis	Experts commenting on this technology did not see potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Bioresorbable everolimus-eluting stent (Absorb) for treatment of coronary artery disease	Patients with coronary artery disease who are eligible for who are eligible for angioplasty	Bioresorbable drug-eluting stent (DES; Absorb) made of polylactide polymer that elutes everolimus; designed to dissolve over the course of 2 years and intended to reduce risk of late thrombosis and reduce need for dual-antiplatelet therapy compared with currently available DESs that are not bioresorbed.  Abbott Laboratories, Abbott Park, IL  Phase I/II ongoing	Other bioresorbable stents in development Conventional DESs Coronary artery bypass graft surgery Medical management	Angina relief Earlier discontinuation of antiplatelet therapy Faster vessel healing Reduced restenosis Reduced thrombosis	Experts commenting on this technology did not see potential for high impact.
Bioresorbable sirolimus-eluting stent (ReZolve) for treatment of coronary artery disease	Patients in whom coronary artery disease has been diagnosed who are eligible for angioplasty	Sirolimus-eluting stent (ReZolve™) is made of a bioresorbable polymer (an iodinated, tyrosine-derived polycarbonate) that gradually degrades over time and is resorbed by the body.  Reva Medical, Inc., San Diego, CA  Pilot trial ongoing	Other drug-eluting stents (DESs) Combination bioabsorbable polymer/DESs Bare-metal stents Drug-eluting balloons	Angina relief Earlier discontinuation of antiplatelet therapy Faster vessel healing Reduced restenosis Reduced thrombosis	Experts commenting on this technology did not see potential for high impact.
Cholesteryl ester transfer protein modulator (dalcetrapib) for prevention and treatment of coronary artery disease	Patients in whom dyslipidemia or coronary artery disease has been diagnosed	Despite availability of effective pharmaceutical interventions, cardiovascular disease remains the leading cause of mortality worldwide. Dalcetrapib is a cholesteryl ester transfer protein (CETP) modulator intended to raise functional high-density lipoprotein by modulating CETP activity through a mechanism that differs from other CETP inhibitors in development. CETP is a plasma protein responsible for lipid transport.  F. Hoffmann-La Roche, Ltd., Basel, Switzerland  Phase III trial	Anacetrapib (in development) Lifestyle changes Omega-3 fatty acids Statins	Improved lipid parameters Improved cardiovascular outcomes	Trials did not meet endpoints; company halted development

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Contrast agent removal system (Cincor) for prevention of contrast-induced nephropathy	Patients undergoing computed tomography angiography, especially those at risk of contrast-induced nephropathy	Cincor™ contrast removal system consists of an 11-French diameter coronary sinus aspiration catheter and a coronary sinus support device placed via a 14-French diameter right internal jugular vein sheath to aspirate contrast media from coronary sinus; purported to be the only direct contrast removal system; other approaches to contrast removal differ in that they use fluid to try to flush the contrast medium from patients' system; intended especially for patients with preexisting chronic renal impairment, contrast load, diabetes, and advancing age.  Osprey Medical, St. Paul, MN  Phase III trial ongoing	None known	Prevention of acute renal injury	Experts commenting on this technology did not see potential for high impact.
Controlled-release diazoxide choline for treatment of hypertriglyceridemia	Patients in whom dyslipidemia has been diagnosed; patients on a statin drug	Adenosine triphosphate-dependent potassium channel agonist  Essentialis, Carlsbad, CA  Phase III trial registered; not yet recruiting; company plans to begin phase III trial in 2012	Lovaza® Fenofibrate	Reduced risk of coronary artery disease	Experts commenting on this technology did not see potential for high impact.
Drug-eluting absorbable metal scaffold (Dreams) for treatment of coronary artery disease	Patients with coronary artery who are eligible for angioplasty	Permanent drug-eluting stents (DESs) are associated with potential complications, such as late-stent thrombosis (LST). Dreams is a stent made of biodegradable magnesium alloy combined with a paclitaxel; it is intended to open occluded vessels and reduce neointimal proliferation, while possibly avoiding LST, because of the stent's ability to degrade over time.  Biotronik SE & Co., KG, Berlin, Germany  Phase I trial	Conventional DESs Coronary artery bypass graft surgery Medical management Other bioresorbable stents in development	Angina relief Earlier discontinuation of antiplatelet therapy Faster vessel healing Reduced restenosis Reduced thrombosis	Experts commenting on this technology did not see potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Drug-eluting balloon (Moxy) for treatment of coronary artery disease	Patients with coronary artery disease who are eligible for angioplasty	<p>Drug-coated balloon (Moxy™) delivers drug dose (paclitaxel, antiproliferative) over several minutes during a percutaneous transluminal angioplasty procedure. The drug remains resident in deep layers of artery wall and is intended to inhibit restenosis and restore inner arterial surface.</p> <p>Lutonix, Inc., Maple Grove, MN</p> <p>Phase I/II trial</p>	<p>Conventional DESs Coronary artery bypass graft surgery Medical management Other bioresorbable stents in development</p>	<p>Angina relief Earlier discontinuation of antiplatelet therapy Faster vessel healing Reduced restenosis Reduced thrombosis</p>	<p>Experts commenting on this technology did not see potential for high impact.</p>
Drug-eluting balloon (Moxy) for treatment of peripheral artery disease	Patients in whom peripheral in-stent restenosis has been diagnosed	<p>Drug-coated balloon (Moxy) delivers paclitaxel for several minutes during a percutaneous transluminal angioplasty procedure. The drug remains resident in deep layers of artery wall to try to inhibit restenosis; allows for restoration of the inner arterial surface.</p> <p>Lutonix, Inc., Maple Grove, MN</p> <p>Phase II trials ongoing</p>	<p>Standard balloon angioplasty Peripheral drug-eluting stents</p>	<p>Improved peripheral circulation Improved quality of life Reduced pain Reduced restenosis</p>	<p>Experts commenting on this technology did not see potential for high impact.</p>
Drug-eluting balloon (Pantera Lux) for treatment of coronary artery disease	Patients with coronary artery disease who are candidates for angioplasty	<p>Repeated percutaneous coronary intervention with drug-eluting stents (DESs) of small vessels is associated with restenosis and adverse outcomes, such as inflammation and injury, which can lead to LST. Pantera® Lux angioplasty balloon is intended to elute the antiproliferative drug paclitaxel during a percutaneous transluminal angioplasty procedure. The drug is intended to remain resident in deep layers of the artery wall, thereby inhibiting restenosis; allows for restoration of the inner arterial surface.</p> <p>Biotronik SE &amp; Co., KG, Berlin, Germany</p> <p>Phase I trial completed; all-comers registry ongoing</p>	<p>Moxy drug-eluting balloon DESs Non-drug-eluting balloons</p>	<p>Angina relief Earlier discontinuation of antiplatelet therapy Faster vessel healing Reduced restenosis Reduced thrombosis</p>	<p>Experts commenting on this technology did not see potential for high impact.</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Drug-eluting balloon (Pantera Lux) for treatment of peripheral artery disease	Patients with peripheral artery disease who are candidates for angioplasty	<p>Stents (drug eluting or bare metal) have not proven viable options for treating long-diffuse disease, small vessels, the infrapopliteals, or in lesions below the knee, because of issues with stent fractures, thrombosis, and restenosis. Pantera® Lux angioplasty balloon is intended to elute the antiproliferative drug paclitaxel during a percutaneous transluminal angioplasty procedure. The drug is intended to remain resident in deep layers of the artery, wall thereby inhibiting restenosis; allows for restoration of the inner arterial surface.</p> <p>Biotronik SE &amp; Co., KG, Berlin, Germany</p> <p>Trial ongoing (no phase listed)</p>	<p>Moxy drug-eluting balloon</p> <p>Drug-eluting stents</p> <p>Nondrug-eluting balloons</p>	<p>Improved peripheral circulation</p> <p>Improved quality of life</p> <p>Reduced pain</p> <p>Reduced restenosis</p>	Experts commenting on this technology did not see potential for high impact.
Neurostimulation (Ischemic Stroke System) for treatment of ischemic stroke	Patients in whom ischemic stroke has been diagnosed	<p>The Ischemic Stroke System comprises a miniature implantable neurostimulator that is placed adjacent to the sphenopalatine ganglion (SPG; a parasympathetic nerve center located near the sinus cavities that is known to innervate the anterior cerebral circulation in mammals). During stimulation sessions, a transmitter is placed on the patient's cheek, attached by a sticker, to transmit electrical energy from the driver (worn on an armband) to the implant. In clinical trials, stimulation occurs for several hours each day over several days. In clinical trials, the treatment has shown some efficacy when used up to 24 hours after stroke onset, which would markedly increase the treatment window compared with tissue plasminogen activator (tPA). Electrical stimulation of the SPG is intended to increase the diameter of blood vessels supplying the brain (vasodilation) to increase blood flow to the brain, potentially reversing or limiting damage.</p> <p>BrainsGate, Caesarea, Israel</p> <p>Pivotal (phase III) trial completed; 2nd pivotal trial was launched</p>	tPA therapy	<p>Increased blood flow to the brain</p> <p>Reversed damage</p> <p>Improved stroke-related outcomes</p>	No development apparent for past 2 years.
REG1 system for anticoagulation during elective percutaneous coronary interventions	Patients who are undergoing elective percutaneous coronary intervention (PCI)	<p>Two-component drug technology that includes selective coagulation Factor IXa inhibiting aptamer (pegnivacogin) and its specific reversal agent (anivamersen).</p> <p>Regado Biosciences, Inc., Basking Ridge, NJ</p> <p>Phase II trial completed</p>	<p>Unfractionated heparin</p> <p>Other anticoagulants</p>	<p>Reduced bleeding episodes during PCI</p> <p>Reduced complications from ischemia</p>	Experts commenting on this technology did not see potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Self-expanding stent (Stentys) for treatment of straight and bifurcated coronary lesions	Patients with coronary artery disease who have a bifurcated vessel lesion and who are eligible for stenting	<p>Stent malapposition increases the risk of stent thrombosis; no approved stents are specifically designed to address malapposition or bifurcated lesions. The Stentys stent represents a new class of coronary stent; it is a self-expanding, self-apposing stent that is made in both bare metal and drug-eluting (paclitaxel) forms; it has potential for utility in bifurcated lesions because of the ability of the stent struts to “detach” during balloon angioplasty, providing a mechanism by which a 2nd stent can be placed through the stent into another vessel without damaging the main vessel stent. The self-expanding stent is designed to accommodate to arterial enlargement (which occurs due to changes in thrombus load and vasoconstriction in the days/weeks after acute myocardial infarction [MI] percutaneous coronary intervention), thereby reducing the risk of malapposition and subsequent stent thrombosis. The stent is made of nitinol Z-shaped mesh, which is linked by small interconnections.</p> <p>Stentys SA, Paris, France</p> <p>Phase III trial completed for acute MI; Conformité Européene (CE) marked in 2010</p>	<p>Dual stenting with conventional stents for bifurcated lesions</p> <p>Single stenting using a drug-eluting stent (in the bifurcated lesion)</p> <p>Other bifurcation stent technologies in development</p>	<p>Prevented malapposition</p> <p>Reduced angina</p> <p>Reduced restenosis of side branch and main arteries</p> <p>Reduced thrombosis</p>	<p>Experts commenting on this technology did not see potential for high impact.</p>
Side branch stent system (Tryton) for treatment of bifurcated lesions	Patients with coronary artery disease who have a bifurcated vessel lesion and who are eligible for stenting	<p>Tryton Side Branch Stent System™ is intended to treat a type of complex Y-shaped coronary lesion that exists in 2 vessels—1 branching off the other. Such lesions are typically treated by using 2 separate stents, 1 in each branch, which has caused significant complications. The Tryton cobalt chromium stent is deployed in the side branch artery using a standard single-wire balloon-expandable stent delivery system so that a conventional drug-eluting stent (DES) can be placed in the main vessel by being threaded through the Tryton stent.</p> <p>Tryton Medical, Inc., Durham, NC</p> <p>Trial ongoing under FDA investigational device exemption status in U.S.; Conformité Européene (CE) marked</p>	<p>Approaches using more than 1 conventional stent DESs (1 only)</p> <p>Other bifurcation stent technologies currently in development</p>	<p>Reduced restenosis of side branch artery (in addition to main artery)</p> <p>Reduced thrombosis</p> <p>Improved cardiovascular outcomes</p>	<p>Experts commenting on this technology did not see potential for high impact.</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Trans-sodium crocetininate for treatment of peripheral artery disease	Patients in whom peripheral artery disease has been diagnosed	Trans-sodium crocetininate is a small molecule intended to treat hypoxia and enhance diffusion of oxygen selectively to oxygen-deprived tissues in arms and legs; intended to enhance diffusion of oxygen through plasma to alleviate pain and ischemia caused by narrowed or blocked peripheral vessels.  Diffusion Pharmaceuticals, LLC, Charlottesville, VA  Phase I/II trials completed	Angioplasty Surgery Cilostazol (Pletal)	Improved circulation in arms and legs Reduced pain Improved ability to walk	Experts commenting on this technology did not see potential for high impact.
Varespladib methyl (A-002) for treatment of acute coronary syndrome	Patients in whom acute coronary syndrome has been diagnosed	Varespladib methyl (A-002) secretory-type phospholipase 2 (sPLA2) inhibitor. Phospholipid molecules in the blood and vessel wall are broken down by sPLA2, producing 2 potentially bioactive fats that can be involved in atherosclerosis; intended to be used as adjunct to statin therapy.  Anthera Pharmaceuticals, Inc., Hayward, CA  Phase III trial ongoing	Lifestyle changes Lipoprotein-associated PLA2 drugs (also being studied)	Reduced angina Reduced plaques	Experts commenting on this technology did not see potential for high impact.
Vernakalant (Kynapid) injection for treatment of acute atrial fibrillation	Patients in whom acute atrial fibrillation has been diagnosed	Vernakalant (Kynapid™) is an injection intended to selectively block ion channels in the atria.  Cardiome Pharma Corp., Vancouver, British Columbia, Canada, and Merck & Co., Inc., Whitehouse Station, NJ  Phase III U.S. trial halted by FDA in Oct 2010 due to cardiogenic shock and now listed as terminated, though company still lists drug in its pipeline; injection formulation approved in EU Sept 2010	Ibutilide (Corvert) Electrical cardioversion	Reduced life-threatening ventricular arrhythmias Reduced hospital admissions	Experts commenting on this technology did not see potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Vernakalant (Kynapid) orally for treatment of atrial fibrillation	Patients with atrial fibrillation (AF) whose rhythm has been successfully restored via cardioversion	<p>Vernakalant (Kynapid) is a longer-acting, slow-release oral formulation of the injectable vernakalant potassium channel inhibitor; intended to selectively block ion channels in the atria. Vernakalant selectively inhibits I<sub>Kur</sub> (Kv1.5), a current that is more predominant in atrial tissue (than in ventricular tissue). It is intended for use after successful cardioversion.</p> <p>Cardiome Pharma Corp., Vancouver, British Columbia, Canada and Merck &amp; Co., Inc., Whitehouse Station, NJ</p> <p>Phase II trial to begin in late 2012</p>	<p>Amiodarone (Cordarone®, Pacerone®)                      Dronedarone (Maltaq®)                      Propafenone (Rythmol®)                      Sotalol (Betapace®)                      Dofetilide (Tikosyn®)                      Flecainide (Tambocor™)</p>	<p>Increased time to recurrence of AF                      Decreased ventricular arrhythmias                      Decreased hospital admissions</p>	<p>Experts commenting on this technology did not see potential for high impact.</p>

**Table 33. AHRQ Priority Condition: 04 Dementia (including Alzheimer’s): 1 Intervention**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Off-label statins for treatment of Alzheimer’s disease	Patients in whom Alzheimer’s disease (AD) has been diagnosed	<p>Statins are hydroxymethylglutaryl coenzyme A reductase inhibitors (class of drug used to reduce cholesterol biosynthesis; upregulate low-density lipoprotein [LDL] receptors in the liver, thereby promoting clearance of LDL from bloodstream); studies have demonstrated a link between statin use and a decreased prevalence of AD, so the drugs are under investigation for use in patients suspected of having AD; exact mechanism of action is unknown.</p> <p>National Institute on Aging, Bethesda, MD</p> <p>Phase III trial completed</p>	Donepezil Galantamine Memantine Rivastigmine	Slowed disease progression Decreased symptoms Improved long-term health outcomes Improved quality of life	Report from Duke Evidence-based Practice Center indicates statins may not be effective for AD treatment.

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Low-dose ondansetron (TO-2061) for treatment of obsessive-compulsive disorder	Patients with obsessive-compulsive disorder (OCD) who have not adequately responded to selective serotonin reuptake inhibitors (SSRIs)	<p>Low-dose ondansetron (TO-2061) (a 5-HT3 [serotonin] receptor antagonist; downregulates dopamine), which is approved for chemotherapy-induced nausea and vomiting, is intended as an adjunctive therapy to SSRIs for patients with OCD who have not responded to other medications. Administered orally.</p> <p>Transcept Pharmaceuticals, Inc., Port Richmond, CA</p> <p>Phase II trial ongoing</p>	Atypical antipsychotic drugs (off label) Cognitive behavior therapy Other combination therapy Psychotherapy SSRIs	Reduced scores on OCD measures Improved quality of life	Experts commenting on this technology did not see potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Loxapine (Adusuve Staccato) inhalation aerosol for acute agitation in schizophrenia or bipolar disorder	Patients with acute agitation related to underlying schizophrenia or bipolar disorder	<p>Inhaled aerosol delivery of loxapine (Adusuve™ Staccato) using “novel” delivery method is intended to alleviate acute agitation episodes.</p> <p>Alexza Pharmaceuticals, Inc., Mountain View, CA</p> <p>FDA rejected new drug application in 2010, requesting additional data on pulmonary safety; company resubmitted approval application in Aug 2011, FDA approval date originally set for Feb. 4, 2012, but extended to May 4, 2012.</p>	Atypical antipsychotics Benzodiazepines Typical antipsychotics	Rapid reduction in agitation symptoms Increased quality of life	Experts commenting on this technology did not see potential for high impact.
Magneto-encephalography for diagnosis of posttraumatic stress disorder	Patients in whom posttraumatic stress disorder (PTSD) is suspected	<p>Magnetoencephalograph (measure of extremely weak magnetic fields generated by the brain) is proposed as a new “biomarker” for PTSD; abnormal brain signals found in part of brain are associated with memory (connected to ability to suppress bad memories). It is purported to identify patients with PTSD 97% of the time.</p> <p>Brain Sciences Center in Minneapolis, MN, and VA Medical Center, Minneapolis, MN</p> <p>Trial completed</p>	Clinical interviews Patient reports	Increased sensitivity and specificity Improved positive and negative predictive value Earlier intervention and treatment	No development apparent for 2 years.
Mecamylamine (TC-5214) for treatment of major depressive disorder	Patients in whom treatment-resistant major depressive disorder has been diagnosed	<p>Mecamylamine blocks alpha 3, beta 4 neural nicotinic receptors (NNRs). Depression symptoms are associated with an overstimulation of NNRs and other receptors in the brain that are activated by the neurotransmitter acetylcholine.</p> <p>AstraZeneca, London, UK Targacept, Inc., Winston-Salem, NC</p> <p>Phase III trials ongoing; preliminary results did not meet 2 of 3 primary endpoints; awaiting results of 2 additional trials (expected in 1st half of 2012). Company plans to file new drug application with FDA in 2nd half of 2012</p>	Combination therapy Deep brain stimulation Electroconvulsive therapy Other antidepressants Psychotherapy Transcranial magnetic stimulation Vagus nerve stimulation	Increased remission rates Reduced symptoms Improved quality of life	Company ceased development.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Serotonin receptor antagonist (ITI-007) for treatment of schizophrenia	Patients in whom schizophrenia has been diagnosed	ITI-007 acts as a 5-HT2A (serotonin) receptor antagonist intended to alter phosphorylation status of phosphoproteins downstream from dopamine receptor to treat symptoms of schizophrenia with fewer side effects (cardiovascular, weight gain, cognitive defects) than current schizophrenia treatments. Taken orally.  Intra-Cellular Therapies, Inc., New York, NY  Phase II trial ongoing	Cognitive behavior therapy Combination drug/behavior therapy Other schizophrenia drugs Psychotherapy	Decreased symptoms Reduced concomitant depression Fewer side effects	Experts commenting on this technology did not see potential for high impact.

**Table 35. AHRQ Priority Condition: 06 Developmental Delays, Attention-Deficit Hyperactivity Disorder, and Autism: 5 Interventions**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Enzyme (CM-AT) to enhance protein digestion in children with autism	Children in whom autism has been diagnosed	An enzyme (CM-AT) is intended to enhance protein digestion, affecting amino-acid building. It is believed that many children in whom autism has been diagnosed do not digest protein properly. Enzyme is formulated as a powder and given orally, with food.  Curemark, LLC, Rye, NY  Phase III trial completed; another phase III trial ongoing; has fast track status from FDA	Behavior and educational programs Medications Other dietary supplements	Improved core symptoms	Experts commenting on this technology did not see potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Hyperbaric oxygen therapy for treatment of autism spectrum disorders	Patients in whom an autism spectrum disorders have been diagnosed	<p>Patients are exposed to high concentration oxygen at elevated pressure for short periods of time over the course of a few months (about 40 treatments of 1 hour each).</p> <p>Johnson Center for Child Health and Development, Austin, TX; Various academic medical research centers</p> <p>Phase I trial completed; other pilot trials completed or ongoing</p>	<p>Off-label treatments, including: acetylcholinesterase inhibitors, alpha-2 adrenergic agonists, carnitine, immunomodulation and anti-inflammatory treatments, melatonin, music therapy, naltrexone, oxytocin, tetrahydrobiopterin, and vitamin C</p> <p>Risperidone Behavioral programs for autistic children</p>	<p>Improvement in symptoms as measured by Clinical Global Impression Scale, Aberrant Behavior Checklist, and Autism Treatment Evaluation Checklist</p>	<p>Experts commenting on this technology did not see potential for high impact.</p>
Interactive robotic dolls for improving social skills in childhood autism	Children in whom autism has been diagnosed	<p>Robotic doll-based therapy intended to improve communication skills and interaction abilities of children who have limited or no verbal skills.</p> <p>Various academic medical research centers and manufacturers including Carnegie Mellon University Entertainment Technology Center, Autism Center, Pittsburgh, PA</p>	<p>Educational and behavioral programs for autistic children</p> <p>Other robotic dolls in development</p>	<p>Improved social skills and human interaction</p> <p>Improved quality of life</p> <p>Improved activities of daily living</p>	<p>Experts commenting on this technology did not see potential for high impact.</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Off-label memantine (Namenda) for treatment of Down syndrome	Patients in whom Down syndrome has been diagnosed	<p>Trisomy 21, or Down syndrome, is a genetic disorder that causes both physical and mental limitations or delays and health problems. Down syndrome occurs in about 1 in 700 births. Some treatments are known to improve complications of Down syndrome, but few options are intended to improve brain function. Memantine (Namenda®) is in a class of medications called N-methyl-D-aspartate (NMDA) receptor antagonists and is already approved by FDA for Alzheimer’s disease. It is intended to work by decreasing abnormal activity in the brain by binding to NMDA receptors on brain cells to block activity of the neurotransmitter glutamate. At normal levels, glutamate is believed to aid in memory and learning, but if levels are too high, glutamate appears to cause neuronal death.</p> <p>University of Colorado School of Medicine, Aurora, in collaboration with Forest Laboratories, Inc., New York, NY</p> <p>Phase IV trial ongoing</p>	Counseling and behavioral training Medications to treat disease complications	Increased brain function and cognitive activity Improved quality of life	Study statuses have not been updated in more than 2 years; clinical trials status designated “unknown.”
Wristband detector system (Q Sensor) to predict severe emotional distress in autism	Children in whom autism spectrum disorders have been diagnosed	<p>The Q Sensor is a device worn on a wristband or anklet and is intended to records physiologic signs of stress and excitement by measuring slight electrical changes in the skin; intended to help predict impending emotional meltdowns for early intervention. System includes software for viewing, comparing, and annotating data in a PC or Mac computer.</p> <p>Affectiva, Inc., Waltham, MA</p> <p>Commercially available (not subject to FDA regulation)</p>	Biofeedback monitors Human observation (teachers, therapists, parents, other caregivers)	Reduced number of meltdowns Reduced self-harm behaviors (e.g., head banging) Improved ability to proactively intervene with calming measures Improved quality of life	Has been available for 2 years; experts commenting do not believe this technology has potential for high impact.

**Table 36. AHRQ Priority Condition: 07 Diabetes Mellitus: 2 Interventions**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Diabetes Insulin Guidance System (DIGS) for management of type 1 or type 2 diabetes requiring insulin	Patients with type 1 or type 2 diabetes mellitus who require daily insulin	<p>Current standard glucose meters provide no guidance or recommendations on insulin dosage. The Diabetes Insulin Guidance System (DIGS™) uses software to analyze blood-sugar levels and recommend to patients how much insulin they should self-administer based on body chemistry. Using applied mathematics, the software program is intended to adjust insulin dosage recommendations using both current and previously obtained blood glucose levels. The device not only provides blood glucose readings, but provides patients with a dose-by-dose insulin recommendation.</p> <p>Hygieia, Inc., Ann Arbor, MI</p> <p>Unphased trials completed</p>	Standard glucose meters	<p>Improved glycemic control</p> <p>Decreased hypoglycemic episodes</p> <p>Decreased secondary complications</p>	This device is being superseded by artificial pancreas components development and has little potential for high impact.
Noninvasive saliva testing (Pop Test) for glucose testing in diabetes	Patients in whom type 1 or type 2 diabetes mellitus has been diagnosed	<p>Glucose test in the form of lollipop (Glucose Pop Test™); intended to detect glucose over the full range from hypoglycemia (equivalent to blood as low as 10 mg/dL) to hyperglycemia levels.</p> <p>Pop Test, LLC, Cliffside Park, NJ</p> <p>Received 1st patent Nov 2010; clinical trial status unspecified</p>	Invasive blood glucose testing	<p>Improved adherence with blood glucose testing, especially in children</p> <p>Improved diabetes management</p> <p>Improved health outcomes</p>	No apparent development in more than 2 years.

**Table 37. AHRQ Priority Condition: 08 Functional Limitations and Disability: 10 Interventions**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
ACE-536 for treatment of anemia in myelodysplastic syndromes	Patients in whom anemia secondary to myelodysplastic syndromes (MDS) has been diagnosed	<p>Anemia is sometimes treated with therapies targeting the erythropoietin pathway; however, these therapies have exposed patients to increased risk of tumor stimulation, progression, and thrombosis. In MDS, defects in red blood cell (RBC) production occur in the latter stages of red cell maturation, whereas current therapies target earlier stages of RBC production. ACE-536 is a ligand trap therapy that inhibits signaling of several members of the transforming growth factor-beta protein super family, responsible for stimulation of RBC production, late cell-type differentiation, and inhibition of tumor growth and metastasis. Essentially, ACE-536 affects late RBC maturation, effectively increasing RBC production for treatment of anemia in MDS.</p> <p>Celgene Corp., Summit, NJ, in collaboration with Acceleron Pharma, Inc., Cambridge, MA (Acceleron will conduct phase I and II trials; Celgene will conduct phase III trials)</p> <p>Phase I trial initiated Sept 2011; suspended Nov 2011 pending resupply of the investigational drug</p>	Erythropoiesis-stimulating agents	<p>Decreased risk of thrombosis and tumor stimulation</p> <p>Increased hemoglobin</p> <p>Reduced fatigue and inflammation</p> <p>Improved quality of life</p>	Drug had not been resupplied as of May 2012.
Activin receptor (ACE-031) for treatment of Duchenne muscular dystrophy	Patients in whom Duchenne muscular dystrophy has been diagnosed	<p>ACE-031 is an activin receptor type IIB (ActRIIB) molecule; ACE-031 is a protein that builds muscle and increases strength by inhibiting signaling through ActRIIB; a decoy of ActRIIB is created that interferes with proteins such as myostatin that limit muscle growth and regeneration.</p> <p>Acceleron Pharma, Inc., Cambridge, MA (developer) Shire Pharmaceuticals, plc, Dublin, Ireland (commercializing)</p> <p>Phase II terminated (based on preliminary safety data); pending further analysis of safety data and discussion with FDA, company considering plans for a new trial; no further development news as of May 2012</p>	Mutation-specific RNA-based drugs	<p>Halted or delayed loss of muscle strength and function</p> <p>Decreased damage and deterioration of skeletal and cardiac muscles</p> <p>Improved ability to walk, breathe, and live independently</p> <p>Survival beyond late-20s (which is expected survival for patients with this disease)</p>	2 phase II trials terminated due to preliminary data; company still trying to pursue, but no active movement in quite some time.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Adenosine A2a receptor antagonist V-81444 for treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	<p>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 for patients with PD could improve quality of life and management of the disease. V-81444 is an oral adenosine A2A receptor antagonist intended to increase "on" time for patients currently 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 inhibition on neurons associated with patients with PD.</p> <p>Vernalis, plc, Winnersh, UK</p> <p>Phase I trial planned</p>	<p>Dipraglurant Dopamine agonists Istradefylline Levodopa/carbidopa Mavoglurant Monoamino oxidase-B inhibitors, etc. NP002</p>	<p>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</p>	<p>Phase I trial planned for quite some time, but as of April 2012, not registered with clinicaltrials.gov; manufacturer had stated phase I trial would start in 2011.</p>
Attenuex IntraVesical System for treatment of stress urinary incontinence	Women in whom stress urinary incontinence has been diagnosed	<p>Current treatment options for stress urinary incontinence include muscle retraining exercises and surgical options, both of which are of limited efficacy. The Attenuex® IntraVesical System is proposed as a nonsurgical alternative for treatment of stress urinary incontinence; the system comprises a small balloon that is inserted into the bladder and is purported to act as a shock absorber to limit the effects of stressors (e.g., laughing, coughing) on the bladder wall muscles and prevent incontinence; balloon is inserted through the urethra and must be replaced every 3 months.</p> <p>Solace Therapeutics, Framingham, MA</p> <p>Phase III trial</p>	<p>Pelvic floor exercises Surgery (e.g., sling procedure)</p>	<p>Improved Stamey grade (measure of incontinence) Decreased incontinence frequency</p>	<p>Development appears halted; status of phase III trial listed as "unknown;" last updated in 2009.</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Bioartificial liver (HepaMate) for treatment fulminant hepatic failure	Patients with fulminant hepatic failure (acute liver failure)	<p>Extracorporeal bioartificial liver support systems are intended to replace lost liver function 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; HepaMate™ uses the company's PICM-19 porcine embryonic liver stem cell line in the bioreactor component and the HepaDrive blood perfusion system.</p> <p>Alliqua, Inc., New York, NY (Formerly HepaLife Technologies)</p> <p>Phase I trial completed; company stated in Sept 2011 that it “will require additional capital in order to execute the longer term aspects of its business plan, including additional research and development efforts related to HepaMate.”</p>	Standard care for acute liver failure (antibiotics to treat infection and lactulose to treat hepatic encephalopathy)	Increased survival while awaiting donor liver	Development appears halted due to financial straits; HepaLife Tech. is a 3rd subsidiary of Alliqua, but there have not been any updates on this technology.
Borate glass nanofiber material (13-98B3) for treatment of venous stasis wounds	Patients with venous stasis wounds	<p>Venous stasis wounds are caused by poor blood circulation in the lower extremities due to weakening of venous valves. Venous stasis ulcers are slow to heal and commonly recur after treatment, progressing to rapidly eroding and deep wounds. Borate glass nanofiber material is intended to mimic the structural properties of fibrin to form a clot and assist in the migration of epidermal cells to the wound site; this material has also been shown to fight against bacterial infection and is said to be easily absorbed by surrounding tissue; the cottony glass nanofiber material is 300 nanometers to 5 micrometers in diameter.</p> <p>Mo-Sci Corp., Rolla, MO</p> <p>Pilot trial completed on 12 participants in Aug 2010</p>	<p>Antibiotics</p> <p>Compression garments</p> <p>Growth factors</p> <p>Occlusive and nonocclusive wound dressing</p> <p>Skin grafts</p> <p>Wound debridement</p>	Improved or resolved venous stasis wounds in shorter time frame	Larger trial was planned for mid-2011, but no additional information available as of May 2012.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
ChemR23 inhibitor (CCX832) for treatment of psoriasis	Patients in whom autoimmune psoriasis has been diagnosed	<p>Existing systemic treatments for psoriasis suppress the immune system to control symptoms and have significant side effects in some patients. CCX832 is an oral, small-molecule drug intended to reduce dermal inflammation by selectively inhibiting the ChemR23 receptor; selectively inhibiting the psoriasis immune response may reduce side effects from existing broad-spectrum immunosuppressants.</p> <p>ChemoCentryx, Inc., Mountain View, CA</p> <p>Phase I trial ongoing</p>	<p>Topical ointments to control itch and scaling</p> <p>Biologic immunosuppressors</p> <p>Methotrexate</p> <p>Cyclosporine</p> <p>Prescription retinoids</p> <p>Antibiotics for secondary infections</p> <p>Phototherapy</p>	<p>Elimination or reduced severity of dermal inflammation</p> <p>Reduced need for symptom control with systemic immunosuppressors, thereby reducing side effects</p>	<p>Development appears halted; not listed in manufacturer pipeline.</p>
Controlled-release phentermine/topiramate (Qnexa) for treatment of obstructive sleep apnea	Patients in whom obstructive sleep apnea (OSA) has been diagnosed	<p>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, which is known to be low. No pharmacologic therapy is approved for OSA.</p> <p>Phentermine/topiramate (Qnexa®) is a combination drug under investigation for treatment of OSA, obesity, and type 2 diabetes mellitus. Phentermine is believed to work on the hypothalamus portion of the brain to stimulate the adrenal glands to release norepinephrine, which is purported to reduce hunger, and topiramate is an anticonvulsant that blocks sodium (Na) channels and is purported to affect weight loss; if approved, the phentermine/topiramate combination would become the 1st approved drug for treatment of OSA. The drug has been administered orally in trials at a dose of 15 mg of phentermine instant release and 92 mg of topiramate controlled release.</p> <p>Vivus, Inc., Mountain View, CA</p> <p>Phase I/II trial (OB-204) completed Dec 2009</p>	<p>CPAP</p> <p>Hypoglossal neurostimulation</p> <p>Lifestyle changes (dietary, weight loss, alcohol reduction, etc.)</p>	<p>Decreased OSA</p> <p>Weight loss</p> <p>Prevention of complications of OSA, including cardiovascular disease and sudden cardiac death</p>	<p>No evidence of ongoing development for 3 years, though drug is on list in company pipeline.</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Embryonic stem-cell therapy (GRNOPC1) for spinal cord injury	Patients with subacute, functionally complete spinal cord injuries with a neurological level between T3 and T10	<p>Stereotactic injection of stem cell product (GRNOPC1) into spinal cord at injury site.</p> <p>Geron Corp., Menlo Park, CA</p> <p>Phase I trials suspended because the manufacturer has ceased funding until a partner is found to continue development of this therapy collaboratively</p>	<p>Palliative care, rehabilitation for spinal-cord-injured patients</p> <p>Investigations of electrical spinal cord stimulation to restore function</p>	<p>Restoration of spinal neurological function</p> <p>Improved function</p> <p>Improved activities of daily living</p> <p>Increased independence</p> <p>Improved quality of life</p>	<p>Company suspended trials because of lack of funding.</p>
Poloxamer compound (ANX-188) for treatment of sickle cell crisis	Patients in whom sickle cell crisis has been diagnosed	<p>ANX-188 is a surfactant-containing, hydrophilic poloxamer that limits adhesion of sickled cells to each other and vascular endothelium, actions responsible for vaso-occlusive crisis (VOC). ANX-188 may shorten duration of painful VOCs and may not present adverse effects associated with current treatments for sickle cell disease. Administered as an intravenous infusion for 48 hours.</p> <p>Adventrx Pharmaceuticals, Inc., San Diego, CA</p> <p>Phase III trial completed in 1999 by another company; Adventrx bought rights and is seeking FDA approval for new phase III trial; has orphan drug designation</p>	<p>Allogeneic stem cell transplant</p> <p>Gene therapy</p> <p>Azacitidine, hydroxyurea, butyrate decitabine, lenalidomide, pomalidomide</p> <p>KCl cotransporter and Gardos channel inhibition</p> <p>Nitrous oxide</p> <p>Sildenafil</p> <p>Statins</p> <p>Antioxidant therapy</p>	<p>Reduced severity and duration of VOCs</p> <p>Reduced health disparities (African Americans)</p> <p>Improved quality of life</p>	<p>No apparent development for more than 2 years.</p>

**Table 38. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 6 Interventions**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
BC-3781 for treatment of acute bacterial skin and skin structure infections	Patients in whom an acute bacterial skin and skin structure infection (ABSSSI) has been diagnosed	Antibacterial resistance has made some of the current treatment options for ABSSSI ineffective; new antibacterials are needed to effectively treat serious infections. BC-3781 may be the 1st pleuromutilin antibiotic for systemic use; BC-3781 targets the bacterial 50s ribosomal subunit inhibiting protein synthesis. Can be administered orally and intravenously, 100–150 mg.  Nabriva Therapeutics AG, Vienna, Austria  Phase II trial completed	Clindamycin Linezolid Minocycline Trimethoprim/sulfa-methoxazole Vancomycin	Increased resolution of infection/cure Decrease in time to early clinical response (cessation of spread of erythema with a lack of fever)	Experts commenting on this technology did not see potential for high impact.
Bioabsorbable gentamicin surgical implant (CollaRx) for postsurgical infection control	Surgical patients at risk for localized, deep-tissue infection	CollaRx® implant is a biodegradable and bioabsorbable matrix of purified fibrillar collagen filled with antibiotic gentamicin intended for local delivery of antibiotic to prevent postsurgical infections.  Innocoll, Inc., Ashburn, VA  Phase III trials planned	Intravenous and oral antibiotic administration	Reduced surgical site infections and subsequent treatment	Experts commenting on this technology did not see potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
<p>Genetically altered strain of <i>Streptococcus mutans</i> (SMaRT) for prevention of tooth decay</p>	<p>Children and adults who are at risk for dental caries</p>	<p>Current therapies (preventive and corrective) have not been able to control and reduce tooth decay in young children; especially in patients of low socioeconomic background who have limited access to dental services. Vertical transmission of bacteria (<i>Streptococcus mutans</i>) usually from caregiver to infant (sharing utensils, food) and its subsequent colonization in the oral cavity is one of the components of the infectious disease triad (host, agent, and environment) involved in tooth decay. By replacing the native <i>S. mutans</i> with a genetically modified <i>S. mutans</i> (SMaRT) that can kill native <i>S. mutans</i> and also not produce pH-lowering acid, both the demineralization of enamel and tooth decay are averted. Intended to permanently replace native <i>S. mutans</i>; SMaRT is topically applied to the teeth by a dentist, pediatrician or primary care physician using a cotton-tipped swab during a single 5-minute treatment.</p> <p>Oragenics, Inc., Tampa, FL</p> <p>Phase I started Apr 2005 and terminated due to lack of enrollment; FDA issued clinical hold letter Jun 2007, clinical hold removed Oct 2007; phase I trial planned but never got off the ground</p>	<p>Antiseptic mouth rinses Fluoride Oral care hygiene program Sealants</p>	<p>Reduced incidence and prevalence of dental caries in pediatric populations Reduced health care costs Improved quality of life</p>	<p>Development appears to be halted due to lack of funding.</p>
<p>GSK2251052 for treatment of complicated intra-abdominal infections</p>	<p>Patients in whom complicated intra-abdominal infections have been diagnosed</p>	<p>Increasing resistance to existing antibiotics has created a critical need for novel therapies for treatment of complicated urinary tract infections caused by gram-negative bacteria. GSK-2251052 is a novel boron-based, systemic antibiotic that specifically targets the bacterial enzyme leucyl-tRNA synthetase, or LeuRS, which is required for bacterial protein synthesis; inhibition of protein synthesis leads to termination of cell growth and cell death. Phase I results suggested that the drug might have efficacy against a broad range of gram-negative bacteria, including <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i>, <i>Citrobacter</i> species (spp.), <i>Serratia marcescens</i>, <i>Proteus vulgaris</i>, <i>Providentia</i> spp., <i>Pseudomonas aeruginosa</i>, and <i>Enterobacter</i> spp., as well as other pathogens. In trials, it was administered in doses of 750–1,500 mg twice daily as intravenous infusion.</p> <p>Anacor Pharmaceuticals, Inc., Palo Alto, CA GlaxoSmithKline, Middlesex, UK</p> <p>Phase IIb trial terminated Apr 2012</p>	<p>Aminoglycosides Meropenem Fluoroquinolones Tigecycline</p>	<p>Clinical response Microbiologic response Reduced morbidity and mortality from infection Resolution of infection</p>	<p>Trial terminated after microbiological findings of resistance on therapy in patients with complicated urinary tract infections.</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
GSK2251052 for treatment of complicated urinary tract infections	Patients in whom complicated urinary tract infections have been diagnosed	<p>Increasing resistance to existing antibiotics has created a critical need for novel therapies for the treatment of complicated urinary tract infections caused by gram-negative bacteria. GSK-2251052 is a novel boron-based, systemic antibiotic that specifically targets the bacterial enzyme leucyl-tRNA synthetase, or LeuRS, which is required for bacterial protein synthesis; inhibition of protein synthesis leads to termination of cell growth and apoptosis. Phase I results suggested that it may have efficacy against a broad range of gram-negative bacteria, including <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i>, <i>Citrobacter</i> species (spp.), <i>Serratia marcescens</i>, <i>Proteus vulgaris</i>, <i>Providentia</i> spp., <i>Pseudomonas aeruginosa</i> and <i>Enterobacter</i> spp., as well as other pathogens. In trials, the drug was administered in doses of 750–1,500 mg, twice daily, by intravenous infusion.</p> <p>Anacor Pharmaceuticals Inc., Palo Alto, CA GlaxoSmithKline, Middlesex, UK</p> <p>Phase IIb trial terminated Mar 2012</p>	Aminoglycosides with or without ampicillin Cephalosporins (3rd generation) Fluoroquinolones Imipenem-cilastatin	Clinical response Microbiologic response Reduced morbidity and mortality from infection Resolution of infection	Trial terminated after microbiological findings of resistance on therapy in patients with complicated urinary tract infection.
Matrix metalloproteinase inhibitor CTS-1027 for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	<p>Patients with HCV infection that is treatment resistant with pegylated interferon plus ribavirin (IFN/RBV) remain more difficult to treat; new therapies with novel mechanisms of action that can reduce the length of infection and adverse events associated with effective HCV infection treatment are needed. CTS-1027 is an oral small molecule that inhibits matrix metalloproteinases, which are believed to be involved in sustained HCV replication and the inhibition of viral clearance by the immune system; CTS-1027 was designed not to inhibit matrix metalloproteinase-1 (MMP-1), because inhibition of MMP-1 has been associated with musculoskeletal side effects. Administered 60 mg, twice daily.</p> <p>Conatus Pharmaceuticals, Inc., San Diego, CA</p> <p>Phase II trial halted due to safety concerns, safety analysis ongoing</p>	Alisporivir Bavituximab IFN/RBV	Earlier 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	Development appears to be halted.

**Table 39. 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
Serotonin-noradrenaline-dopamine reuptake inhibitor (tesofensine) for treatment of obesity	Patients in whom obesity has been diagnosed	Tesofensine is a serotonin-noradrenaline-dopamine reuptake inhibitor; intended to result in twice the amount of weight loss as achievable with currently approved drugs.  NeuroSearch a/s, Ballerup, Denmark  Phase II trial completed (in Denmark)	Other antiobesity drugs	Total body weight loss Adverse events	Experts commenting on this technology did not see potential for high impact.

**Table 40. 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	Reason
Bronchial thermoplasty system (Alair) for treatment of poorly controlled asthma	Adults in whom asthma has been diagnosed that is not well controlled with inhaled corticosteroids and long-acting beta agonists	Bronchial thermoplasty system (Alair®) uses thermoplasty to thin airway smooth muscle tissue mass; intended to decrease narrowing of airways without causing tissue damage or scarring.  Asthmatx, Inc., Sunnyvale, CA  FDA approved Apr 27, 2010; diffusion has accelerated; number of sites offering doubled between Jan and Jul 2011; as of Mar 2012, 84 clinical sites in 30 U.S states offered the procedure	Albuterol Ipratropium bromide Epinephrine Corticosteroids Long acting beta-adrenoceptor agonists Leukotriene antagonists Mast cell stabilizers	Reduced emergency department visits Reduced missed work and school days Reduced need for rescue medication Improved quality of life	Reached horizon scanning system's expiration date of 2 years post-FDA approval.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Corticosteroid/beta 2 agonist (Relovair) for treatment of COPD	Patients in whom chronic obstructive pulmonary disease (COPD) has been diagnosed	Relovair™ (100/25 mg) is an inhaled corticosteroid/long-acting beta-agonist combination treatment made up of fluticasone furoate and vilanterol that may relieve chronic inflammation and resultant fibrosis, leading to obstruction of small airways caused in COPD; might replace current treatment that uses corticosteroids, short-acting or long-acting beta agonists, or a combination of both that may be administered twice daily or more frequently. Relovair is administered once daily, which could address the unmet need of better adherence, greater convenience for patients.  GlaxoSmithKline, Middlesex, UK Theravance Inc., San Francisco, CA  Pivotal phase III trial ongoing	Symbicort Advair Perforomist Short-acting beta agonists Flovent	Improved adherence with therapy Reduced symptoms Reduced health disparities	Little potential for high impact; considered to be an incremental potential benefit that is not a significant unmet need.

**Table 41. AHRQ Priority Condition: 14 Substance Abuse: 4 Interventions**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Off-label carvedilol for treatment of cocaine dependence	Patients with cocaine dependency who are recently abstinent from cocaine	Carvedilol is a nonselective beta blocker/alpha-1 blocker indicated for treatment of mild to moderate heart failure, but has been observed to lessen cocaine cravings. It is under study (but not by the manufacturer) for reducing cocaine self-administration in cocaine-dependent participants.  GlaxoSmithKline, Middlesex, UK (manufacturer) National Institute on Drug Abuse, Bethesda, MD; University of Arkansas, Little Rock; Yale University, New Haven, CT (investigators)  Phase II trials ongoing	Antabuse (off label) Gamma-vinyl gamma aminobutyric acid Other beta blockers (off label) TA-CD Vaccine (off label) Tiagabine (off label) Topiramate (off label)	Reduced self-administration of cocaine Prevented relapse Long-term abstinence from cocaine Improved health outcomes associated with abstinence	Experts commenting on this technology did not see potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Off-label gabapentin for initiating abstinence in alcohol dependence	Patients with alcoholism who are experiencing alcohol withdrawal symptoms	<p>Gabapentin is an analog of gamma aminobutyric acid (GABA; chief inhibitory neurotransmitter in the vertebrate central nervous system). Gabapentin is indicated for antiseizure purposes and is being explored for anti-alcohol dependence indications (but not by the manufacturer).</p> <p>Pfizer, Inc. (Parke-Davis), New York, NY, and Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel (manufacturers) New York State Psychiatric Institute, New York, NY (investigator)</p> <p>Phase II/III trial ongoing</p>	<p>Benzodiazepine (for withdrawal) Anti-seizure medications (for seizures associated with withdrawal) Drugs for alcohol dependence (disulfiram [Antabuse®], acamprosate [Campral®], Trexan) Drugs for depression associated with alcohol abuse (Prozac®)</p>	<p>Reduced relapse rates Delayed relapse</p>	<p>Experts commenting on this technology did not see potential for high impact.</p>
Opioid receptor antagonist (nalmefene) for treatment of alcohol dependence	Patients in whom alcohol dependence has been diagnosed	<p>No medications that can be taken on an as-needed basis are approved for alcohol dependence. Nalmefene is a small-molecule, tablet, opioid receptor antagonist that inhibits the reward pathway in the brain responsible for desire/craving for alcohol. It is intended to lessen a person's desire to drink, thereby potentially controlling and limiting their intake of alcohol. Nalmefene is designed to be taken on an as-needed basis; not intended for abstinence, only to reduce intake to less harmful levels; indicated for but then discontinued for reversal of opioid drug effects.</p> <p>Biotie Therapies Corp., Turku, Finland; licensed to H. Lundbeck a/s, Valby, Demark</p> <p>Phase III trial completed; submitted application in Dec 2011</p>	<p>Acamprosate Disulfiram Naltrexone</p>	<p>Reduced harmful levels of alcohol consumption Improved willingness to initiate abstinence treatment Improved sense of control over disease Improved long-term health outcomes</p>	<p>Not in development for U.S. market.</p>

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Pentoxifylline for treatment of alcoholic hepatitis	Patients in whom severe alcoholic hepatitis has been diagnosed	<p>Pentoxifylline (normally used to improve circulation) has anti-TNF (tumor necrosis factor) properties. It is a competitive, nonselective, phosphodiesterase inhibitor. Intended to inhibit TNF-alpha (TNF promotes inflammation; probably why it has an effect on these patients) and has antifibrogenic properties; being studied as adjunctive therapy to corticosteroids.</p> <p>University Hospital of Lille in France</p> <p>Phase III trial completed</p>	Stand-alone corticosteroid therapy	<p>Increased progression-free survival</p> <p>Increased overall survival</p> <p>Improved quality of life</p>	Experts commenting on this technology did not see potential for high impact.

**Table 42. AHRQ Priority Condition: 15 Cross-Cutting: 2 Interventions**

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Portable ultrasound to assess pedicle and intrathoracic omental flap	Patients requiring surgical reconstruction of chest wall using intrathoracic omental flap (part of the peritoneum) transposition technique (often associated with deep sternal wound infections after coronary artery bypass grafting)	<p>Use of portable ultrasound scanner to assess the viability and perfusion of buried intrathoracic omental flap following surgical reconstruction of the chest wall; intended to address deep sternal wound infections.</p> <p>University of Amsterdam, the Netherlands</p> <p>Case studies completed</p>	Postoperative computed tomography scans	<p>Rapid bedside assessment of viability and perfusion of the omental flap</p> <p>Avoided unnecessary revision surgery</p> <p>Reduced cost of care</p>	Experts commenting on this technology did not see potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Reservation or appointment-making system for hospital emergency department visits	Patients with non-life-threatening conditions who intend to seek care in an emergency department (ED)	<p>The national average for ED wait times is more than 4 hours (and can be as long as 8 hours in places such as Utah). Long wait times are costly, inconvenient for patients, and can result in poorer patient outcomes. InQuickER® is an online service that forms partnerships with hospitals, so patients with non-life-threatening injuries or illnesses can “reserve” an “appointment” time at their local ED, then wait at home until that time comes. The service is a “check-in process” that holds a patient’s place in line and projects his or her anticipated treatment time, using data from EDs. Once patients arrive at the hospital at the projected time, the service guarantees that they will be seen in 15 minutes or their convenience fee (\$9.99) is refunded. Checkpoints are put in place to ensure that patients with emergent injuries or illnesses do not wait at home.</p> <p>InQuickER, LLC, Nashville, TN</p> <p>Launched in Sept 2011</p>	Traditional approach to ED visits	<p>Reduced wait times for patients Improved patient convenience and quality of life Improved outcomes for patients (especially those with life-threatening injuries or illnesses)</p>	Experts commenting on this technology did not see potential for high impact.

## **Section 4. Interventions Identified and Not Tracked: 0 Interventions**

**Table 43. 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 44. 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 45. 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 46. 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 47. 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 48. 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 49. AHRQ Priority Condition: 08 Functional Limitations and Disability: 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: 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 51. 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 52. 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 53. 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 54. 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 55. 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 56. 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