AHRQ Healthcare Horizon Scanning System – Status Updates

Horizon Scanning Status Update: January 2013

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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

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Preface

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

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

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

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

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Introduction

The AHRQ Healthcare Horizon Scanning System produces reports and status updates from its activities. Two years have passed since the initiation of the system and this issue of the Status Update reflects two new changes in the horizon scanning protocol beginning January 2013. First, the horizon time frame has been narrowed to identify topics anticipated to be within 2–3 years of possible diffusion into clinical practice. A few surrogates are used to determine this horizon, such as clinical investigation in phase III trials for interventions subject to regulatory processes of the U.S. Food and Drug Administration (FDA). Topics with orphan drug status, fast-track status, or FDA innovation pathway designation would be considered if Phase II trials are ongoing. Second, for the broad priority area of "Functional Limitations and Disability" AHRQ has designated use of the definition of disability used by the Department of Health and Human Services, which slightly narrows the horizon scanning focus for this priority area. As a result of these two changes, nearly 500 topics have been deleted from tracking in the system for this report, compared with previous reports.

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

Criteria for including topics in the Status Update are provided in detail in the newly revised "Horizon Scanning Protocol and Operations Manual," which is available on the Effective Health Care Web site (Protocol and Operations Manual). Briefly, broad scanning is performed for each priority condition to detect "leads" to interventions and innovations that are anticipated to be 2-3 years from potential diffusion into clinical practice. Sets of questions are applied to determine whether any given intervention addresses an "unmet need" such as a gap in effective ways to screen, diagnose, treat, monitor, manage, or provide or deliver care for a health condition or disease. Interventions might be lacking entirely, or existing options may be less than optimal. Leads that appear to address an unmet need are assigned to horizon scanning analysts and are assessed for grouping into potential topics. Potential topics are then described according to the PICO framework: potential patient Population, the Intervention, potential Comparators to the intervention, and potential Outcomes of interest for the patient population.

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

Topics accepted for tracking may also be designated during the meeting for further searches to collect more in-depth information about them. Such topics must be far enough along in development (typically in phase III trials for drugs, in phase II or III trials for devices, and pilot information for care delivery innovation topics) to have some preliminary efficacy and safety data available. The horizon scanning medical librarians and analysts proceed with more in-depth and topic-specific searching for information on the topics selected for advancement.

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

Populating the horizon scanning system has been ongoing since December 2010. During that time, more than 13,000 leads have been uploaded into the system and reviewed by analysts, from which about 1,850 topics have been initially identified and moved through the system. This Status Update report contains 481 identified interventions we are tracking, of which 15 are new topics entered into the system this reporting period. We archived 67 topics during this reporting period. The reason for archiving each topic is provided in the respective tables of archived topics. Three reasons account for the majority of archived topics: expert commenters saw no high-impact potential at this time in the areas of interest to AHRQ; companies halted development; or topics that had been tracked met criteria for retiring from the system because they have diffused since tracking started or are 2 years past approval by the U.S. Food and Drug Administration.

In this update, four priority areas comprise about 68% of the interventions (including programs) being tracked. Interventions related to cancer account for 35% (168/481) of tracked topics. The other priority areas with the most tracked topics in descending order of number of topics are as follows: functional limitations and disability (16%,78/481), cardiovascular diseases (9%, 43/481), and infectious diseases (8%, 39/481).

Interventions being tracked in the remaining 10 priority conditions (arthritis, dementia, depression and other mental illness, developmental delays, diabetes, obesity, peptic ulcer disease and dyspepsia, pregnancy and childbirth, pulmonary diseases, and substance abuse) plus an additional area we designate as cross-cutting, account for less than 5% each, or a combined total of about 32% (153/481) of topics being tracked in the system.

In terms of overall types of interventions, abut 91% fall into one of two general categories, and the proportions of topics in these categories have changed only slightly since initial reporting. About 70% of topics in the system are a pharmaceutical/biotechnology (i.e., drug, vaccine, biologic); about 12% are devices—either implanted or used to deliver treatments externally; about 5% are technologies intended to screen, diagnose, identify risk, identify gene mutations, and/or monitor a disease state. About 4% are innovative programs, services, or care delivery practices. Other categories include surgical procedures, other procedures, alternative/complementary medicine, assistive technologies (i.e., rehabilitative or physical support), and information technology, which together constitute about 9% of interventions in the system.

Section 1. Currently Tracked Interventions: 466 Interventions

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Atacicept for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	Investigators have not found a permanent cure for SLE, and current treatments provide only partial relief of symptoms. Atacicept is a biologic that purportedly decreases the activity of autoreactive B cells, which may play a key role in the pathogenesis of SLE. Atacicept is a recombinant protein that consists of domains from the proteins B-lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL), which are involved in the maintenance, proliferation, and antibody production of B cells, fused to the constant domain of immunoglobulin. Because BLyS and APRIL bind the TACI (transmembrane activator and calcium-modulating and cyclophilin ligand [CAML] interactor) receptor, atacicept is also called TAC-Ig. Atacicept is purportedly an antagonist for the TACI receptor. Atacicept is hypothesized to selectively impair mature B cells and plasma cells more than memory B cells or progenitor cells. Atacicept is administered subcutaneously, 75 or 150 mg, once weekly. EMD Serono, Inc., Rockland, MA Phase II/III trial ongoing; estimated completion Oct 2012	Belimumab Corticosteroids Cyclophosphamide Methotrexate Tumor necrosis factor-alpha inhibitors Rituximab	Delayed disease progression Reduced symptoms Fewer flares Improved quality of life
Autologous conditioned serum for treatment of osteoarthritis (knee and back)	Patients in whom osteoarthritis (OA) has been diagnosed	Currently no regenerative treatments are approved for patients with OA. Autologous conditioned serum (ACS) consists of serum collected from the patient that has components purported to be regenerative or protective—such as interleukin (IL)-1Ra which is believed to dampen IL-1-mediated inflammation—isolated from the sample. The conditioned serum is reinjected into the arthritic joint. By specifically enriching for desired molecules, not simple fractionation/concentration, ACS purportedly has different effects from platelet-rich plasma therapy. NY Spine Medicine, Schottenstein Pain & Neurology, New York, NY Pilot studies completed; procedure currently diffusing in the U.S.	Lifestyle modification (weight loss, exercise) Mesenchymal stem-cell therapy Nonsteroidal anti-inflammatory drugs Physical therapy Platelet-rich plasma Viscosupplementation	Reduced pain Improved mobility Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous mesenchymal stems cells for treatment of joint osteoarthritis	Patients in whom osteoarthritis (OA) has been diagnosed	Current conservative therapies for osteoarthritis (OA) target disease symptoms such as pain and inflammation; however, they do not address the underlying pathology of the disease or halt its progression. Treating osteoarthritic joints with mesenchymal stem cells has the potential to be the 1st treatment could restore the large cartilage defects found in patients with OA. Mesenchymal stem cells are adult stem cells that are progenitor cells that retain the ability to differentiate into a number of cell types, including chondrocytes, which are the cells responsible for maintaining cartilage. The stem cells can be isolated from several tissues, including bone marrow, synovium, periosteum, skeletal muscle, and adipose tissue. When 1st isolated from the patient, mesenchymal stem cells constitute a small fraction of the cells present in the sample and must either be concentrated by centrifugation or be passaged multiple times in vitro to expand the mesenchymal cell population. The condition of the patient may influence the attributes of the mesenchymal stem cells that are produced, and both patient age and the presence of OA have been shown to affect the ability of isolated mesenchymal stem cells to proliferate and differentiate into chondrocytes. Regenerative Sciences, Inc., Broomfield, CO Arthritis Treatment Center, Frederick, MD Phase II/III trial ongoing	Lifestyle modification (weight loss, exercise) Mesenchymal stem-cell therapy Nonsteroidal anti-inflammatory drugs Physical therapy Platelet-rich plasma Viscosupplementation	Reduced pain Improved mobility Improved quality of life
Autologous platelet-rich plasma therapy for treatment of joint osteoarthritis	Patients in whom osteoarthritis (OA) has been diagnosed	Other than joint replacement and symptom management, effective treatment for OA to restore long-term function is not available. Viscosupplementation provides temporary relief and improves short-term function for some patients, but long-term nonsurgical treatments are needed. Platelet-rich plasma (PRP) therapy involves collection, separation, and concentration of autologous platelets from a patient's blood, which usually takes place at a community blood bank (e.g., American Red Cross) or a hospital's own blood bank. The PRP is re-infused in an outpatient setting at the desired anatomic site (i.e., knee). PRP contains and releases (through degranulation) at least 7 different growth factors that are intended to stimulate bone and soft-tissue healing. Orthohealing Center, Los Angeles, CA Phase III trials ongoing	Lifestyle modification (weight loss, exercise) Mesenchymal stem-cell therapy Nonsteroidal anti-inflammatory drugs Physical therapy Viscosupplementation	Decreased pain Increased mobility Improved quality of life

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	Investigators have not found a permanent cure for SLE, and available treatments provide only partial relief of symptoms, so better treatments 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 purportedly a broad inhibitor of BAFF; it is purportedly a novel proprietary fusion protein called a peptibody. Administered weekly via subcutaneous injection. Anthera Pharmaceuticals, Inc., Hayward, CA Phase IIb trial ongoing; phase III trials planned to begin in Feb 2013	Belimumab Corticosteroids Cyclophosphamide Methotrexate Tumor necrosis factor-alpha inhibitors Rituximab	Delayed disease progression Symptom relief Improved quality of life
Epratuzumab for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	Investigators have not found a permanent cure for SLE, and available treatments provide only partial relief of symptoms, so better treatments are needed. Epratuzumab is a fully humanized, monoclonal antibody that purportedly binds and modulates the activity of CD22, an antigen found on B cells purported to prevent autoreactive responses. Autoreactive B cells are believed to play a major role in SLE pathogenesis. The drug is administered as a subcutaneous injection once monthly in clinical trials. UCB S.A., Brussels, Belgium Phase III trials ongoing	Belimumab Corticosteroids Cyclophosphamide Methotrexate Tumor necrosis factor-alpha inhibitors Rituximab	Delayed progression of disease Reduced symptoms Fewer flares Improved quality of life
Fostamatinib disodium for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	RA is a chronic inflammatory disease causing polyarthritis with frequent progression to permanent joint damage, deformity, and functional disability. Fostamatinib disodium, previously referred to as R788, is a spleen tyrosine kinase inhibitor that reversibly blocks lymphocyte signaling involved in inflammation and tissue degradation in RA. It is intended for treating early stage RA to reduce swelling and tissue destruction. The drug is taken orally. Rigel Pharmaceuticals, Inc., South San Francisco, CA Phase III trials ongoing	Corticosteroids Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine Nonsteroidal anti-inflammatory drugs Tocilizumab Tofacitinib (investigational) Tumor necrosis factor-alpha inhibitors	Decreased inflammation Slowed disease progression Reduced pain Improved function and activities of daily living Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interleukin-17 antagonist (secukinumab) for treatment of ankylosing spondylitis	Patients in whom ankylosing spondylitis has been diagnosed	Investigators have not found a cure for ankylosing spondylitis. Treatments are intended to reduce inflammation and improve mobility but are not effective for all patients. Secukinumab is purportedly a monoclonal antibody antagonist for interleukin-17 (IL-17). IL-17 purportedly is involved in developing delayed-type hypersensitivity reactions by increasing chemokine production, which promotes the recruitment of inflammatory cells such as monocytes and neutrophils to the local area. By blocking the effects of IL-17 localized autoimmune reactions associated with ankylosing spondylitis, pathology could be blocked while minimizing the systemic immunosuppression associated with tumor necrosis factor (TNF) blockers, which are often used in treatment. Administered subcutaneously, 75 or 150 mg, monthly. Novartis International AG, Basel, Switzerland Phase III trial ongoing	Corticosteroids Disease-modifying antirheumatic drugs Nonsteroidal anti-inflammatory drugs Physical therapy Sulfasalazine (Azulfidine) TNF inhibitors	Reduced signs and symptoms Improved mobility Improved quality of life
KIT tyrosine kinase inhibitor masitinib for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	RA is a chronic inflammatory disease causing polyarthritis with frequent progression to permanent joint damage, deformity, and functional disability. Biologic therapies have become standard of care for patients with RA that no longer responds to disease-modifying antirheumatic drugs (DMARDs). However, biologics must be administered by injection and are associated with increased incidence of serious infections, including tuberculosis. DMARDs with improved efficacy and tolerability as well as convenient dosing are needed. Masitinib is an orally administered tyrosine kinase inhibitor that purportedly targets the activity of mast cells, which are involved in mediating inflammation in the synovium. Masitinib purportedly targets mast cells through selectively inhibiting KIT, platelet-derived growth factor receptor, Lyn, and to a lesser extent, fibroblast growth factor receptor 3. In clinical trials, masitinib is administered orally, 3 or 6 mg/kg of body weight, daily. AB Science S.A., Paris, France Phase II/III trial ongoing	Corticosteroids Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine Nonsteroidal anti-inflammatory drugs Tocilizumab Tofacitinib (investigational) Tumor necrosis factor-alpha inhibitors	Improved symptom scores as measured by American College of Rheumatology 20/50/70 instruments Improved quality of life

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tabalumab, (LY2127399) for treatment of systemic lupus erythematosus	Patients in whom systemic lupus erythematosus (SLE) has been diagnosed	Investigators have not found a permanent cure for SLE, and current treatments provide only partial relief of symptoms. Tabalumab is a monoclonal antibody that acts against B-cell activating factor (BAFF), a protein related to tumor necrosis factor that promotes survival of B cells as they exit the bone marrow and also prevents them from undergoing apoptosis later. BAFF overexpression was found in a diseased brain and BAFF was subsequently referred to as a B cell–targeted therapy. The drug is delivered by subcutaneous injection every 2 or 4 weeks and taken with standard care. Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing	Belimumab Corticosteroids Cyclophosphamide Methotrexate Tumor necrosis factor-alpha inhibitors Rituximab	Improved SLE Responder Index Improved quality of life
Tofacitinib (Xeljanz) for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	RA is a chronic inflammatory disease causing polyarthritis with frequent progression to permanent joint damage, deformity, and functional disability. Tofacitinib (Xelijanz) is a selective and potent oral tyrosine kinase inhibitor that is a new targeted disease-modifying antirheumatic drug (DMARD) for treating RA. Tofacitinib inhibits a Janus kinase (JAK 3) signaling pathway believed to mediate several processes involved in chronic inflammatory diseases, such as antibody production by B cells, production of rheumatic factor and activation of T cells. By inhibiting the JAK 3 pathway, tofacitinib may suppress the inflammatory reactions that are the basis of RA. In trials, tofacitinib was administered in once daily, 20 mg, or twice daily, 1, 3, 5, 10, and 15 mg. A therapy targeted to reducing RA-specific inflammatory processes in the way tofacitinib purports to might provide better symptom control with fewer adverse events than other DMARDs or nonsteroidal anti-inflammatory drug-activated anti-inflammatory pathways. FDA approved the drug for a dosage of 5 mg, twice daily, for adults with moderate to severe, active RA whose disease has had an inadequate response or who are intolerant to methotrexate. Tofacitinib may be used alone or in combination with methotrexate or other nonbiologic DMARDs. Pfizer, Inc., New York, NY FDA approved Nov 2012 as 1st new oral DMARD for RA in more than 10 years and 1st JAK inhibitor approved	Corticosteroids DMARDS: hydroxychloroquine, methotrexate, sulfasalazine Nonsteroidal anti-inflammatory drugs Tocilizumab Tumor necrosis factor-alpha inhibitors	Reduced inflammation Improved symptoms Improved activities of daily living Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Urate transport inhibitor (lesinurad) for treatment of hyperuricemia and allopurinol-refractory gout	Patients in whom hyperuricemia has been diagnosed and thus are at high risk of acute gout	Only 30% to 40% of gout patients respond adequately to the available allopurinol. Lesinurad (RDEA594) is a selective urate transporter inhibitor. Inhibition leads to uric acid excretion to reduce uric acid and crystal formation to potentially alleviate symptoms of acute gout. Ardea Biosciences, Inc., acquired Jun 2012 by AstraZeneca, London, UK Phase III trials ongoing	Treatment: Colchicine Nonsteroidal anti-inflammatory drugs Steroids Prophylaxis: Allopurinol Febuxostat Probenecid	Reduced accumulation of uric acid and crystal formation Reduced acute flares

Table 2. AHRQ Priority Condition: 02 Cancer: 165 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
5-Aminolevulinic acid fluorescence guidance for identifying glioma-clear surgical margins	Patients undergoing surgery for glioma	Complete surgical resection of glioma improves outcomes in patients who are eligible for surgery; however, the highly invasive nature of glioma and the high degree of similarity between glioma tumors and surrounding healthy brain tissue make complete surgical resection and identification of clear surgical margins difficult. 5-Aminolevulinic acid (5-ALA) is a small-molecule prodrug that is converted to protoporphyrin IX (PIX) in neoplastic cells, but not in normal cells. Illuminating PIX with ultraviolet light induces fluorescence in the visible light spectrum, potentially serving as a marker for glioma tissue. Researchers postulate that surgical resection guided by the pattern of PIX fluorescence could increase the percentage of glioma tissue removed, thereby improving outcomes. 5-ALA is administered as an oral medication about 3–5 hours before surgery. Medac GmbH, Hamburg, Germany Phase III trial ongoing; commercially available as Gliolan® in Europe	Standard surgical resection without fluorescence	Increased overall survival Increased progression-free survival Improved quality of life
Abiraterone (Zytiga) for treatment of castration-resistant prostate cancer	Patients with metastatic castration-resistant prostate cancer (mCRPC)	Median overall survival for patients with mCRPC is only about 18 months. Administered in combination with prednisone, abiraterone (Zytiga™) inhibits a cytochrome P-450 subunit (CYPC17) responsible for a step in the androgen biosynthetic pathway. mCRPC may escape androgen inhibition/removal through autocrine androgen signaling/upregulation of the androgen receptor. Blocking the tumor cell's ability to produce testosterone and/or further reducing extra-gonadal androgen generation may inhibit tumor growth. Janssen Biotech unit of Johnson & Johnson, New Brunswick, NJ FDA approved Apr 2011 for treating patients who have previously undergone treatment with docetaxel; FDA approved Dec 2012 for treating patients who are chemotherapy naïve	Cabazitaxel Docetaxel Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Afatinib (BIBW 2992, Tomtovok) for treatment of breast cancer	Patients in whom HER2-positive breast cancer has been diagnosed	Afatinib (BIBW 2992, Tomtovok™, previously Tovok) is a small-molecule, irreversible inhibitor of both epidermal growth factor receptor (EGFR) (HER1) and HER2 receptor tyrosine kinases; these receptor tyrosine kinases are seen overexpressed in breast cancers (about 20% of patients). Targeted EGFR-like receptor inhibition in these cancers has a high relative success rate. Although multiple receptor tyrosine kinases are available, afatinib is unique in that its inhibition is irreversible. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials ongoing	Lapatinib plus capecitabine Trastuzumab plus chemotherapy (e.g., paclitaxel, docetaxel, vinorelbine, capecitabine) Trastuzumab plus lapatinib	Increased overall survival Increased progression-free survival Improved quality of life
Afatinib (BIBW 2992, Tomtovok) for treatment of head and neck cancer	Patients in whom head and neck cancer has been diagnosed	Afatinib (BIBW 2992, Tomtovok™, previously Tovok) is a small-molecule, irreversible inhibitor of both epidermal growth factor receptor (EGFR) (HER1) and HER2 receptor tyrosine kinases. Targeted EGFR-like receptor inhibition in head and neck cancers has a high relative success rate. Although multiple receptor tyrosine kinase inhibitors are available, afatinib is unique in that its inhibition is irreversible. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials ongoing	Cetuximab (Erbitux®)	Increased overall survival Increased progression-free survival Improved quality of life
Afatinib (BIBW 2992, Tomtovok) for treatment of nonsmall cell lung cancer	Patients in whom nonsmall cell lung cancer (NSCLC) has been diagnosed	Afatinib (BIBW 2992, Tomtovok™, previously Tovok) is a small-molecule, irreversible inhibitor of both epidermal growth factor receptor (EGFR) (HER1) and HER2 receptor tyrosine kinases. EGFR (HER1) and HER2 receptor tyrosine kinases are mutated/overexpressed in NSCLC in about 10% of patients; targeted EGFR-like receptor inhibition in these cancers has a high relative success rate. Although multiple receptor tyrosine kinase inhibitors are available, Afatinib is unique in that its inhibition is irreversible. Boehringer Ingelheim, GmbH, Ingelheim, Germany 1 phase III trial complete and met primary endpoint; additional phase III trials ongoing	1st-line NSCLC: platinum based chemotherapy 2nd- and 3rd-line NSCLC: docetaxel, erlotinib, pemetrexed	Increased overall survival Increased progression-free survival Improved quality of life

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	Current 2nd-line and adjunctive treatments for advanced, recurrent CRC have poor response rates and this patient population has a poor overall prognosis. Aflibercept (Zaltrap™) is a vascular endothelial growth factor (VEGF)-signaling inhibitor that contains multiple copies of the VEGF receptor extracellular domain designed to bind VEGF. It is an antiangiogenic agent intended to reduce tumor vascularization, thereby inhibiting tumor growth. Being tested as an adjunct to the standard chemotherapy treatment of leucovorin, irinotecan, and 5-fluorouracil (5-FU). Collaboration between Regeneron Pharmaceuticals, Inc., Tarrytown, NY, and Sanofi, Paris, France FDA approved Aug 2012 for use with the chemotherapy regimen folinic acid, fluorouracil and irinotecan (FOLFIRI) for treating adults with CRC whose tumors have progressed after treatment with an oxaliplatin-containing regimen	5-FU-based therapy plus bevacizumab FOLFIRI (folinic acid [leucovorin], 5-FU, and irinotecan) FOLFIRI plus cetuximab or panitumumab Irinotecan with or without cetuximab	Increased overall survival Increased progression-free survival Improved quality of life
Albumin-coupled doxorubicin (INNO-206) for treatment of soft tissue sarcoma	Patients in whom unresectable soft tissue sarcoma has been diagnosed	Patients with soft tissue sarcoma have few treatment options and a poor prognosis. INNO-206 is a novel formulation of doxorubicin, a chemotherapy compound approved for use in treating soft tissue sarcoma, intended to provide targeted delivery of the compound to tumors. In this formulation, doxorubicin is coupled to albumin via an acid-sensitive linker. Circulating albumin preferentially accumulates in tumor tissues, which also generate acidic microenvironments. In these acidic conditions, the linker is cleaved, potentially releasing active doxorubicin locally at the site of the tumor. CytRx Corp., Los Angeles, CA Phase IIb initiated Dec 2011; FDA granted orphan drug status	Doxorubicin	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Algenpantucel-L (HyperAcute-Pancreas) immunotherapy for pancreatic cancer	Patients in whom surgically resectable (stage I or II) adenocarcinoma of the pancreas has been diagnosed	Patients in whom pancreatic cancer has been diagnosed have a 5-year survival rate of about 5%. Algenpantucel-L immunotherapy is a treatment intended to stimulate an immune response against the patient's pancreatic cancer cells. The therapy consists of 2 allogeneic pancreatic cancer cell lines that have been genetically engineered to express the enzyme alpha (1,3) galactosyl transferase, which marks the cells with a nonhuman carbohydrate that elicits a strong antibody immune response. Antibody binding to the cell lines leads to complement-mediated cell lysis, potentially leading to the uptake of pancreatic cancer antigens and a systemic immune response against the patient's cancer. In current clinical trials, HyperAcute®-Pancreas is being administered by injection in combination with standard of care postoperative chemotherapy. NewLink Genetics Corp., Ames, IA Phase III trial ongoing under special protocol assessment with FDA; FDA granted fast track and orphan drug status	Standard chemotherapy alone (gemcitabine plus or minus 5-fluorouracil)	Increased overall survival Increased progression-free survival Improved quality of life
Allogeneic DNA immunotherapy (Allovectin-7) for advanced melanoma	Patients in whom stage III or IV melanoma has been diagnosed	Advanced melanoma is associated with a poor prognosis. New, effective treatments with acceptable safety profile are needed. Allovectin-7® is a DNA-based immunotherapeutic composed of a lipid encapsulated plasmid expressing human leukocyte antigen (HLA)-B7 and beta2 microglobulin (required to generate a functional major histocompatibility complex ([MHC] I molecule). The therapeutic is designed to stimulate innate and adaptive immune responses against local and distant tumors. Expression of tumor antigens in the context of the MHC I molecule HLA-B7 generates an allogeneic response against tumors; lipid/DNA complexes have adjuvant activity for the vaccine. It is given as an intratumoral injection on an outpatient basis. Vical, Inc., San Diego, CA Phase III trial ongoing; FDA granted orphan drug and fast track status for invasive and metastatic melanoma	Dacarbazine Interferon Interleukin-2 Ipilimumab Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Angiopoietin 1/2 neutralizing peptibody (trebananib, AMG 386) for treatment of ovarian, peritoneal, and fallopian tube cancers	Patients with epithelial ovarian, primary peritoneal, or fallopian tube cancer that is partially platinum sensitive or resistant	Patients with treatment-resistant ovarian, peritoneal, or fallopian tube cancer have a poor prognosis, and more effective treatments are needed. Trebananib is a peptibody that binds to the signaling molecules angiopoietin 1 and angiopoietin 2 and consists of a peptide specific for angiopoietin 1/2 fused to the Fc region of a human antibody. It is intended to block activation of the TIE2 receptor by angiopoietin 1/2; the angiopoietin/TIE2 pathway acts in parallel with the vascular endothelial growth factor (VEGF)/VEGF receptor pathway to promote angiogenesis. The drug represents a novel 1st-in-class neutralizing inhibitor of angiopoietin 1/2. In clinical trials for ovarian cancer, trebananib is being administered in combination with pegylated liposomal doxorubicin or paclitaxel. Amgen, Inc., Thousand Oaks, CA Phase III trials ongoing	Docetaxel Etoposide Gemcitabine Liposomal doxorubicin Paclitaxel Topotecan	Increased overall survival Increased progression-free survival Improved quality of life
Antibody-drug conjugate (gemtuzumab ozogamicin) for treatment of acute myeloid leukemia	Patients in whom acute myeloid leukemia (AML) has been diagnosed	With current treatments, the 5-year survival rate for patients with AML ranges from 20% to 70%, depending on disease subtype. Gemtuzumab ozogamicin is a treatment for AML that conjugates a highly toxic chemotherapy agent to a monoclonal antibody specific for a cell surface marker expressed on most AML cells (CD33). The conjugate is intended to preferentially target AML cells with the toxic chemotherapy. Gemtuzumab ozogamicin is administered intravenously; a variety of dosing schedules have been reported. During a recently completed phase III trial, investigators administered gemtuzumab ozogamicin in combination with a standard chemotherapy regimen using daunorubicin and cytarabine. Pfizer, Inc., New York, NY FDA approved under accelerated approval in 2000 for treating AML. Drug was withdrawn from U.S. market in 2010 after negative study results and high toxicity observed in postmarket trials. Drug remains available in Europe, where trials have shown benefit using an altered dosing scheme. Pfizer is analyzing data to determine whether to make new FDA submissions. The drug is available in the U.S. only to patients already taking it.	Standard chemotherapy with daunorubicin and cytarabine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Antibody-drug conjugate (glembatumumab vedotin) for treatment-resistant breast cancer	Patients with advanced, treatment-refractory or resistant, glycoprotein NMB (GPNMB)-expressing breast cancer	Breast cancer is responsible for about 40,000 deaths in the U.S. each year. Therapies that can improve survival rates and/or quality of life for these patients are needed. Glembatumumab vedotin is an antibody-drug conjugate that links a highly toxic chemotherapy drug to a monoclonal antibody specific for GPNMB, a protein known to be overexpressed in some breast tumors. GPNMB has been implicated in enhancing the metastatic potential of breast cancer cells, particularly the triple-negative breast cancer subtype. A companion diagnostic test to determine whether a patient's cancer expresses GPNMB will be used to determine patient eligibility for treatment with glembatumumab vedotin. Celldex Therapeutics, Inc., Needham, MA Phase IIb trial complete; FDA granted fast track status for treating treatment-resistant or refractory breast cancer	Albumin-bound paclitaxel Capecitabine Docetaxel Doxorubicin Eribulin Gemcitabine Ixabepilone Liposomal doxorubicin Paclitaxel Vinorelbine	Increased overall survival Increased progression-free survival Improved quality of life
Antibody-drug conjugate (inotuzumab ozogamicin) for treatment-refractory acute lymphoblastic leukemia	Patients in whom recurrent or treatment-refractory acute lymphoblastic leukemia (ALL) has been diagnosed	Among patients who experience an ALL relapse, only about 30% will achieve long-term remission with subsequent therapies. Inotuzumab ozogamicin is an antibody-drug conjugate that links the cytotoxic antibiotic calicheamicin to an antibody specific for CD22, a marker highly expressed by ALL cells. In clinical trials, inotuzumab ozogamicin monotherapy is being administered once weekly, by intravenous infusion. Pfizer, Inc., New York, NY Phase III trial ongoing	Various combinations of the following chemotherapy agents: Anthracyclines Asparaginase Cyclophosphamide Cytarabine (ara-C) Epipodophyllotoxins Vincristine	Increased overall survival Increased progression-free survival Improved quality of life
Antibody-drug conjugate (inotuzumab ozogamicin) for treatment-refractory or recurrent non-Hodgkin's lymphoma	Patients with treatment-resistant or recurrent CD20- and CD22-positive non-Hodgkin's lymphoma (NHL) who are not candidates for high-dose chemotherapy	With current treatment options, patients with recurrent or treatment-resistant NHL have a poor prognosis. Only 5% to 10% of patients are alive 2 years after diagnosis. Cases of NHL typically express B-cell cell-surface markers such as CD20 and CD22. Although an anti-CD20 antibody (rituximab) has been used in treating NHL for several years, an effective treatment targeting CD22 is not yet available. Inotuzumab ozogamicin is a novel antibody-drug conjugate that couples a CD22-specific antibody to a highly toxic chemotherapeutic agent. In clinical trials, inotuzumab ozogamicin (1.8 mg/m^2 of body surface area by intravenous infusion once every 4 weeks) is being administered as an adjunct to treatment with rituximab. Pfizer, Inc., New York, NY Phase III trial ongoing	Combination chemotherapy including one or more of the following: Cisplatin Cyclophosphamide Dexamethasone Doxorubicin Etoposide Gemcitabine Lenalidomide Prednisone, Procarbazine, Rituximab Vincristine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anti-CS1 monoclonal antibody (elotuzumab) for treatment of multiple myeloma	Patients in whom newly diagnosed multiple myeloma or relapsed/refractory multiple myeloma has been diagnosed	Although treatments for multiple myeloma have improved, the median life expectancy for patients in whom multiple myeloma is diagnosed is only 5–7 years. Immunotherapeutic options for multiple myeloma are not available. CS1 has been identified as a glycoprotein expressed preferentially on multiple myeloma cells. Elotuzumab is a humanized, monoclonal antibody specific for CS1 that purportedly has an anticancer effect through antibody-dependent cellular cytotoxicity. In clinical trials, elotuzumab is being administered as an adjunct to conventional therapy with a combination of lenalidomide and dexamethasone. Bristol-Myers Squibb, New York, NY Phase III trials ongoing	For stem cell transplant eligible patients, 1st-line therapy such as: Bortezomib/ dexamethasone Cyclophosphamide/ dexamethasone For patients ineligible for stem cell transplant, 1st-line therapy such as: Bortezomib/ dexamethasone Lenalidomide/low-dose dexamethasone, Melphalan/ prednisone plus bortezomib	Increased overall survival Increased progression-free survival Improved quality of life
Anti-CTLA-4 monoclonal antibody (ipilimumab, Yervoy) for treatment of advanced nonsmall cell lung cancer	Patients with recurrent or metastatic nonsmall cell lung cancer (NSCLC) who have not received previous systemic therapy	Only about 25% of patients with advanced NSCLC respond to standard 1st-line therapies such as carboplatin/paclitaxel. Ipilimumab (Yervoy™) is a 1st-in-class, targeted, anticytotoxic, T-lymphocyte antigen 4 therapy; it is intended to block the activity of cytotoxic T lymphocyte antigen 4, which could lead to increased antitumor cytotoxic activity (reduce immune tolerance to tumor cells). As 1st-line NSCLC treatment in trials, ipilimumab is being administered in combination with carboplatin and paclitaxel. Bristol-Myers Squibb, New York, NY Phase III trial ongoing	Bevacizumab Carboplatin/ paclitaxel Carboplatin/ pemetrexed Cisplatin/pemetrexed Erlotinib Crizotinib	Increased overall survival Increased progression-free survival Improved quality of life
Anti-CTLA-4 monoclonal antibody (ipilimumab, Yervoy) for treatment of metastatic hormone-refractory prostate cancer	Patients in whom metastatic, chemotherapy-naïve or docetaxel-treated castration-resistant prostate cancer (CRPC) has been diagnosed	Men with progressive metastatic CRPC have a poor prognosis and few treatment options. Ipilimumab (Yervoy™) is a 1st-in-class targeted anticytotoxic T-lymphocyte antigen 4 therapy; it is intended to block the activity of cytotoxic T-lymphocyte antigen 4, which could lead to increased antitumor cytotoxic activity (reduce immune tolerance to tumor cells). Bristol-Myers Squibb, New York, NY Phase III trials ongoing	Abiraterone Cabazitaxel Docetaxel Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Antifolate receptor monoclonal antibody (farletuzumab) for treatment of ovarian cancer	Patients with recurrent ovarian cancer that is platinum-sensitive, platinum-resistant, or platinum-refractory	Patients with recurrent ovarian cancer have median overall survival times of less than 2 years and few treatment options. Farletuzumab is a monoclonal antibody specific for the folate receptor, which is expressed on the majority of ovarian cancer cells, but not on cells of normal tissues. Farletuzumab's action purportedly leads to antibody-dependent cell-mediated cytotoxicity of folate-receptor-expressing cells. In late-phase clinical trials, farletuzumab is being administered intravenously, once weekly, at a dose of 1.25 or 2.5 mg/kg of body weight. In platinum-sensitive disease, farletuzumab is being tested in combination with carboplatin/taxane doublet therapy. In platinum-resistant/refractory disease, farletuzumab is being tested in combination with taxane monotherapy. Morphotek, Exton, PA, a subsidiary of Eisai Co., Ltd., Tokyo, Japan Phase III trial in platinum-resistant disease terminated in Dec 2011 after determination by Independent Data Monitoring Committee that trial was unlikely to meet primary endpoint; phase III trial in platinum-sensitive disease ongoing	Platinum-sensitive ovarian cancer: combination chemotherapy including one or more of the following: Carboplatin Docetaxel Gemcitabine Paclitaxel Pegylated liposomal doxorubicin Topotecan Platinum-refractory ovarian cancer: Docetaxel Etoposide Gemcitabine Paclitaxel Pegylated liposomal doxorubicin Topotecan	Increased overall survival Increased progression-free survival Improved quality of life
Anti-GD2 monoclonal antibody (ch14.18) for treatment of neuroblastoma	Patients with high-risk neuroblastoma who have undergone induction therapy and autologous stem cell transplantation	Current treatments for patients with high-risk neuroblastoma result in 5-year survival rates of only about 25% to 35%. A monoclonal antibody, ch14.18 is specific for a tumor-associated disialoganglioside, GD2, that exhibits low levels of expression on normal tissues (e.g., neurons, skin melanocytes, peripheral sensory nerve fibers). It purportedly targets neuroblastoma cells via antibody-dependent, cell-mediated cytotoxicity. In clinical trials, ch14.18 was administered in combination with cytokines (granulocyte macrophage colony-stimulating factor and interleukin-2) that enhance immune response and the standard neuroblastoma maintenance therapy isotretinoin. United Therapeutics Corp., Silver Spring, MD, in collaboration with the National Cancer Institute, Bethesda, MD Phase III trial complete; company lists phase III trials as ongoing but status not updated in National Clinical Trials database since Aug 2011; orphan drug designation in U.S. and Europe	Isotretinoin	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Antigen-specific cancer immunotherapeutic (GSK2132231A) for advanced melanoma	Patients with stage IIIB or IIIC cutaneous melanoma that expresses melanoma antigenic epitope (MAGE)-A3 antigen who have macroscopic lymph node involvement suitable for surgery	Patients with stage III melanoma frequently experience disease recurrence after surgical resection of the primary tumor. Current immunotherapies used in the adjuvant setting have shown little effect on the duration of overall survival in this patient population. GSK2132231A is a peptide-based therapeutic vaccine directed at the cancer-specific antigen MAGE-A3, which is expressed by a significant proportion of melanomas. It is being tested in the adjuvant setting for treating melanoma. GSK2132231A is being administered as a course of 13 injections over 27 months in a multicenter, international phase III trial of 1,349 patients. GlaxoSmithKline, Middlesex, UK Phase III trial ongoing	Granulocyte-macrophage colony stimulating factor Interferon-alpha Interleukin-2 Radiation therapy	Increased overall survival Increased progression-free survival Improved quality of life
Aurora A kinase inhibitor (alisertib) for treatment of peripheral T-cell lymphoma	Patients in whom relapsed/refractory peripheral T-cell lymphoma (PTCL) has been diagnosed	Current treatment options for relapsed/refractory PTCL are largely palliative and generate responses in fewer than 50% of patients (with the exception of brentuximab vedotin for the anaplastic large cell lymphoma [ALCL] subtype). Alisertib is an Aurora A kinase inhibitor under study for treating PTCL. Aurora A kinase is an important regulator of the mitotic spindle and is required for progression through the mitotic phase of the cell cycle. Inhibition of aurora A has been shown to cause mitotic errors, potentially leading to aneuploidy, apoptosis, and/or cellular senescence. Alisertib is administered orally, 50 mg, twice daily. Millennium Pharmaceuticals, Inc., subsidiary of Takeda Pharmaceutical Co., Ltd., Osaka, Japan Phase III trials ongoing	Alemtuzumab Brentuximab vedotin (ALCL subtype only) Bortezomib Cyclosporine (angioimmunoblastic T-cell lymphoma subtype only) Denileukin diftitox Gemcitabine Pralatrexate Radiation therapy Romidepsin	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Autologous vascularized lymph node transfer for mastectomy-associated lymphedema	Patients who have undergone mastectomy	During mastectomy, lymph nodes under the arm closest to the affected breast are removed, which often leads to chronic swelling and soreness in the arm (lymphedema). Lymphedema 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; 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. Before node implantation, scar tissue may be excised to remove blockage of lymph vessels. Service de Chirurgie Thoracique, Hôpital Européen Georges Pompidou, Paris, France Procedure appears to be done rarely in U.S.; randomized trial beginning in France	Compression garments Physical therapy	Ability to stop physiotherapy Decreased, or resolved lymphedema assessed by isotopic lymphangiography Improved skin elasticity Improved mobility Resolution of pain
Automated breast ultrasound for breast cancer screening of patients with dense breast tissue	Women with dense breast tissue who are undergoing screening mammography	The presence of dense breast tissue limits the accuracy of screening mammography, and screening mammography's sensitivity for tumors in women with dense breast tissue is as low as 30% to 50%. Ultrasound imaging has been used for some time in breast imaging; however, it is not routinely used in screening of asymptomatic women in the U.S. The somo.v automated breast ultrasound system generates 3-dimensional images of the breast in an automated fashion. The system is under study as an adjunct to conventional mammographic screening in women with dense breast tissue. U-Systems, Inc., acquired Nov 2012 by General Electric Co., Fairfield, CT FDA cleared for diagnostic use; premarket approval application submitted to FDA for screening indication. In Sept 2012, the system received FDA approval	Screening mammography alone Screening magnetic resonance imaging	Increased breast cancer sensitivity and specificity Improved positive predictive and negative values for breast cancer
Axitinib (Inlyta) for treatment-resistant advanced renal cell carcinoma	Patients previously treated for metastatic renal cell carcinoma (RCC)	Axitinib is an oral and selective inhibitor of vascular endothelial growth factor (VEGF) receptor 1 (VEGFR1), VEGFR2 and VEGFR3, which appear to have roles in tumor growth, vascular angiogenesis, and metastatic progression of cancer (the spread of tumors). Pfizer, Inc., New York, NY FDA approved Jan 2012 for RCC that has not responded to prior treatment	Everolimus Sorafenib Temsirolimus Tivozanib (in development)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Belagenpumatucel-L (Lucanix) for treatment of nonsmall cell lung cancer	Patients with advanced (stage III or IV) nonsmall cell lung cancer (NSCLC) whose disease has responded to 1st-line platinum-based chemotherapy	Five-year survival rates for patients with advanced NSCLC are less than 15% with current treatments. Belagenpumatucel-L (Lucanix™) is an allogeneic tumor-cell vaccine intended to delay disease progression after successful 1st-line treatment with platinum-based chemotherapy. The vaccine consists of 4 NSCLC cell lines that are administered intradermally once monthly for up to 2 years. The tumor-cell lines have been genetically modified to express an antisense version of transforming growth factor beta 2 (TGFB2), which is intended to inhibit the expression of TGFB2. TGFB2 has been shown to have antagonistic effects on various components of the immune system, and the developer hypothesizes that its inhibition could enhance an immune response generated by the tumor-cell vaccine. NovaRx, San Diego, CA Phase III trial ongoing under a special protocol assessment with FDA; FDA granted fast track status	Watchful waiting after successful 1st-line therapy Maintenance therapy (various chemotherapy regimens determined according to NSCLC subtype)	Increased overall survival Increased progression-free survival Improved quality of life
Bevacizumab (Avastin) for treatment of ovarian cancer	Patients in whom advanced or recurrent ovarian cancer has been diagnosed	Ovarian cancer is the 2nd deadliest cancer after pancreatic cancer; no new 1st-line treatment options have been made available in the past decade; new treatment options are needed. Bevacizumab (Avastin®) is a monoclonal antibody on the market for several other indications; intended to bind vascular endothelial growth factor (VEGF) and prevent the interaction of VEGF with its receptors (Flt-1 and KDR) on the surface of endothelial cells. By preventing the interaction of VEGF with its receptors, bevacizumab prevents the proliferation of endothelial cells and the formation of new blood vessels needed to nourish growing tumors. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Multiple phase III trials ongoing; preliminary data has been reported from 4 phase III trials	Combination chemotherapy including one or more of the following: Carboplatin Gemcitabine Paclitaxel Pegylated liposomal doxorubicin Topotecan Paclitaxel monotherapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bispecific T-cell-engager (BiTE) anti-CD19 antibody (blinatumomab) for treatment of acute lymphoblastic leukemia	Patients in whom relapsed/ refractory Philadelphia chromosome–negative acute lymphoblastic leukemia (ALL) has been diagnosed and patients in whom minimal residual disease-positive ALL has been diagnosed	No new treatments for Philadelphia chromosome–negative relapsed/refractory ALL have been developed in 30 years; 5-year survival for this patient population is only 7%. Blinatumomab is the most advanced molecule from a novel class of antibody-based compounds intended to link tumor cells to cytotoxic T cells; the molecule consists of 2 separate antibody antigen binding domains: (1) specific for CD19, an antigen expressed by the immature lymphocytes expanded in ALL, and (2) specific for CD3 a molecule expressed on the surface of cytotoxic T cells; blinatumomab purportedly leads to tumor apoptosis by bridging an interaction between tumor cells and T cells. Micromet, Inc., Rockville, MD, acquired in Jan 2012 by Amgen, Thousand Oaks, CA Phase II trials ongoing; results released May 2012; FDA granted orphan drug status	Relapsed/refractory ALL: Anthracyclines (doxorubicin, daunorubicin), Asparaginase Cyclophosphamide cytarabine (ara-C) Epipodophyllotoxins (etoposide, teniposide) Vincristine Minimal residual disease–positive ALL: No current standard of care	Increased overall survival Increased progression-free survival Improved quality of life
Blocking radiation exposure of limb-draining lymph nodes for prevention of lymphedema	Patients with early-stage breast cancer who are undergoing postsurgical adjuvant radiation therapy	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 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; it is considered generally incurable and can severely restrict activity. 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; patients were limited to those with early-stage breast cancer with negative sentinel lymph node biopsy or only micrometastases to sentinel lymph nodes. Mayo Clinic, Rochester, MN Unphased small trial ongoing	Standard external beam radiation therapy	Decreased rate of lymphedema Decreased radiation dose to critical lymph nodes Equivalent cancer-related progression-free survival Equivalent cancer-related overall survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
BRAF kinase inhibitor (dabrafenib) for treatment of metastatic melanoma	Patients in whom metastatic melanoma characterized as having activated *BRAF* mutations has been diagnosed	Dabrafenib (GSK2118436) is an activated BRAF kinase inhibitor. The developer describes it as "a highly potent and selective adenosine triphosphate competitive BRAF inhibitor with more than 100-fold selectivity for mutant (mut) BRAF. It displays dose-dependent inhibition of MEK and extracellular signal-regulated kinase phosphorylation in mut BRAF cell lines and tumor regression in xenograft models." GlaxoSmithKline, Middlesex, UK Positive results reported in Jun 2012 for phase III trial of dabrafenib as a monotherapy; earlier phase trials ongoing in combination with the MEK inhibitor trametinib; new drug application submitted to FDA in Aug 2012	High dose interleukin-2 Dacarbazine Ipilimumab Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life
Brentuximab vedotin (Adcetris) for treatment of recurrent/refractory anaplastic large cell lymphoma	Patients in whom recurrent and/or chemotherapy-refractory systemic CD30-positive anaplastic large cell lymphoma (ALCL) has been diagnosed	Brentuximab vedotin (Adcetris™, SGN-35 or cAC10-vcMMAE) is a monoclonal antibody-drug conjugate; monoclonal antibody portion of the drug recognizes the CD30 antigen present on some ALCLs; drug portion is the highly cytotoxic monomethyl auristatin E, which inhibits mitosis by blocking tubulin polymerization. For 2 indications: (1) treating patients with Hodgkin's lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least 2 prior multiagent chemotherapy regimens in patients who are not ASCT candidates, and (2) treating patients with systemic ALCL after failure of at least 1 prior multiagent chemotherapy regimen. Seattle Genetics, Inc., Bothell, WA FDA approved Aug 2011 for treating systemic ALCL after failure of at least 1 prior multiagent chemotherapy regimen	Allogeneic stem cell transplantation ASCT	Increased overall survival Increased progression-free survival Improved quality of life
Brentuximab vedotin (Adcetris) for treatment of recurrent/refractory Hodgkin's lymphoma	Patients in whom recurrent and/or radiation/chemo-therapy-refractory Hodgkin's lymphoma has been diagnosed	Hodgkin's lymphoma is a CD30-positive hematologic malignancy with limited salvage therapy options. Brentuximab vedotin (Adcetris, SGN-35 or cAC10-vcMMAE) is a monoclonal antibody-drug conjugate. Seattle Genetics, Inc., Bothell, WA FDA approved Aug 2011, for treating patients with Hodgkin's lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least 2 prior multi-agent chemotherapy regimens in patients who are not ASCT candidates. Phase III trial in patients at high risk of relapse post-ASCT ongoing; phase I trial in patients with newly diagnosed disease ongoing	Standard of care	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cabozantinib (Cometriq) for treatment of advanced medullary thyroid cancer	Patients in whom unresectable, locally advanced, or metastatic medullary thyroid cancer has been diagnosed	No treatments exist for advanced medullary thyroid cancer (MTC) that target MET, which may be responsible for drug resistance in patients treated with current receptor tyrosine kinase inhibitors. Cabozantinib (Cometriq™) is an oral, small-molecule, receptor tyrosine kinase inhibitor that targets MET and vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2). MET plays key roles in proliferation, migration, invasion, and angiogenesis; overexpression of the hepatocyte growth factor ligand of MET and activation of the MET pathway supports tumors; VEGFR2 and MET allow tumors to overcome hypoxia and stimulate angiogenesis. VEGF and MET also appear to stimulate osteoclasts and osteoblasts, thus showing potential for treating bone metastasis. Selective anti-VEGF therapies do not inhibit MET, which may be responsible for tumor evasiveness and drug resistance in patients who receive VEGF tyrosine kinase inhibitors, making MET/VEGF co-inhibition an emerging target in cancer therapy. The recommended dose on the labeling approved by FDA in Nov 2012 is for 140 mg orally, taken once daily. Exelixis, Inc., South San Francisco, CA FDA approved Nov 2012 for treating progressive metastatic MTC; labeling carries a black box warning for risk of gastrointestinal perforations and fistulas and hemorrhage	Radiotherapy Sorafenib Sunitinib Vandetanib	Increased overall survival Increased progression-free survival Improved quality of life
Cabozantinib (Cometriq) for treatment of castration-resistant prostate cancer	Patients with castration-resistant prostate cancer (CRPC) that may include bone metastasis	Median overall survival for patients with CRPC is only about 18 months. No treatments for CRPC are available that target MET, which may be responsible for prostate cancer drug resistance in patients treated with current receptor tyrosine kinase inhibitors. Cabozantinib (Cometriq™) is an oral, small-molecule, receptor tyrosine kinase inhibitor that targets MET and vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2). MET plays key roles in proliferation, migration, invasion, and angiogenesis; overexpression of the hepatocyte growth factor ligand of MET and activation of the MET pathway supports tumors; VEGFR2 and MET allow tumors to overcome hypoxia and stimulate angiogenesis. VEGF and MET also appear to stimulate osteoclasts and osteoblasts, thus showing potential for treating bone metastasis. Selective anti-VEGF therapies do not inhibit MET, which may be responsible for tumor evasiveness and drug resistance in patients who receive VEGF tyrosine kinase inhibitors, making MET/VEGF co-inhibition an emerging target in cancer therapy. In trials, administered 100 mg, once daily. Exelixis, South San Francisco, CA Phase II and phase III trials ongoing	Abiraterone Cabazitaxel Denosumab Docetaxel Enzalutamide Radium-223 (in development)	Reduced bone metastasis Reduced bone pain Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Carfilzomib (Kyprolis) for treatment of multiple myeloma	Patients in whom recurrent or treatment-refractory multiple myeloma has been diagnosed	Multiple myeloma patients typically respond to current therapy only 11% of the time and typically survive for only 6–10 months after diagnosis, so effective treatments are needed. Carfilzomib (Kyprolis™) is a small-molecule inhibitor of the proteasome; the proteasome is responsible for the degradation of cellular proteins, and inhibition of the proteasome can lead to accumulation of unwanted proteins, cell cycle arrest, and apoptosis. Product labeling states that it is administered intravenously over 2–10 minutes on 2 consecutive days each week for 3 weeks (days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (days 17–28) with a recommended cycle 1 dose of 20 mg/m^2 of body surface area/day and if tolerated increased for cycle 2 and subsequent cycles doses to 27 mg/m^2/day. Onyx Pharmaceuticals, Inc., South San Francisco, CA FDA granted accelerated approval Jul 2012 for treating patients “with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy.”	Combination therapies Cytotoxic chemotherapies (bendamustine, cyclophosphamide, doxorubicin, melphalan, vincristine) Immunomodulatory drugs (lenalidomide, thalidomide) Proteasome inhibitors (bortezomib) Steroids (dexamethasone, prednisone)	Increased overall survival Increased progression-free survival Improved quality of life
CD34-positive cell selection system (CliniMACS) for treatment of acute myeloid leukemia	Patients with acute myeloid leukemia (AML) who are undergoing allogeneic stem cell transplantation (SCT)	Allogeneic SCT is the most effective treatment for AML; however, its use is complicated by potential adverse events including the development of graft-versus-host disease (GVHD), in which donor immune cells attack recipient tissues. Methods to prevent GVHD include pretransplant depletion of the donor T cells thought to be the cause of GVHD. However, no FDA-approved device is available to perform T-cell depletion, and its use has been hampered by the potential for poor engraftment and/or AML relapse in patients treated with processed grafts. The CliniMACS® CD34 reagent system is intended to prepare T-cell depleted stem cell grafts. The system uses CD34 monoclonal antibodies coupled to magnetic particles to isolate CD34-positive hematopoietic stem cells while simultaneously passively removing differentiated T cells. Miltenyi Biotec, GmbH, Bergisch Gladbach, Germany Phase II trial complete; company filed for humanitarian use device exemption with FDA, so phase III trials may not be required for clinical use	Noncommercial, manual methods of T-cell depletion	Improved engraftment rate Increased duration of disease-free survival Improved rate of acute GVHD Improved rate of chronic GVHD

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
CD56-specific antibody-drug conjugate (lorvotuzumab mertansine) for treatment of multiple myeloma	Patients in whom CD56-positive relapsed or relapsed/ refractory multiple myeloma has been diagnosed	Patients in whom relapsed multiple myeloma has been diagnosed have few treatment options and median survival of less than 1 year. Lorvotuzumab mertansine (IMGN901) is a novel antibody-drug conjugate that links the highly cytotoxic agent mertansine to a monoclonal antibody specific for CD56, a cell surface marker expressed on multiple cancer types including multiple myeloma. In ongoing trials, lorvotuzumab mertansine is being administered as an adjunct to a conventional cytotoxic chemotherapy regimen of lenalidomide and dexamethasone. ImmunoGen, Inc., Waltham, MA Phase I trial ongoing; FDA granted orphan drug status	Lenalidomide plus dexamethasone	Increased overall survival Increased progression-free survival Improved quality of life
CD56-specific antibody-drug conjugate (lorvotuzumab mertansine; IMGN901) for treatment of small cell lung cancer	Patients in whom advanced small cell lung cancer (SCLC) has been diagnosed; may be chemotherapy naïve or have received previous systemic chemotherapy treatment	The 5-year survival rate for patients in whom SCLC is diagnosed is only about 15%. Lorvotuzumab mertansine (IMGN901) is a novel antibody-drug conjugate that links the highly cytotoxic agent mertansine to a monoclonal antibody specific for CD56, a cell surface marker expressed on multiple cancer types including small cell lung cancer. In current clinical trials, lorvotuzumab mertansine is being administered as an adjunct to a conventional cytotoxic chemotherapy regimen of carboplatin plus etoposide. ImmunoGen, Inc., Waltham, MA Phase II trial ongoing; FDA granted orphan drug status	Carboplatin plus etoposide	Increased overall survival Increased progression-free survival Improved quality of life
Computer-assisted system (Sedasys) for automated propofol sedation during gastrointestinal endoscopy procedures	Patients who are undergoing propofol-induced sedation during colonoscopy or upper gastrointestinal (GI) procedures	The Sedasys® system integrates physiologic patient monitoring (oxygen saturation, respiratory rate, heart rate, blood pressure, end-tidal carbon dioxide and patient responsiveness) with personalized drug delivery (system automatically responds to signs of over-sedation) for delivery of propofol. The system is intended to enable nonanesthesiologists (i.e., other physicians or nurses) to administer sedation for endoscopic GI procedures. Ethicon Endo-Surgery unit of Johnson & Johnson, New Brunswick, NJ Premarket approval (PMA) rejected by FDA Oct 2010; Ethicon appealed and in Mar 2011 FDA agreed to a 2nd review by the Medical Devices Dispute Resolution Panel, which was scheduled to meet mid-Dec 2011; however, before panel meeting FDA agreed to undertake a 2nd review of the PMA; Ethicon received an approvable letter for Sedasys in Mar 2012	Propofol sedation administered and monitored by anesthesiologist	Successful and safe propofol sedation without need for an anesthesiologist

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Concomitant colorectal cancer screening and annual influenza vaccination program	Patients recommended for routine colorectal cancer (CRC) screening (i.e., between 50 and 75 years of age) who are receiving influenza vaccinations	Although CRC screening methods are widely available and known to be effective in reducing morbidity and mortality from CRC, adherence with the recommended screening guidelines is low. In the annual influenza vaccination and CRC screening (FLU-FOBT) program, nurses in community clinics provide patients seeking annual influenza vaccinations with fecal occult blood tests (FOBT) for CRC screening. University of California, San Francisco Large randomized control trials completed	Primary care physician recommended CRC screening	Increased rate of adherence with CRC screening guidelines Reduced morbidity from CRC Reduced mortality from CRC Reduced costs of care through earlier intervention Reduced health disparities
Crizotinib (Xalkori) for treatment of nonsmall cell lung cancer	Patients with nonsmall cell lung cancer (NSCLC) that harbors a genetic rearrangement that leads to constitutive activation of anaplastic lymphoma kinase (ALK)	ALK is an oncogenic tyrosine kinase that was identified in gene fusions that caused activation of ALK in lymphoblastoma. Crizotinib (Xalkori®) inhibits ALK (and MET kinase) activity; in tumors that are driven by constitutive ALK activity, it may reduce tumor growth and survival. Pfizer, Inc., New York, NY FDA approved Aug 2011 for treating locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test; additional phase III trials ongoing and met primary endpoints	1st-line: combination chemotherapy (e.g., pemetrexed plus cisplatin) 2nd-line: chemotherapy(e.g., docetaxel plus pemetrexed) Erlotinib	Increased overall survival Increased progression-free survival Improved quality of life
Custirsen (OGX-011) for treatment of advanced nonsmall cell lung cancer	Patients in whom nonsmall cell lung cancer (NSCLC) has been diagnosed	Custirsen (OGX-011) is an antisense RNA molecule intended for treating advanced, unresectable NSCLC. It is given intravenously in combination with docetaxel: 3 loading doses of custirsen 640 mg are given over 2 hours in 5–9 days prior to day 1 of cycle 1; then custirsen 640 mg weekly every 21-day cycle. OncoGenex Pharmaceuticals, Inc., Bothell, WA Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel Phase III trials ongoing	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
Custirsen (OGX-011) for treatment of metastatic castration-resistant prostate cancer	Patients in whom castration-resistant prostate cancer (CRPC) has been diagnosed	Median overall survival for patients with CRPC is only about 18 months. Custirsen (OGX-011) is an antisense RNA molecule designed to reduce expression of clusterin, a cell survival protein. Custirsen is an injected agent intended as an adjunct to chemotherapy. OncoGenex Pharmaceuticals, Inc., Bothell, WA Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel Phase III trials (SATURN and SYNERGY) ongoing under FDA special protocol assessment; FDA granted fast track status	Abiraterone Cabazitaxel Docetaxel Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
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) that is intended to be delivered before conventional treatment (surgery, radiotherapy, chemotherapy). The manufacturer asserts that this is when the immune system is best able to mount an immune response. The cytokine mixture is delivered directly to the tumor and nearby lymph nodes 5 times a week for 3 weeks. CEL-SCI Corp., Vienna, VA Phase III trial ongoing	Chemoradiation therapy Surgical resection	Increased overall survival Increased progression-free survival Improved quality of life
Dendritic cell vaccine (ICT-107) for treatment of glioblastoma multiforme	Patients in whom glioblastoma multiforme has been diagnosed who have undergone surgical debulking and chemoradiation therapy	Glioblastoma multiforme is difficult to treat, with few effective options. New therapies that can improve survival and slow disease progression are needed. Personalized dendritic cell vaccine (ICT-107) is a dendritic cell-based therapeutic vaccine targeting multiple autologous tumor associated antigens including AIM2, HER2, gp-100, melanoma antigenic epitope-1, TRP-2, and interleukin-13Ra2 for the potential intradermal treatment of glioblastoma. ImmunoCellular Therapeutics Ltd., Los Angeles, CA Phase IIb trial ongoing; FDA granted orphan drug status in 2010; drug will likely have abbreviated regulatory pathway	Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Digital breast tomosynthesis for mammography screening	Women undergoing routine mammography to screen for breast cancer	A limitation of 2-dimensional (2-D) conventional mammography is that the x-ray images capture information from all tissue constituents along the path from the x-ray source to the detector. Therefore, features of the breast may be obscured by tissues that are in line with the x-ray path and above or below the feature of interest. Digital breast tomosynthesis is x-ray imaging that purports to overcome this potential pitfall by imaging stabilized breast tissue in multiple angles for a given view by rotating the x-ray source in an arc around the target tissue. Breast tissue features that may obscure each other in 1 angle are shifted relative to one another in other angles. By combining the information from each beam angle at the point where it crosses a given depth in the breast under examination, digital breast tomosynthesis can reconstruct images that represent serial slices through the breast. Developers propose that this imaging technology will improve mammographic imaging, potentially resulting in reduced number of recalls for inconclusive results, reduced number of biopsies, and increased cancer detection. The 1st commercially available system was the Selenia® Dimensions® 3D System. This system is a software and hardware upgrade to the existing Selenia Dimensions 2D full-field digital mammography system. Hologic, Inc., Bedford, MA FDA approved for marketing Mar 2011	Standard 2-D digital mammography	Increased sensitivity and specificity Increased predictive values Reduced unnecessary followup procedures
Diphtheria toxin expression vector (BC-819) for treatment of pancreatic cancer	Patients with locally advanced, unresectable pancreatic adenocarcinoma that is amenable to intratumoral injection under ultrasound guidance and expresses high levels of H19	Patients in whom pancreatic cancer has been diagnosed have a 5-year survival rate of only 5%, and effective treatment options are not available. H19 is a noncoding RNA that is expressed in a wide variety of cancers, including many pancreatic cancers, but is not actively transcribed in the majority of adult tissues. BC-819 is a DNA plasmid that encodes the highly cytotoxic diphtheria toxin under the control of the H19 promoter and is intended to induce the expression of diphtheria toxin exclusively in H19-expressing cancer cells. In current clinical trials, BC-819 is administered by intratumoral injection as an addition to the standard systemic chemotherapy drug gemcitabine. BioCancell Therapeutics, Inc., Jerusalem, Israel Phase IIb trial ongoing; FDA granted fast track status	5-Fluorouracil/ leucovorin monotherapy Gemcitabine monotherapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Dual p16-INK4a/ Ki-67 staining test (CINtec PLUS) for triage of abnormal cervical cancer screening results	Patients who have received an abnormal cervical cancer screening test result (e.g., atypical squamous cells of undetermined significance [ASC-US], low-grade squamous intraepithelial lesion [LSIL], Pap negative/human papilloma virus [HPV] positive)	The prognostic value of identification of dysplastic lesions of the uterine cervix cannot be adequately determined by Pap (Papanicolaou) cytology/HPV testing alone, potentially leading to underdiagnosis or delayed treatment of cervical cancer and/or excessive colposcopy procedures. Two molecular markers that may aid in the diagnosis of abnormal Pap results are p16-INK4a (a cell cycle regulator overexpressed in neoplastic cells) and Ki-67 (a marker of cellular proliferation). The CINtec PLUS testing kit detects both of these markers as indicators of cell cycle dysregulation that occurs in transformed cells. In clinical trials, the CINtec PLUS test kit has been used to triage abnormal Pap results and Pap-negative/HPV-positive results. Roche mtm laboratories AG, Heidelberg, Germany Multiple clinical trials completed as of Sept 2011; Conformité Européene (CE) marked; device will initially be available in the U.S. as a Class I in vitro diagnostic product without claims as to an application; the company intends to submit a premarket approval application	Colposcopy HPV testing Watchful waiting with repeat Pap smears	Increased sensitivity and specificity for cases of CIN2+ in women exhibiting ASC-US, LSIL, or Pap-negative/HPV-positive Improved diagnostic accuracy Improved quality of life
EGFRvIII-directed immunotherapy (rindopepimut) for treatment of glioblastoma multiforme	Patients with newly diagnosed glioblastoma multiforme who have undergone primary resection of the bulk tumor	Glioblastoma multiforme typically recurs within 6 months; a splice variant of the epidermal growth factor receptor (EGFR) that is found predominantly on cancerous tissues, EGFRvIII represents a potential target antigen for anticancer therapy. Rindopepimut (CDX-110) is a peptide based vaccine designed to be specific for the EGFRvIII variant, In clinical trials, rindopepimut is being administered in combination with the immune stimulant granulocyte macrophage colony-stimulating factor and standard maintenance chemotherapy (temozolomide). Celldex Therapeutics, Inc., Needham, MA Phase III trial ongoing	Temozolomide alone	Increased overall survival Increased progression-free survival Improved quality of life
Electrical impedance scanner (Nevisense) for melanoma diagnosis	Patients in whom a suspicious skin lesion that may be melanoma has been identified	Distinguishing melanoma from nonmelanotic skin lesions is difficult and requires a significant amount of training. The Nevisense™ uses differences in electrical impedance between melanotic tissue and other tissue types to detect melanoma in an automated fashion; the system consists of an impedance spectrometer and a disposable probe that has microscopic electrode spikes that penetrate the skin. SciBase AB, Stockholm, Sweden International pivotal investigational device exemption SIMPS trial completed (1,900 patients; 2,400 lesions); FDA premarket approval submission planned for 1st quarter 2013; Europe and Australia launch planned for 1st quarter 2013	Dermatologist diagnosis MelaFind computer-aided multispectral dermatoscope	Increased sensitivity and specificity for melanoma Improved positive and negative predictive values Reduction in unnecessary biopsies

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Enzalutamide (Xtandi) for treatment of castration-resistant prostate cancer	Patients in whom metastatic castration-resistant prostate cancer (mCRPC) has been diagnosed	Median overall survival for patients with CRPC is only about 18 months. Most prostate cancer tumors are dependent on androgen signaling for growth and survival; multiple androgen signaling inhibitors are available (e.g., bicalutamide, abiraterone); however, many metastatic prostate cancers do not respond to these therapies or develop resistance. Enzalutamide (Xtandi) is an androgen receptor antagonist that purportedly inhibits androgen signaling at 3 levels by blocking testosterone binding to the androgen receptor, inhibiting nuclear translocation of the activated androgen receptor and inhibiting DNA binding of activated androgen receptor. By more completely inhibiting androgen signaling, enzalutamide may overcome limitations of current antiandrogen therapies. Enzalutamide is an oral drug being tested in both chemotherapy-naïve patients and patients who have previously been treated with docetaxel. Enzalutamide is administered at a dose of 160 mg (four 40-mg capsules) taken orally, once daily. Medivation, Inc., San Francisco, CA Astellas Pharma, Inc., Tokyo, Japan FDA approved Aug 2012, for patients with mCRPC who have previously been treated with docetaxel; trials ongoing for patients with chemotherapy-naïve prostate cancer	Chemotherapy-naïve CRPC: Abiraterone plus prednisone Docetaxel Sipuleucel-T Pretreated CRPC: Abiraterone plus prednisone Cabazitaxel	Increased overall survival Increased progression-free survival Improved quality of life
Everolimus (Afinitor) for treatment of angiomyolipoma	Patients with tuberous sclerosis complex or sporadic lymphangioleio-myomatosis who develop angiomyolipomas	Angiomyolipomas are benign tumors that typically arise in the kidneys of patients with tuberous sclerosis complex or the lung disease lymphangioleiomyomatosis. Large angiomyolipomas may lead to renal failure and/or hemorrhage. No pharmacotherapies are available to treat angiomyolipomas. Loss-of-function mutations in the tuberous sclerosis complex (*TSC*) genes are thought to give rise to angiomyolipomas. A consequence of TSC loss of function is activation of the protein mTOR; therefore, using an mTOR inhibitor such as everolimus may be beneficial in treating these patients. Everolimus is taken once daily, as an oral tablet. Novartis International AG, Basel, Switzerland Phase III trial complete; everolimus is marketed as Afinitor® for multiple cancer indications	Angiomyolipoma embolization	Tumor size reduction Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Everolimus (Afinitor) for treatment of estrogen-receptor-positive breast cancer	Patients with metastatic estrogen-receptor-positive breast cancer that has progressed after 1st-line hormone therapy	For patients whose breast cancer progresses following 1st-line treatment with antiestrogen therapy, followup antiaromatase therapy may delay progression; however, not all patients respond. Everolimus (Afinitor®) is a small-molecule inhibitor of the protein mTOR, which is a central regulator of cell growth. Inhibition of mTOR by everolimus has been demonstrated to be effective in treating multiple cancer types (e.g., renal cell carcinoma, astrocytoma); however, its use in breast cancer treatment has not yet been approved. In the current clinical trial, everolimus is being administered in combination with the 2nd-line hormone therapy exemestane. Novartis International AG, Basel, Switzerland FDA approved Jul 2012 for treating postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR-positive breast cancer) in combination with exemestane after failure of treatment with letrozole or anastrozole	Exemestane monotherapy	Increased overall survival Increased progression-free survival Improved quality of life
Everolimus (Afinitor) for treatment of pancreatic neuroendocrine tumors	Patients with surgically unresectable pancreatic neuroendocrine tumors (PNETs) that have progressed within the past year	Patients with PNETs have few treatment options, and existing treatments are of limited efficacy. The mTOR/phosphoinositide 3-kinase pathway is a central regulator of cell growth, cell proliferation, cell death, and cell migration. Inhibition of mTOR has exhibited anticancer activity in a number of disease settings. Everolimus (Afinitor®) is an mTOR inhibitor FDA approved for treating renal cell carcinoma and subependymal giant cell astrocytomas. It is proposed for treating PNETs. In clinical trials of patients with PNETs, everolimus was administered in a daily, oral dose of 10 mg. Novartis International AG, Basel, Switzerland FDA approved May 2011 for treating PNETs	5-Fluorouracil Capecitabine Dacarbazine Doxorubicin Streptozocin Sunitinib Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ex vivo expanded cord blood (StemEx) for allogeneic bone marrow transplant for hematologic malignancies	Patients with hematologic malignancies who need a bone marrow transplant and for whom no suitable matched donor is available	Suitably-matched bone marrow donors are not available for all patients with hematologic malignancies who could benefit from a transplant because of the difficulty in identifying suitably matched donors. An exact match is needed for adult marrow transplants to avoid complications from graft-versus-host disease (GVHD), and cord blood is associated with a lower risk of GVHD. However, the number of stem cells in cord blood is not sufficient to provide complete bone marrow engraftment. StemEx is a graft of stem cells and progenitor cells isolated from a single unit of cord blood. Stem cells and progenitor cells are enriched ex vivo by means of copper chelation, which reduces the availability of copper and purportedly promotes cell proliferation over differentiation. The enriched cell population is then infused to the patient along with the remainder of the cord blood unit. Gamida Cell, Ltd., Jerusalem, Israel Phase III trial ongoing	Pooled unexpanded cord blood transplant Unexpanded cord blood transplant	Improved bone marrow engraftment rate Improved neutrophil recovery rate Improved platelet recovery rate Increased overall survival
Gene-mediated cytotoxic immunotherapy (ProstAtak) for prostate cancer	Patients in whom intermediate to high-risk localized prostate cancer has been diagnosed	Prostate cancer recurrence rates following front-line treatment range between 10% and 60% depending on whether tumor pathology indicates that the tumor is low risk or high risk; therefore, therapies that could reduce this recurrence rate are highly sought. A gene-mediated cytotoxic immunotherapy (GMCI), ProstAtak™ is being tested for preventing recurrence following conventional therapy. GMCI purports to lead to direct tumor cytotoxicity as well as a protective immune response. The treatment consists of an adenovirus vector that contains an herpes simplex virus (HSV) thymidine kinase gene (Adv-tk). Following injection of the virus into the tumor site, the patient receives the anti-HSV drug valacyclovir, which is activated by the tk transgene and produces an active drug that kills rapidly dividing cells. This, in turn, leads to local cytotoxicity through local release of activated valacyclovir and the release of tumor antigens that may be taken up by dendritic cells and produce a systemic immune response. In treating prostate cancer, GMCI is being administered in combination with radiation therapy. Advantagene, Inc., Auburndale, MA Phase III trial ongoing under FDA Special Protocol Assessment	Androgen deprivation therapy Radiation therapy Surgical resection	Increased overall survival Increased disease-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Genetic test (Methylated Septin 9 Plasma DNA Test) for colorectal cancer screening	All patients undergoing routine colorectal cancer (CRC) screening	Genetic test (Methylated Septin 9 Plasma DNA Test; RealTime mS9 Colorectal Cancer Test) screens DNA from plasma samples for a specific methylated version of the septin 9 gene that is commonly found in CRC. Epigenomics AG, Berlin, Germany (developer) Abbott Laboratories, Abbott Park, IL (licensee) First-generation test kit (Epi proColon) available in Europe; 2nd-generation test kit (Epi proColon 2.0) was anticipated to be available in Europe in 2011; Epigenomics planned to submit the 3rd module of a premarket approval application to FDA in Dec 2012	Colonoscopy Computed tomographic colonography Fecal DNA tests Sigmoidoscopy	Increased sensitivity and specificity Increased predictive values Avoided unnecessary followup procedures Improved adherence with colorectal screening Earlier intervention for identified cancer
Ghrelin receptor agonist (anamorelin) for treatment of cancer-related cachexia/anorexia	Patients in whom cancer-related cachexia/anorexia (CRCA) has been diagnosed	Although a number of treatments have been applied to CRCA, many patients do not respond to current treatment options. CRCA may limit the ability of patients to tolerate further treatment and may directly affect survival. CRCA is caused by metabolic and neurochemical alterations in the body that lead to the loss of the desire to eat (anorexia) and the wasting of skeletal muscle mass (cachexia). Ghrelin, through its activity on the growth hormone secretagogue receptor, may increase appetite and inhibit leptin and proinflammatory cytokine expression. Anamorelin is an orally administered, ghrelin receptor agonist that has the potential to address both the appetite and metabolic (e.g., proinflammatory) aspects of CRCA. In clinical trials it is administered as a daily dose of 100 mg. Helsinn Healthcare S.A., Lugano/Pazzallo, Switzerland Phase III trials ongoing	Anti-cytokine antibodies Appetite stimulants: Cannabinoids Corticosteroids Cyproheptadine Progesterone derivatives Dietary counseling Melanocortin antagonists Metabolic disturbance modulators: Pentoxifylline Thalidomide	Improved lean body mass Improved muscle strength Increased body weight Increased overall survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gonadotropin-releasing hormone analogs for prevention of chemotherapy-induced menopause	Women undergoing systemic chemotherapy for cancer	About 25% of women undergoing systemic chemotherapy for conditions such as breast cancer experience premature menopause as a side effect of treatment. No consensus on treatment exists for preventing this side effect. Gonadotropin-releasing hormone analogs (e.g., goserelin, triptorelin) may protect ovarian function against the effects of chemotherapy through several mechanisms, including decreasing the number of primordial follicles entering the relatively chemotherapy-sensitive differentiation stage; decreasing ovarian perfusion, thereby reducing ovarian exposure to chemotherapy; upregulating intragonadal antiapoptotic molecules (e.g., sphingosine-1-phosphate); and protecting ovarian germline stem cells. In clinical trials, gonadotropin-releasing hormone analogs are administered concomitantly with standard cytotoxic chemotherapy regimens. SWOG, Ann Arbor, MI, and International Breast Cancer Study Group IBCSG, Bern, Switzerland Phase III trial complete	No standard therapies available	Decreased rate of amenorrhea at 12 months post-chemotherapy Improved quality of life
HER2 therapeutic cancer vaccine (NeuVax) for breast cancer	Patients with HER2-positive early stage breast cancer. Patients must be positive for human leukocyte antigen (HLA)-A2 and/or HLA-A3.	Although many patients in whom early-stage breast cancer has been diagnosed achieve remission after 1st-line chemotherapy, a significant proportion eventually have disease recurrence. Although some patients undergo maintenance therapy with trastuzumab, only patients whose tumors express high levels of HER2 are eligible for trastuzumab. NeuVax™ is a therapeutic cancer vaccine that combines an HER2-derived peptide (E75) with the immune stimulant granulocyte macrophage colony-stimulating factor. The vaccine is designed to induce a cytotoxic T-cell response against cells expressing HER2. NeuVax is under study as maintenance therapy for patients whose tumors express low levels of the HER2 protein. RXi Pharmaceuticals Corp., Worcester, MA Phase III ongoing under FDA special protocol assessment	Aromatase inhibitors Tamoxifen	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
High-intensity focused ultrasound (Ablatherm-HIFU system) for treatment of localized prostate cancer	Patients in whom localized prostate cancer has been diagnosed	High-intensity focused ultrasound (HIFU) is a noninvasive treatment under study for treating prostate cancer. HIFU ablates tissue by using sound waves to generate heat within a small, focused area, leaving surrounding tissue unaffected. The noninvasive and targeted nature of HIFU has the potential to reduce side effects associated with invasive procedures and radiation therapy and, unlike these procedures, may also be repeated in the event of local recurrence. HIFU ablation is performed in a 1–3 hour outpatient procedure. The most advanced clinical trial of the Ablatherm®-HIFU system in the U.S. is studying its use in treating patients who have localized prostate cancer and have not undergone previous prostate cancer treatment. EDAP TMS S.A., Lyon, France Phase II/III trial ongoing; system available in Europe since 2000	Brachytherapy External beam radiation Observation Radical prostatectomy Other HIFU systems (in development)	Increased overall survival Increased progression-free survival Improved patient quality of life
High-intensity focused ultrasound (Sonablate 500 system) for treatment of localized prostate cancer	Patients in whom localized prostate cancer has been diagnosed	High-intensity focused ultrasound (HIFU) is a noninvasive treatment under study for treating prostate cancer. HIFU ablates tissue by using sound waves to generate heat within a small, focused area, leaving surrounding tissue unaffected. The noninvasive and targeted nature of HIFU has the potential to reduce side effects associated with invasive procedures and radiation therapy and, unlike these procedures, may also be repeated in the event of local recurrence. HIFU ablation is performed in a 1–3 hour outpatient procedure. The most advanced clinical trial of the Sonablate® 500 system in the U.S. is studying its use in treating patients with localized prostate cancer that has recurred following initial therapy with external beam radiation therapy. USHIFU, LLC, Charlotte, NC Phase III trial ongoing; system available in Europe since 2001	Brachytherapy External beam radiation Observation Radical prostatectomy Other HIFU systems (in development)	Increased overall survival Increased progression-free survival Improved patient quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Histamine dihydrochloride (Ceplene) for treatment of acute myeloid leukemia	Patients with acute myeloid leukemia (AML) who are in remission following consolidation chemotherapy	Although many patients in whom AML has been diagnosed will achieve remission following induction and consolidation chemotherapy, the majority of these patients will experience disease recurrence. Ceplene® is being studied as a maintenance therapy to prevent disease recurrence in this setting; it purportedly acts as an immune stimulant, which may activate a T-cell response against leukemia cells. In clinical trials, it is being administered as an adjunct to the cytokine interleukin-2. Ceplene is administered as a subcutaneous injection. EpiCept Corp., Tarrytown, NY Phase III trial completed; new drug application submitted to FDA late 2010 and rejected; EpiCept is working with FDA to generate a special protocol assessment for a new phase III Ceplene trial; Ceplene is approved for use in EU. Phase IV trial is recruiting participants.	No consensus treatment exists for postremission patients	Decreased relapse rate Increased overall survival Improved quality of life
Histone deacetylase inhibitor (panobinostat) for treatment of relapsed multiple myeloma	Patients with multiple myeloma whose disease requires retreatment following at least 1 round of chemotherapy treatment	Although treatments for multiple myeloma have improved, the median life expectancy for patients in whom multiple myeloma is diagnosed is only 5–7 years. Additionally, as several newer treatments for multiple myeloma have been moved into the frontline setting as combination therapies, additional salvage treatments are needed. Histone deacetylase (HDAC) inhibitors are a class of anticancer drugs whose exact mechanism of action is unclear but might be related to inhibition of DNA-damage repair or modification of cell cycle proteins. Although 2 HDAC inhibitors (vorinostat and romidepsin) have been approved for treating cutaneous T-cell lymphoma, no HDAC inhibitor is approved for treating multiple myeloma. In an ongoing registration-phase clinical trial, panobinostat is being tested in combination with the proteasome inhibitor bortezomib and the glucocorticosteroid dexamethasone. Novartis International AG, Basel, Switzerland Phase III trial ongoing	Chemotherapy at standard or high doses including one or more of the following: Bendamustine Bortezomib Cisplatin Cyclophosphamide Dexamethasone Doxorubicin Etoposide Lenalidomide Thalidomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Histone deacetylase inhibitor (vorinostat) for treatment of multiple myeloma	Patients with multiple myeloma who have undergone at least 1 prior round of chemotherapy	Although treatments for multiple myeloma have improved, the median life expectancy for patients in whom multiple myeloma is diagnosed is only 5–7 years. Additionally, as several newer treatments for multiple myeloma have been moved into the frontline setting as combination therapies, additional salvage treatments are needed. Histone deacetylase (HDAC) inhibitors are a class of anticancer drugs whose exact mechanism of action is unclear, but might be related to DNA damage repair inhibition or modification of cell cycle proteins. Although 2 HDAC inhibitors (vorinostat and romidepsin) have been approved for treating cutaneous T-cell lymphoma, no HDAC inhibitor is approved for treating multiple myeloma. In an ongoing pivotal clinical trial, vorinostat (oral tablets at 400 mg/day) is being tested in combination with the proteasome inhibitor bortezomib. Merck & Co. Inc., Whitehouse Station, NJ Phase III trial ongoing; preliminary results released in Dec 2011 indicated that vorinostat met its primary endpoint of extending progression-free survival, which was extended by 25 days	Chemotherapy at standard or high doses including one or more of the following: Bendamustine Bortezomib Cisplatin Cyclophosphamide Dexamethasone Doxorubicin Etoposide Lenalidomide Thalidomide	Increased overall survival Increased progression-free survival Improved quality of life
Hsp90 inhibitor (ganetespib) for treatment of advanced nonsmall cell lung cancer	Patients with treatment-resistant, advanced or metastatic nonsmall cell lung cancer (NSCLC)	Patients with advanced NSCLC that has progressed after prior chemotherapy have a poor prognosis and few treatment options. Ganetespib is a novel anticancer agent that acts as an inhibitor of hsp90 activity. Hsp90 is a molecular chaperone that is responsible for the proper folding and stability of a wide range of proteins in the cell. In particular, hsp90 has been implicated in maintaining the stability of multiple mutated proteins with proneoplastic properties including mutated p53, BCR-ABL, Raf-1, Akt, ErbB2, and hypoxia-inducible factor 1 alpha. In addition, hsp90 has been shown to increase the activity of proteins known to have a cytoprotective effect in cells exposed to cytotoxic chemotherapy; therefore, hsp90 inhibition might act synergistically with cytotoxic agents. In treating NSCLC, ganetespib is being tested as an adjunct to the cytotoxic agent docetaxel. Synta Pharmaceuticals Corp., Lexington, MA Phase II/III trial ongoing	Docetaxel monotherapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Hypoxia-activated DNA alkylating agent (TH-302) for treatment of advanced and metastatic soft tissue sarcoma	Patients in whom locally advanced, unresectable or metastatic soft tissue sarcoma has been diagnosed	The disordered growth of tumors often leads to areas of tissues with inadequate blood supply, leading to hypoxic conditions. These hypoxic areas of tumors are often refractory to conventional chemotherapy because of the tissues' inaccessibility to standard drugs and/or slow rate of cell division. TH-302 is a novel cytotoxic agent that purportedly is preferentially activated in hypoxic conditions. In its activated form, TH-302 is a potent DNA alkylating agent (dibromo isophoramide mustard). Selective activation of TH-302 in hypoxic conditions might target alkylating activity to tumors. In clinical trials for soft tissue sarcoma, TH-302 is being used as 1st-line therapy in combination with doxorubicin to try to target both the hypoxic and normoxic regions of the tumor. Threshold Pharmaceuticals, South San Francisco, CA Merck & Co., Inc. Whitehouse Station, NJ Phase III trial ongoing in soft tissue sarcoma; also under study in other cancer types including pancreatic cancer; companies signed agreement in Feb 2012 to codevelop and commercialize TH-302	Doxorubicin monotherapy	Increased overall survival Increased progression-free survival Improved quality of life
Ibrutinib (Pci32765) for treatment of B-cell non-Hodgkin's lymphomas	Patients in whom B-cell non-Hodgkin's lymphoma (chronic lymphocytic leukemia/small lymphocytic lymphoma, diffuse large B-cell lymphoma, or mantle cell lymphoma) has been diagnosed	Patients with treatment-resistant B-cell malignancies have a poor prognosis and few treatment options. Many B-cell malignancies depend on B-cell receptor (BCR) signaling for survival. Ibrutinib 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. Ibrutinib is administered orally, once daily. Pharmacyclics, Inc., Sunnyvale, CA Phase III trials ongoing	Various cytotoxic chemotherapy regimens combined with various immunotherapeutic drugs	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Immature PSA ([-2]proPSA) assay as a decision aid regarding prostate cancer biopsy	Patients with elevated levels of serum prostate-specific antigen (PSA) levels of 4–10 ng/mL but normal results on digital rectal examination who must decide whether to undergo prostate biopsy	Prostate cancer screening using serum PSA is problematic because of its inability to distinguish between benign prostate conditions and prostate cancer. This exposes many men without prostate cancer to unneccesary prostate biopsies. [-2]proPSA is a partially processed form of PSA purported to be elevated in patients with prostate cancer that has the potential to improve upon the specificity of existing PSA-based screening. The [-2]proPSA test measures levels of the analyte using an immunoassay. Results of the assay are combined with total PSA and free PSA measurements obtained from the same sample to generate a "Prostate Health Index," which purportedly indicates the likelihood of prostate cancer. Beckman Coulter, Inc., Brea, CA FDA approved Jul 2012; available in Europe since 2010	PSA testing alone Free PSA testing alone Percent-free-PSA testing Prostate cancer antigen 3 (PCA3) testing	Improved positive and negative predictive values Improved sensitivity Improved specificity Reduced number of unnecessary biopsies
Immunomodulator (Imprime PGG) for treatment of advanced colorectal cancer	Patients in whom advanced colorectal cancer (CRC) has been diagnosed	Many patients with late-stage CRC are unable to tolerate or do not benefit from current chemotherapeutic regimens; new therapies to treat advanced CRC are needed. Imprime PGG® is a novel beta glucan immunomodulator purportedly induces an antitumor response through binding and stimulating neutrophils, which typically play a major role in innate immune responses, but not antitumor responses; Imprime PGG purportedly works synergistically with monoclonal antibody therapy such as cetuximab. Administered 4 mg/kg of body weight injection, weekly, in each treatment cycle. Biothera, Eagan, MN Phase III trial ongoing	Cetuximab monotherapy Regorafenib	Increased overall survival Increased progression-free survival Improved quality of life
Injected hydrogel (SpaceOAR) to protect healthy tissue during radiation therapy	Patients undergoing radiation therapy treatment for cancers that are adjacent to delicate healthy structures (e.g., prostate cancer)	SpaceOAR™ system (spacing organs at risk) is a hydrogel injected as a liquid that becomes solid in the body and is intended for use during radiation therapy to distance organs at risk of collateral radiation damage from the targeted tumor (e.g., displace the rectum from the prostate). Augmenix, Inc., Waltham, MA Phase III trial ongoing; approved for marketing in EU; May 2011, Varian Medical Systems, Inc., Palo Alto, CA, invested in Augmenix with option to buy company	Radiation therapy without normal-tissue spacer	Reduced radiation-associated side effects to healthy tissue

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Insulin-like growth factor receptor inhibitor (linsitinib) for treatment of adrenocortical carcinoma	Patients in whom locally advanced or metastatic adrenocortical carcinoma has been diagnosed	Current 2nd- and 3rd-line treatments for adrenocortical carcinoma are largely ineffective, and only about 10% of patients with metastatic disease survive 5 years after the disease is diagnosed. Insulin-like growth factor (IGF) signaling has been implicated in adrenocortical carcinoma pathogenesis through the finding that IGF-2 is often upregulated in these tumors. Linsitinib is an orally administered, small-molecule inhibitor of an IGF-2 target, the IGF-1 receptor (IGF-1R). IGF-1R signaling purportedly regulates multiple cancer-related properties in cells, including growth, energy metabolism, differentiation, and apoptosis; therefore, its inhibition may have anticancer activity. In clinical trials, linsitinib is being administered twice daily, at a dose of 150 mg. Astellas Pharma, Inc., Tokyo, Japan (previously developed by Osi Pharmaceuticals, which was acquired by Astellas) Phase III trial complete	Etoposide/doxorubicin/ cisplatin plus mitotane Streptozotocin plus mitotane	Increased overall survival Increased progression-free survival Improved quality of life
Integrated positron emission tomography and magnetic resonance imaging system (Biograph mMR) for diagnosis and monitoring of cancer	Patients in whom cancer has been diagnosed	Imaging exams that combine positron emission tomography (PET) with MRI (Biograph™ mMR) to provide simultaneous acquisition of morphologic, functional, and metabolic imaging data; intended to take 30 minutes to perform the exam, compared with 60 minutes or more for sequential PET with MRI exams. Siemens AG, Munich, Germany 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 cell 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. Treatment is intended for use against newly diagnosed glioblastoma that exhibits methylation of the methylguanine-DNA methyltransferase gene (a marker of temozolomide sensitivity). In clinical trials, cilengitide is administered in a twice-weekly, intravenous dose of 2,000 mg in combination with standard therapy using temozolomide and radiation therapy. EMD Serono, Inc., Rockland, MA Phase III trial ongoing; also in trials for nonsmall cell lung cancer	Temozolomide plus radiation therapy	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interleukin 1α antagonist (Xilonix) for treatment of cancer-related cachexia	Patients in whom cancer-related cachexia has been diagnosed	While a number of treatments have been developed to address cancer-related cachexia (wasting of skeletal muscle mass), many patients do not respond to current treatment options. Cancer-related cachexia may limit the ability of patients to tolerate further treatment and/or directly affect survival. Cancer-related cachexia is caused by metabolic and neurochemical alterations in the body that lead to the wasting of skeletal muscle mass. While the mechanism by which tumors induce cachexia is poorly understood, one hypothesis states that interleukin-1α-mediated pro-inflammatory signals to the central nervous system may induce systemic cachexia. Xilonix is a monoclonal antibody that acts as an interleukin-1α antagonist potentially disrupting this pro-inflammatory signaling. It is administered intravenously. XBiotech, Austin, Texas Phase III trial planned; FDA granted fast-track status	Appetite stimulants: Cannabinoids, Corticosteroids Cyproheptadine, Progesterone derivatives Dietary counseling Melanocortin antagonists Metabolic disturbance modulators: Anti-cytokine antibodies Pentoxifylline Thalidomide	Increased body weight Increased lean body mass Increased muscle strength Increased overall survival Improved quality of life
Interleukin-12 gene therapy (TheraPlas, EGEN-001) for recurrent or persistent ovarian cancer	Patients with recurrent or persistent ovarian or fallopian tube cancer who have received at least 1 round of treatment with a platinum-based cytotoxic chemotherapy regimen	Patients in whom advanced ovarian cancer has been diagnosed often have recurrent disease and a poor prognosis. EGEN-001 (TheraPlas™) is a novel gene therapy intended to induce the expression of interleukin-12 (IL-12) in tumor cells; IL-12 expression purportedly leads to 3 antitumor activities: (1) activation and proliferation of natural killer (NK) cells, leading to an innate immune response against the tumor; (2) maturation and proliferation of T lymphocytes, leading to an adaptive immune response against the tumor; and (3) activation of NK cells and T lymphocytes leading to upregulation of interferon gamma, which has antiangiogenic properties. EGEN-001 is administered by intraperitoneal catheter to the local tumor microenvironment. EGEN, Inc., Huntsville, AL Phase II trial ongoing; FDA granted orphan drug status	Combination chemotherapy including one or more of the following: Carboplatin Cisplatin Docetaxel Etoposide Gemcitabine Liposomal doxorubicin Paclitaxel Topotecan	Increased overall survival Increased progression-free survival Improved quality of life
Ipilimumab (Yervoy) for treatment of metastatic melanoma	Patients in whom metastatic melanoma has been diagnosed	Few effective treatments exist for metastatic melanoma, particularly for patients in whom *BRAF* mutation-negative melanoma has been diagnosed. Ipilimumab (Yervoy™) is a 1st-in-class targeted anticytotoxic T-lymphocyte antigen 4 therapy; it is intended to block the activity of cytotoxic T-lymphocyte antigen 4, which could lead to increased antitumor cytotoxic activity (reduce immune tolerance to tumor cells). Bristol-Myers Squibb, New York, NY FDA approved Mar 2011	Dacarbazine High-dose interleukin-2 Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Irreversible electroporation (NanoKnife) for treatment of hepatocellular carcinoma	Patients with early-stage hepatocellular carcinoma (HCC) that is not surgically resectable	Surgical resection and/or ablation of locally advanced tumors is the only potentially curative treatment option for patients with HCC. However, many patients are not eligible for surgical resection because the location of their tumors is in close proximity to essential structures (e.g., major blood vessels). The NanoKnife® system uses a novel treatment modality known as irreversible electroporation in which pulses of high-voltage direct current are applied to the target tissue using needle-like electrodes, a process that induces the irreversible formation of nanopores in cellular membranes. The formation of these nanopores is highly toxic to cells, leading to cell death via an apoptosis-like process. Unlike other local ablation technologies (e.g., radiofrequency [RF] ablation, cryotherapy), irreversible electroporation does not suffer heat sink effects and can leave the extracellular structure of large blood vessels intact, potentially allowing local ablation of tumors in close proximity to vessels while retaining vessel patency. In treating HCC, irreversible electroporation is performed in a minimally invasive laparoscopic procedure. AngioDynamics, Latham, NY Phase II trial ongoing; cleared by FDA through the 510(k) process for the surgical ablation of soft tissue; under investigational device exemption status for a premarket approval application for this indication	Cryotherapy RF ablation	Increased overall survival Increased clinical downstaging to surgically resectable tumor Improved adverse event profile Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Irreversible electroporation (NanoKnife) for treatment of pancreatic cancer	Patients in whom locally advanced pancreatic cancer that is not resectable by surgery has been diagnosed	Surgical resection and/or ablation of locally advanced tumors is the only potentially curative treatment option for patients in whom pancreatic cancer has been diagnosed. However, many patients are not eligible for surgical resection because the location of their tumors is in close proximity to essential structures (e.g., major blood vessels). The NanoKnife® system uses a novel treatment modality known as irreversible electroporation in which pulses of high voltage direct current are applied to the target tissue using needle-like electrodes, a process that induces the irreversible formation of nanopores in cellular membranes. The formation of these nanopores is highly toxic to cells, leading to cell death via an apoptosis-like process. Unlike other local ablation technologies (e.g., radiofrequency [RF] ablation, cryotherapy), irreversible electroporation does not suffer heat sink effects and can leave the extracellular structure of large blood vessels intact, potentially allowing local ablation of tumors in close proximity to vessels while retaining vessel patency. In treating pancreatic cancer, irreversible electroporation is performed in a minimally invasive laparoscopic procedure. AngioDynamics, Latham, NY Phase II trial ongoing; cleared by FDA through the 510(k) process for the surgical ablation of soft tissue; in trials for various cancer applications under premarket approval process	Cryotherapy RF ablation	Increased overall survival Increased rate of clinical downstaging to surgically tumor Improved adverse event profile Improved quality of life
Lansoprazole (PrevOnco) for treatment of advanced unresectable hepatocellular carcinoma	Patients in whom advanced, unresectable hepatocellular carcinoma has been diagnosed	PrevOnco™ incorporates lansoprazole, a proton-pump inhibitor (commonly marketed antiulcer compound). It uses proprietary NexACT drug delivery technology, which is designed to reduce by 7 times the dose needed. The drug has shown strong anticancer activity in mice bearing human liver tumors. It is taken orally. Apricus Biosciences, Inc., San Diego, CA Phase III trial special protocol assessment under discussion with FDA; FDA granted orphan drug status	Doxorubicin Sorafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Liposome encapsulated irinotecan (MM-398) for treatment of pancreatic cancer	Patients with treatment-refractory, metastatic pancreatic cancer	Only about 25% of patients with metastatic pancreatic cancer have disease that responds to 1st-line therapy with gemcitabine; patients have a poor prognosis with current 2nd-line treatment options. MM-398 (PEP-02) is a novel formulation of the topoisomerase 1 inhibitor irinotecan that encapsulates the drug in liposomal particles and is intended to be used as a 2nd-line treatment. Liposomal encapsulation of irinotecan has 3 potential benefits: (1) liposomal particles may preferentially accumulate in tumor tissues because of increased porosity of tumor vasculature; (2) liposomes may provide slow release of the active drug, potentially increasing duration of exposure to therapeutic dose; and (3) irinotecan is hydrolyzed to a relatively inert form in aqueous solutions and liposomal encapsulation might protect the drug from this hydrolysis. In clinical trials, MM-398 is being administered by intravenous infusion as a monotherapy. Merrimack Pharmaceuticals, Inc., Cambridge, MA Phase III trial ongoing; FDA granted orphan drug status for treating 2nd-line pancreatic cancer	Capecitabine Capecitabine/ oxaliplatin FOLFOX (folinic acid [leucovorin], 5-fluorouracil, oxaliplatin) Gemcitabine	Increased overall survival Increased progression-free survival Improved quality of life
Liposome encapsulated vincristine (Marqibo) for treatment of acute lymphoblastic leukemia	Adult patients with recurrent Philadelphia chromosome–negative acute lymphoblastic leukemia (ALL)	Adult patients with recurrent ALL have a poor prognosis and few treatment options. The microtubule-assembly inhibitor vincristine is a mainstay of ALL treatment both in the frontline and salvage settings. However, the effectiveness of vincristine is limited by the inability to maintain therapeutic levels of the drug for long periods of time and the inability to further escalate the dose because of toxicity. Marqibo® is a novel liposomal formulation of vincristine that purportedly allows the slow release of vincristine over a period of time, potentially maintaining therapeutic levels of vincristine and improving efficacy. It is administered as a once-weekly injection. The labeling includes a boxed warning that it must be administered intravenously because other injection methods, such as injection into spinal fluid, could result in death. Talon Therapeutics, Inc., San Mateo, CA FDA granted Marqibo orphan drug status for treating ALL in the salvage setting; FDA approved Aug 2012 for patients whose leukemia has recurred 2 or more times, or whose leukemia has progressed after 2 or more therapy regimens	Combination chemotherapy including one or more of the following: Anthracyclines Asparaginase Methotrexate High-dose cytarabine Steroids Vincristine	Increased overall survival Increased disease-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Liver chemosaturation drug/device combination (melphalan-Chemosat) for treatment of melanoma metastases to the liver	Patients with ocular melanoma that has metastasized to the liver	Liver cancer is largely refractory to standard systemic chemotherapy. Although targeted chemotherapy delivery options are available for treating liver cancer (e.g., hepatic artery delivered chemotherapy, trans-arterial chemoembolization), systemic side effects preclude the use of maximum chemotherapy doses. The Chemosat® system is a delivery method that introduces a chemotherapy drug (melphalan) through the hepatic artery and removes the drug by filtering blood exiting the liver through the venous system. In this way, high doses of chemotherapy can be delivered while sparing the patient systemic side effects. Adjunctive therapy to treat the primary melanoma and nonhepatic metastases may also be administered. Delcath Systems, Inc., New York, NY Phase III trial completed; FDA returned new drug application (NDA) in Feb 2011 asking for further safety data; pre-NDA held with FDA in Jan 2012 and company intended to refile NDA in 2nd quarter 2012; Conformité Européene (CE) marked for liver cancer. Company submitted a new NDA in Aug 2012 which was accepted by FDA in Oct 2012. FDA decision date is set for Jun 15, 2013.	Hepatic artery-delivered chemotherapy Trans-arterial chemoembolization	Increased overall survival Increased progression-free survival Improved quality of life
Magnetic resonance imaging and ultrasound image fusion for image-guided prostate biopsy	Patients who are suspected of having prostate cancer based on elevated prostate-specific antigen (PSA) or abnormal digital rectal exam	Transrectal ultrasound (TRUS)-guided biopsy has been the standard of care for many years. However, TRUS does not have the ability to discriminate normal tissue from cancerous tissue; therefore, a random sampling procedure is used and some cancers may be missed. MRI has the potential to identify prostate tissue that may be cancerous, and some institutions have adopted the use of MRI-guided biopsy. Although this procedure may improve cancer detection rates, MRI-guided biopsy is expensive, time consuming, and cumbersome because of the need to perform the biopsy within the MRI machine gantry. A new procedure uses MRI data to guide prostate biopsies performed in an office setting by a urologist—rather than by a radiologist—followed by fusion of MRI image data with TRUS image data. It might enable evaluation of areas of suspicion that were identified using MRI to be targeted using TRUS-guided biopsy. Philips Healthcare unit of Royal Philips Electronics, Amsterdam, the Netherlands Philips has initiated a phase III trial. Pilot studies completed by multiple institutions (e.g., Kyoto Prefectural University of Medicine, Kyoto, Japan; University of Regensburg, Regensburg, Germany)	MRI-guided biopsy TRUS-guided biopsy	Improved positive and negative predictive values Improved sensitivity Improved specificity

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
MarginProbe System for intraoperative identification of positive margins during breast cancer lumpectomy	Patients undergoing breast lumpectomy	Successful breast lumpectomy requires that the margins of a resected tumor be free of cancerous tissue; however, with current standard of care, up to 30% of patients undergo a 2nd lumpectomy because cancer-positive margins are identified by pathology results several days after the initial operation. The MarginProbe® System enables intraoperative identification of cancer-positive margins in excised tissues thereby allowing the surgeon to resect additional tissue during the same surgical procedure; the system uses radiofrequency spectroscopy to discern differences in the electromagnetic signature of cancerous cells relative to normal tissue. Dune Medical Devices, Inc., Framingham, MA FDA approved Jan 2, 2013, for intra-operative tissue assessment of surgical margins during surgery for early-stage breast cancer; system has been available in Europe since 2008	No marketed comparator in the U.S.	Reduced number of reexcision surgeries performed Improved rate of complete surgical resection (e.g., no positive margin)
Marine depsipeptide (plitidepsin) for treatment of relapsed/refractory multiple myeloma	Patients with multiple myeloma who have undergone at least 3 treatments, including bortezomib- and lenalidomide-based regimens	Although treatments for multiple myeloma have improved, the median life expectancy for patients in whom multiple myeloma is diagnosed is only 5–7 years. Additionally, as several newer treatments for multiple myeloma have been moved into the frontline setting as combination therapies, additional salvage treatments are needed. Plitidepsin is a cyclodepsipeptide that demonstrated anticancer activity in preclinical studies and was isolated from the tunicate *Aplidium albicans*. The purported mechanism of action of plitidepsin is the induction of cell cycle arrest and apoptosis through the induction of oxidative stress, activation of Rac1, and the sustained activation of Jun-N terminal kinase and p38 mitogen-activated protein kinase. In a late-stage clinical trial for treating multiple myeloma, plitidepsin is being administered by infusion at a dose of 5 mg/m^2 of body surface area in combination with orally administered dexamethasone. PharmaMar subsidiary of Grupo Zeltia, Madrid, Spain Phase III trial ongoing	Combination chemotherapy including one or more of the following: Bendamustine Bortezomib Cisplatin Cyclophosphamide (including high dose) Dexamethasone 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
MEK inhibitor (trametinib) for treatment of advanced melanoma with activating *BRAF* mutation	Patients with stage IIIc or IV malignant cutaneous melanoma that harbors an activating *BRAF* mutation	Patients with metastatic melanoma have a poor prognosis with current treatments yielding a 5-year survival rate of less than 10%. Melanomas harboring activating *BRAF* mutations are driven in part by activation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway of which MEK is a member; trametinib (GSK1120212) is an inhibitor of MEK 1 and MEK 2, which may have antineoplastic activity in tumors dependent on MAPK/ERK pathway activation. GlaxoSmithKline, Middlesex, UK New drug application for this indication submitted to FDA in Aug 2012; phase II trial ongoing in patients previously treated with or without a *BRAF* inhibitor; phase II trial ongoing in combination with the *BRAF* inhibitor dabrafenib	High dose interleukin-2 Dacarbazine Ipilimumab Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life
Microtubule destabilizing agent (ombrabulin) for treatment of soft tissue sarcoma	Patients with advanced soft tissue sarcoma who have undergone prior systemic chemotherapy with anthracycline (e.g., doxorubicin) and ifosfamide	Doxorubicin is the only FDA-approved treatment for soft tissue sarcomas (excluding gastrointestinal stromal tumors and liposarcomas), and no consensus on treatment exists for patients whose disease has progressed during doxorubicin-based chemotherapy. Ombrabulin (AVE8062) is a novel, small-molecule agent that purportedly functions through the depolymerization of microtubules. Although the exact antitumor mechanism of ombrabulin is unclear, it is thought to act as a vascular targeting agent that preferentially disrupts existing tumor vasculature, leading to ischemia and subsequent tumor necrosis. In a late-phase trial, ombrabulin is being administered by intravenous infusion in combination with cisplatin. Sanofi, Paris, France Phase III trial ongoing	Pazopanib Sorafenib (off label) Sunitinib (off label)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mitochondrial metabolism disruptor (CPI-613) for treatment of various cancers	Patients with an advanced malignancy, in particular pancreatic cancer or acute myeloid leukemia (AML)	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 purportedly functions by leading to the inhibition of a mitochondrial enzyme (pyruvate dehydrogenase) that is essential for conversion of pyruvate to acetyl coenzyme A (acetyl-CoA). Cancer cells may be particularly sensitive to this disruption because the metabolic state of cancer cells downregulates both pyruvate dehydrogenase activity and other metabolic pathways that could provide a source of acetyl-CoA (e.g., fatty acid metabolism). Cornerstone Pharmaceuticals, Inc., Cranbury, NJ Phase I/II trials ongoing in hematologic malignancies; phase I/II trial ongoing in pancreatic cancer; FDA granted orphan drug status for AML and pancreatic cancer	Various chemotherapy regimens	Increased overall survival Increased progression-free survival Improved quality of life
MUC1 therapeutic vaccine (CVac) for ovarian cancer	Patients with ovarian cancer who are in 1st or 2nd remission after cytoreduction and chemotherapy	No maintenance therapies are approved to preserve remission in ovarian cancer treatment. CVac™ is an autologous dendritic cell-based vaccine that is primed with mucin-1 (a tumor antigen) coupled to mannan (a sugar derivative that acts as an immune stimulant). The vaccine is intended to induce an immune response to ovarian cancer cells, preventing or slowing recurrence. Prima BioMed, Ltd., Melbourne, Australia Phase II/III trial ongoing	Bevacizumab Paclitaxel	Increased of overall survival Increased progression-free survival Improved quality of life
MUC1 therapeutic vaccine (TG4010) for nonsmall cell lung cancer	Patients with chemotherapy-naïve nonsmall cell lung cancer (NSCLC) who are mucin-1 (MUC-1)-positive	Only about 25% of patients with NSCLC respond to standard 1st-line therapies such as carboplatin/paclitaxel. TG4010 is a therapeutic cancer vaccine administered by subcutaneous injection, and it comprises a viral vector encoding both a tumor antigen (MUC-1) and an immune stimulant (interleukin-2); about 60% of NSCLC tumors express MUC-1. Patients' tumors must be MUC-1-positive, and patients must have normal levels of natural killer cells at the time of treatment initiation. In current clinical trials, TG4010 is being administered in combination with standard of care cytotoxic chemotherapy. Transgene SA, Cedex, France Phase IIb/III trial ongoing; FDA granted fast track status	Melanoma antigenic epitope-A3 therapeutic vaccine in development Paclitaxel/carboplatin	Increased overall survival Increased progression-free survival Improved quality of life

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multikinase inhibitor (lenvatinib) for treatment of differentiated thyroid cancer	Patients with differentiated thyroid cancer that is resistant to radioiodine therapy	Differentiated thyroid cancer (e.g., papillary, follicular) comprises the majority of diagnosed thyroid cancers. Although many differentiated thyroid cancers are treated successfully with radioiodine, patients with disease that is resistant to radioiodine have few treatment options and a poor prognosis. Lenvatinib is a small-molecule multikinase inhibitor with activity against multiple tyrosine kinases involved in signaling pathways that regulate cell growth, cell proliferation, and angiogenesis (e.g., vascular endothelial growth factor receptors 2 and 3). In a late-phase clinical trial, lenvatinib is being administered as a once-daily dose of 24 mg, taken in an oral tablet. Eisai Co., Ltd., Tokyo, Japan Phase III trial ongoing	Pazopanib (off label) Sorafenib (off label) Sunitinib (off label)	Increased overall survival Increased progression-free survival Improved quality of life
Multikinase inhibitor (masitinib) for treatment of activating *c-KIT* mutation-positive, metastatic melanoma	Patients with nonresectable or metastatic melanoma that harbors an activating mutation in the *c-KIT* gene	A subset of melanomas harbor an activating mutation in the *c-KIT* gene, which encodes a receptor tyrosine kinase (mast/stem cell growth factor receptor, KIT, CD117). In particular, between 10% and 20% of acral and mucosal melanomas harbor activating *c-KIT* mutations. Although KIT kinase inhibitors have been developed for other cancers dependent on KIT activity (e.g., imatinib for treating gastrointestinal stromal tumors), no KIT kinase inhibitor is approved for treating *c-KIT* mutation-positive melanoma. Masitinib is an orally administered, kinase inhibitor with activity against KIT as well as platelet-derived growth factor receptors, the intracellular kinase Lyn, and to a lesser extent, fibroblast growth factor receptor 3. Masitinib is under study as a monotherapy for treating melanoma. AB Science S.A., Paris, France Phase III trial ongoing	Dacarbazine Interleukin-2 Ipilimumab Nilotinib (in development)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Multikinase inhibitor (midostaurin) for treatment of acute myeloid leukemia bearing FLT3 mutations	Patients with newly diagnosed acute myeloid leukemia (AML) bearing an internal tandem duplication in the *FLT3* gene (ITD-FLT3)	The presence of activating *FLT3* mutations in AML is associated with a poor prognosis, and patients identified as having disease bearing such a mutation more often experience disease recurrence after initial therapy. Midostaurin is a small-molecule kinase inhibitor that has activity against FLT3 and additional tyrosine kinases (e.g., c-KIT). Addition of midostaurin's anti-FLT3 activity to conventional 1st-line therapy (cytarabine and daunorubicin) might improve response rates and decrease recurrence. Treatment is intended for patients younger than 60 years of age who are able to tolerate high-dose cytarabine consolidation therapy. In a late-stage clinical trial, midostaurin is given in a twice-daily oral dose for 2 weeks. Patients are administered midostaurin following both induction therapy with cytarabine and daunorubicin and consolidation therapy with high-dose cytarabine. Novartis International AG, Basel, Switzerland Phase III trial ongoing	Cytarabine/ daunorubicin	Increased overall survival Increased progression-free survival Improved quality of life
Necitumumab for treatment of advanced nonsmall cell lung cancer	Patients in whom advanced squamous nonsmall cell lung cancer (NSCLC) has been diagnosed	Advanced NSCLC has a high mortality rate and patients have a poor prognosis; new therapies that can improve survival are needed. Necitumumab is a monoclonal antibody antagonist directed against the epidermal growth factor (EGF) receptor protein, which may downregulate tumor activity; necitumumab may competitively inhibit the binding of EGF and other ligands, such as transforming growth factor-alpha, and block activation of receptor-associated kinases, resulting in inhibition of cell growth and induction of apoptosis. Necitumumab may also mediate antibody-dependent cellular cytotoxicity. The drug is in a similar class as cetuximab, which is used for treating many cancers but is not labeled for treating NSCLC. It may be administered as an 800-mg intravenous infusion on days 1 and 8 of every 3-week cycle and may be used in combination with gemcitabine-cisplatin. Eli Lilly and Co., Indianapolis, IN Bristol-Myers Squibb, New York, NY Phase III trials ongoing	Cetuximab (off label) Erlotinib 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
Nintedanib (Vargatef) for chemotherapy-resistant ovarian cancer	Patients in whom chemotherapy-naïve treatment-resistant ovarian cancer has been diagnosed	A significant fraction of patients with ovarian cancer have disease that is resistant or refractory to current 1st-line treatments. Nintedanib (Vargatef™) is a tyrosine kinase inhibitor that has activity against vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor tyrosine kinases, which regulate tumor growth and angiogenesis. In late-phase clinical trials, nintedanib is being tested as an adjunct to the conventional 1st-line therapy of intravenous carboplatin plus paclitaxel. Nintedanib is administered as an oral tablet, twice daily. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trial ongoing	Intraperitoneal carboplatin/paclitaxel Intravenous carboplatin/paclitaxel	Increased overall survival Increased progression-free survival Improved quality of life
Nintedanib (Vargatef) for treatment-resistant nonsmall cell lung cancer	Patients with nonsmall cell lung cancer (NSCLC) whose disease has progressed during or after 1st-line systemic chemotherapy	The 5-year survival rate for patients in whom NSCLC has been diagnosed is less than 15%, and patients whose disease progresses following 1st-line chemotherapy have few treatment options. Nintedanib is a tyrosine kinase inhibitor that has activity against vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor tyrosine kinases, which regulate tumor growth and angiogenesis. In late-phase clinical trials, nintedanib is being tested as an adjunct to conventional 2nd-line therapies (i.e., pemetrexed monotherapy, docetaxel monotherapy). Nintedanib is administered as an oral tablet, twice daily. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials ongoing	Various combination therapies including: Bevacizumab Carboplatin Crizotinib Docetaxel Erlotinib Pemetrexed	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label human papillomavirus vaccination (Gardasil and Cervarix) to prevent head and neck cancer	Persons engaging in oral sexual activity and kissing	Oncogenic human papillomavirus (HPV) strains can cause cervical and anal cancer, as well as other cancers including head and neck cancer. Between 1984 and 1989, only 16% of oropharyngeal cancers were linked to HPV, but 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 preventing 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. Merck & Co., Inc., Whitehouse Station, NJ (Gardasil) GlaxoSmithKline, Middlesex, UK (Cervarix) Both vaccines FDA approved for preventing cervical cancer	Abstinence No vaccination Safer sex practices Selective choice of partners	Reduced incidence of head and neck cancers and precancers
Off-label metformin for treatment of breast cancer	Patients in whom breast cancer has been diagnosed	Retrospective studies of patients with diabetes taking metformin, preclinical studies of in vitro cell lines, and in vivo cancer models have demonstrated that metformin may have antineoplastic properties. Metformin may exert its effects through activation of AMP-activated protein kinase, which functions to limit downstream components of the mammalian target of rapamycin pathway. Additionally, metformin's actions in reducing circulating insulin levels may be antineoplastic because of the potential growth-stimulating activity of insulin. Metformin is being studied in multiple breast cancer settings and could represent a novel treatment with a relatively low side-effect profile. Phase II trials ongoing in neoadjuvant setting; phase III trial ongoing in adjuvant setting to prevent recurrence; phase I/II trials ongoing in metastatic disease	Various chemotherapy regimens Various hormone therapies	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label rosuvastatin to prevent colon cancer recurrence	Patients who have had a stage I or II colon cancer surgically resected	Patients who undergo curative resection of stage I or II colon cancers have a 50% recurrence rate within the 1st 3 years after surgery, making a chemopreventive agent for this patient population highly sought. Retrospective studies of clinical trials assessing the use of statins for cardiovascular applications suggested that patients treated with statins had a reduced incidence of precancerous colon polyps; therefore, rosuvastatin is believed to have potential as a chemopreventive agent for colon cancer. National Surgical Adjuvant Breast and Bowel Project, Pittsburgh, PA (investigator) National Cancer Institute, Bethesda, MD (investigator) Phase III trial ongoing	No commonly used chemopreventive agent exists for treating colorectal cancer Compounds under investigation include: Aspirin Calcium supplements Curcumin Nonsteroidal anti-inflammatory drugs Omega-3 fatty acids	Reduced recurrence rate of adenomatous polyps Increased overall survival
Off-label zoledronic acid (Zometa) for treatment of breast cancer	Postmenopausal women with stage II/III breast cancer who have undergone surgery and/or surgical resection	Zoledronic acid (Zometa®) is a bisphosphonate used to prevent skeletal fractures in cancer patients at risk of fracture from bone metastases. Recent studies suggest that the drug may also treat the primary cancer, improve overall survival, and reduce cancer recurrence rates in women with low estrogen levels (e.g., postmenopausal patients). Given that the drug is commercially available, its off-label use for this may be an option exercised by oncologists. Novartis International AG, Basel, Switzerland Two phase III trials completed; 1 trial (ABCSG-12) reported positive results; however, a 2nd (AZURE) trial observed a benefit only in postmenopausal women. Based on AZURE trial results, Novartis decided not to pursue expanded label for zoledronic acid; however, physicians may prescribe off label; additional phase III trials of zoledronic acid for breast cancer are ongoing	Chemotherapy Hormone therapy	Increased overall survival Increased progression-free survival Improved quality of life
Off-label zoledronic acid (Zometa) for treatment of early stage multiple myeloma	Patients in whom early stage multiple myeloma has been diagnosed	Zoledronic acid (Zometa®) is a bisphosphonate used to prevent skeletal fractures in cancer patients, including those in whom multiple myeloma is diagnosed. Recent studies suggest that zoledronic acid confers increased overall survival in patients with multiple myeloma, which may support off-label use. In a trial, the drug was given with and without thalidomide. Zoledronic acid dose was 4 mg^2 intravenously on day 1 every 84 days for 1 year and once per year thereafter. Mayo Clinic, Rochester, MN, in collaboration with National Cancer Institute, Bethesda, MD Phase III trial (NCT00432458) completed Apr 2012	Chemotherapy Hematopoietic stem-cell transplantation Medicines: Alendronate Etidronate Oral clodronate (trial comparator) Pamidronate Other bisphosphonates	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Omacetaxine mepesuccinate, (Synribo) for treatment of tyrosine kinase inhibitor–resistant chronic myelogenous leukemia	Patients with tyrosine kinase inhibitor–resistant chronic myelogenous leukemia (CML)	CML often responds to treatment with tyrosine kinase inhibitors targeting the BCR-ABL fusion gene; however, patients whose disease progresses after 1st- and 2nd-line tyrosine kinase inhibitor treatment have few treatment options and a poor prognosis. Omacetaxine mepesuccinate (Omapro®) is a cytotoxic alkaloid derived from the evergreen tree *Cephalotaxus harringtonia*. Omacetaxine mepesuccinate purportedly acts as a reversible, transient inhibitor of protein elongation. This inhibition leads to cell death through multiple mechanisms of action, including inhibition of HSP90, which leads to destabilization of BCR-ABL and downregulation of the antiapoptotic protein MCL-1. In clinical trials, omacetaxine mepesuccinate was administered twice daily, by subcutaneous injection. Cephalon unit of Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, (previously developed by ChemGenex Pharmaceuticals, Ltd., which was acquired by Cephalon) FDA approved Oct 2012 for treating adults with CML whose disease is resistant to or who cannot tolerate other FDA-approved drugs for CML	Allogeneic stem cell transplantation Ponatinib	Increased overall survival Increased progression-free survival Improved quality of life
Onartuzumab, (MetMAb) for treatment of advanced nonsmall cell lung cancer	Patients with Met-positive advanced (stage IIIb/IV) nonsmall cell lung cancer (NSCLC) that has progressed after 1st-line systemic chemotherapy	Patients with advanced/metastatic NSCLC that has progressed following 1st-line therapy have a poor prognosis and few treatment options. MET (also known as hepatocyte growth factor receptor) is a receptor tyrosine kinase that regulates cell growth and survival. MET has been implicated in the development of tumor resistance to epidermal growth factor receptor (EGFR) inhibition. Onartuzumab (MetMAb) blocks ligand-mediated activation of the MET receptor tyrosine kinase and is being studied in combination with the EGFR inhibitor erlotinib in treating NSCLC. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trial ongoing	Crizotinib Docetaxel Erlotinib monotherapy Pemetrexed Tivantinib (c-Met kinase inhibitor in development)	Increased overall survival Increased progression-free survival Improved quality of life
Oncolytic reovirus (Reolysin) for treatment of platinum-resistant head and neck cancer	Patients with platinum-resistant head and neck cancer who have undergone 1st-line treatment with a platinum-based chemotherapy regimen	Reolysin® is an oncolytic reovirus being developed to treat various cancer and cell proliferative disorders. It replicates specifically in cells that have activated RAS, which may play a role in more than 2/3 of all cancers. Reolysin is administered in combination with paclitaxel and carboplatin. Oncolytics Biotech, Inc., Calgary, Alberta, Canada Phase III trial ongoing	Various platin-based multiple agent chemotherapy regimens 5-fluorouracil Bleomycin Docetaxel Gemcitabine Ifosfamide Methotrexate Paclitaxel	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
OncoVex GM-CSF for treatment of advanced melanoma	Patients in whom advanced melanoma has been diagnosed	Patients with advanced melanoma have a poor prognosis and few treatment options, suggesting a need for novel treatment options. OncoVex granulocyte macrophage colony-stimulating factor (GM-CSF; talimogene laherparepvec) is an oncolytic virus; the virus purportedly replicates only in tumor cells. OncoVex is engineered to lyse tumor cells and express tumor-specific antigens and GM-CSF, which help to generate tumor specific immune responses for additional benefit. In trials, it is administered up to 4 mL of 10^8 pfu/mL/per intratumoral injection. Amgen, Inc., Thousand Oaks, CA Phase III trial ongoing	Dacarbazine Interleukin-2 Ipilimumab Temozolomide Vemurafenib	Increased overall survival Increased progression-free survival Improved quality of life
Orteronel (TAK 700) for treatment of castration-resistant prostate cancer	Patients in whom castration-resistant prostate cancer (CRPC) has been diagnosed	Median overall survival for patients with CRPC is only about 18 months. Many prostate tumors remain dependent on androgens for growth and survival; new treatments that can disrupt the production of bioactive androgens may provide effective tumor therapy. Orteronel (TAK 700) is a steroid 17-alpha-hydroxylase inhibitor; this enzyme is involved in forming 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-naïve patients or after docetaxel, in combination with prednisone. Millennium Pharmaceuticals subsidiary of Takeda Pharmaceutical Co., Ltd., Osaka, Japan Phase III trials ongoing	Abiraterone Cabazitaxel Docetaxel Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
Pazopanib (Votrient) for preventing recurrence of ovarian cancer after successful 1st-line therapy	Patients with stage II–IV ovarian cancer, fallopian tube, or primary peritoneal carcinoma who have undergone surgical debulking and successful treatment with platinum agent/taxane combination therapy	Patients in whom ovarian cancer is diagnosed often respond to 1st-line treatment with cytoreduction and chemotherapy; however, a large number of these patients will experience disease recurrence, and therapies intended to prolong remission are needed. Pazopanib (Votrient™) is a tyrosine kinase inhibitor with activity against multiple kinases including vascular endothelial growth factor (VEGF) receptor 1 (VEGFR1), VEGFR2, VEGFR3, platelet-derived growth factor receptor-alpha/beta, and c-KIT. Inhibition of these kinases may limit tumor angiogenesis and/or tumor growth. In late-phase clinical trials, pazopanib is administered as an oral tablet, at a dosage of 800 mg/day, for up to 2 years. GlaxoSmithKline, London, UK Phase III trial ongoing; FDA approved for renal cell carcinoma	Bevacizumab may be used as maintenance therapy after bevacizumab-containing treatment regimens Paclitaxel Watchful waiting	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pazopanib (Votrient) for treatment of soft tissue sarcomas	Patients with advanced soft tissue sarcoma (excluding gastrointestinal stromal tumors [GIST] and liposarcomas) who have undergone prior systemic chemotherapy	Doxorubicin is the only FDA-approved treatment for soft tissue sarcomas (excluding GIST and liposarcomas), and no consensus treatment exists for patients who have progressed on doxorubicin chemotherapy. Pazopanib (Votrient™) is a multikinase inhibitor that has activity against multiple receptor tyrosine kinases (vascular endothelial growth factor receptor 1 [VEGFR1], VEGFR2, VEGFR3, platelet-derived growth factor receptor, c-KIT) and has the potential to inhibit tumor angiogenesis and growth. Although other multikinase inhibitors (e.g., sorafenib, sunitinib) have been used off label to treat soft tissue sarcoma, no such compound has been approved by FDA. GlaxoSmithKline, Middlesex, UK FDA approved Apr 2012	No consensus 2nd-line treatment for soft tissue sarcoma Placebo Sorafenib (off label) Sunitinib (off label)	Increased overall survival Increased progression-free survival Improved quality of life
Pegylated arginine deiminase (ADI-PEG 20) for treatment of hepatocellular carcinoma	Patients with advanced hepatocellular carcinoma (HCC) whose disease has failed to respond to 1 prior course of systemic therapy	For patients who cannot be cured by surgical removal of the tumor, survival rates for HCC are very low (about 5%), with median survival after diagnosis of only about 6 months. ADI-PEG 20 is a pegylated preparation of arginine deiminase, which acts by depleting the essential amino acid arginine from the bloodstream. Research has demonstrated that the cells of many tumor types are unable to autonomously synthesize arginine and, therefore, tumor cells are preferentially affected by the loss of arginine supply in the blood. It is administered through intramuscular injection on outpatient basis. Polaris Pharmaceuticals, Inc., San Diego, CA Phase III trial initiated under FDA special protocol assessment; FDA granted orphan drug status	Placebo	Increased overall survival Increased progression-free survival Improved quality of life
Peptide-cytokine complex (NGR-hTNF) for treatment of malignant pleural mesothelioma	Patients with malignant pleural mesothelioma who have undergone treatment with pemetrexed and cisplatin	NGR-hTNF (human tumor necrosis factor) is a peptide-cytokine complex; NGR peptide binds preferentially to tumor vasculature and TNF may induce an immune cell reaction/apoptosis, thereby destroying tumors. Given in dosage of 0.8 mcg/m² of body surface area as a 60-minute intravenous infusion every 3 weeks until confirmed evidence of disease progression or unacceptable toxicity occurs. MolMed, S.p.A., Milan, Italy Phase III trial ongoing in 2nd-line setting; phase II trial ongoing in 1st-line setting; received patent from European Patent Office in Jun 2012	Pemetrexed plus cisplatin as 1st-line treatment Single-agent chemotherapy as a 2nd-line treatment (e.g., doxorubicin, gemcitabine, vinorelbine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Perifosine (KRX-0401) for treatment of multiple myeloma	Patients in whom multiple myeloma has been diagnosed	Perifosine (KRX-0401) anticancer agent inhibits Akt activation in the phosphoinositide 3-kinase pathway; also affects other key signal transduction pathways, including c-Jun amino-terminal kinase (JNK); intended for treating several tumor types. Administered as a single oral agent and in combination with standard multiple myeloma therapies. Aeterna Zentaris, Inc., Quebec, Quebec, Canada; all license rights reverted back to Aeterna Zentaris from Keryx Biopharmaceuticals, Inc., New York, NY, in May 2012 Phase III trials ongoing for multiple myeloma under FDA special protocol assessment	Various combination chemotherapeutic regimens that include 1 or more of the following: Bendamustine Bortezomib Cyclophosphamide Dexamethasone Etoposide Lenalidomide Liposomal doxorubicin Thalidomide	Increased overall survival Increased progression-free survival Improved quality of life
Pertuzumab (Perjeta) for treatment of metastatic breast cancer	Patients with metastatic HER2-positive breast cancer who are receiving 1st-line trastuzumab and docetaxel	No curative treatment for patients with metastatic breast cancer has been identified, and patients with HER2-positive breast cancer receiving trastuzumab-based chemotherapy have median survival times of only about 3 years. Trastuzumab is an FDA-approved monoclonal antibody specific for HER2 that purportedly functions by causing a reduction in the level of HER2 protein at the cell surface and by inhibiting proteolytic cleavage and release of the extracellular domain of HER2. Pertuzumab (Perjeta®) is a novel HER2-specific monoclonal antibody that binds to a different site on the HER2 extracellular domain; pertuzumab purportedly functions by inhibiting the heterodimerization of HER2 with other HER receptors, which is required for HER2 activation. Originally tested as a monotherapy with limited benefit, pertuzumab is undergoing studies in combination with trastuzumab to ascertain whether a more comprehensive inhibition of HER2 activity can improve outcomes in patients with metastatic breast cancer. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials ongoing; phase III trial in previously untreated, metastatic breast cancer met primary endpoint Jul 2011; biologics license application submission accepted for priority review by FDA in Feb 2012; FDA approved Jun 2012	Trastuzumab plus capecitabine, docetaxel, or vinorelbine Trastuzumab plus paclitaxel with or without 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
Phosphoinositide 3-kinase inhibitor (BKM120) for treatment-refractory metastatic breast cancer	Patients with aromatase inhibitor or mTOR inhibitor–refractory, hormone receptor–positive, HER2-negative metastatic breast cancer	Patients with hormone receptor–positive breast cancer typically develop resistance to 1st-line therapy with estrogen receptor–targeted therapies. The phosphoinositide 3 kinase (PI3K)/mTOR pathway is a cell signaling pathway that is frequently activated in a wide range of cancers and, in particular, may underlie tumor resistance to estrogen receptor–targeted therapies. BKM120 is a pan-PI3K inhibitor (i.e., inhibits all PI3K isoforms) that is intended to block PI3K/mTOR pathway activity. In clinical trials, BKM120 is being administered orally, in combination with the antiestrogen drug fulvestrant. Novartis International AG, Basel, Switzerland Phase III clinical trials in hormone receptor–positive breast cancer ongoing; BKM120 is also under study for endometrial cancer, glioblastoma, HER2-positive breast cancer, melanoma, nonsmall cell lung cancer, prostate cancer, and urothelial cancer	Fulvestrant monotherapy Everolimus plus exemestane	Increased overall survival Increased progression-free survival Improved quality of life
Photodynamic therapy with Tookad photosensitive agent for treatment of localized prostate cancer	Patients in whom localized low-risk prostate cancer has been diagnosed	Current treatment of localized prostate cancer can adversely affect surrounding healthy tissue and also lead to debilitating temporary and long-term side effects or complications. Tookad is a photosensitive agent that can be excited by a specific wavelength of light to release energy that can cause local necrosis. In a photodynamic therapy procedure using Tookad, the drug is injected by needle into the prostate. After the drug diffuses into the prostate, laser light is used to excite the drug, potentially leading to destruction of targeted prostate tissue while sparing surrounding healthy tissue. Steba Biotech S.A., Cedex, France Phase III trial ongoing	Radiation therapy Radical prostatectomy Watchful waiting	Increased overall survival Increased progression-free survival Fewer therapy-related side effects Improved quality of life
PI3 kinase delta isoform inhibitor (GS-1101) for treatment of chronic or small lymphocytic leukemia	Patients in whom chronic lymphocytic leukemia or small lymphocytic leukemia has been diagnosed	GS-1101 (formerly CAL-101) inhibits the activity of a novel target: phosphoinositide 3-kinase (PI3K) delta, which is a kinase that promotes cell survival, division, and growth. The delta isoform of Class I PI3K is only expressed in the blood, and targeted inhibition could treat blood-based cancers without side effects on nonblood tissues. Under study in combination with rituximab. Gilead Sciences, Inc., Foster City, CA Phase III trial ongoing	Various combination chemotherapies including 1 or more of the following: Cyclophosphamide Doxorubicin Fludarabine Prednisolone Rituximab Vincristine	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Poly ADP-ribose polymerase inhibitor (iniparib) for treatment of metastatic nonsmall cell lung cancer	Patients in whom treatment-naïve stage IV metastatic nonsmall cell lung cancer (NSCLC) has been diagnosed	The 5-year survival rate for patients with stage IV NSCLC is less than 10%, and effective treatments are needed. Iniparib is intended to inhibit poly adenosine diphosphate (ADP)-ribose polymerase (PARP), which functions in 1 type of DNA repair. It has been observed that cancers are often deficient in a 2nd type of DNA repair, and loss of both types of DNA repair is hypothesized to result in cancer cell lethality in response to DNA damage. No PARP inhibitors are on the market. Iniparib is being administered in combination with a DNA damage inducing chemotherapy regimen (gemcitabine, carboplatin). BiPar Sciences, San Francisco, CA Sanofi, Paris, France Phase III trial ongoing	Cytotoxic chemotherapy (e.g., gemcitabine, carboplatin) alone	Increased overall survival Increased progression-free survival Improved quality of life
Polydisperse oligonucleotide (defibrotide) for treatment of chemotherapy-induced severe veno-occlusive disease	Patients receiving chemotherapy in whom severe veno-occlusive disease has been diagnosed	Veno-occlusive disease is a side effect of the high-dose chemotherapy that is used as part of hematopoietic stem cell transplantation procedures. Severe veno-occlusive disease has a mortality rate approaching 100% with current treatments. Defibrotide is an orally administered, polydisperse oligonucleotide with local antithrombotic, anti-ischemic, and anti-inflammatory activities. Study investigators have suggested that the drug may increase survival of endothelial cells and preserve the function of microvasculature. In a phase III trial, the drug was administered at daily doses of 20 or 40 mg/kg of body weight. Gentium S.p.A., Villa Guardia, Italy Phase III trial complete. FDA granted orphan drug and fast track status; Gentium submitted new drug application to FDA in Jul 2011; FDA issued a refuse to file response and the company withdrew the application in Aug 2011, stating that it would work to address the issues and resubmit	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
Pomalidomide for treatment-refractory multiple myeloma	Patients with treatment-resistant (i.e., lenalidomide and bortezomib) multiple myeloma	Treatments for multiple myeloma have improved, but the median life expectancy for patients in whom it is diagnosed is only 5–7 years. Additionally, as several newer treatments for multiple myeloma have moved to the 1st -line setting as combination therapies, additional salvage treatments are needed in cases in which the disease no longer responds to treatment. Pomalidomide is a novel thalidomide derivative that has modulatory effects on angiogenesis, inflammation, and immune cell costimulation. In clinical trials for treating multiple myeloma, pomalidomide is administered orally, at a daily dose of 4 mg, in combination with low-dose dexamethasone. Celgene Corp., Summit, NJ Phase III trial ongoing; in Apr 2012, Celgene submitted a new drug application to FDA for accelerated approval on the basis of phase II trial results; FDA Oncologic Drugs Advisory Panel meeting scheduled for Nov 2012 to review product was canceled; FDA decision date was set for Feb 10, 2013	Combination chemotherapy including one or more of the following: Bendamustine Bortezomib Cisplatin Cyclophosphamide (including high dose) Dexamethasone Doxorubicin Etoposide Thalidomide	Increased overall survival Increased progression-free survival Improved quality of life
Ponatinib (Iclusig) for treatment of chronic myelogenous leukemia or Philadelphia chromosome–positive acute lymphoblastic leukemia	Patients in whom chronic myelogenous leukemia (CML) or Philadelphia chromosome–positive negative acute lymphoblastic leukemia (ALL) has been diagnosed	Patients with treatment-refractory CML or ALL generally have a poor prognosis, rapidly progressing disease, and few treatment options, 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 (Iclusig™) is a next-generation BCR-ABL tyrosine kinase inhibitor rationally designed to be effective against common mutations conferring resistance to current BCR-ABL tyrosine kinase inhibitors. Administered orally, 45 mg, once daily. Ariad Pharmaceuticals, Inc., Cambridge, MA FDA granted accelerated approval in Dec 2012 for patients with CML or Philadelphia chromosome–positive ALL that is resistant or intolerant to available tyrosine kinase inhibitors; phase III trial in first-line treatment of CML ongoing	Dasatinib Imatinib Nilotinib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Progesterone receptor antagonist (mifepristone, Korlym) for treatment of endogenous Cushing's syndrome	Patients with endogenous Cushing's syndrome who experience persistent hypercortisolemia after surgery or radiation therapy or whose tumor is ineligible for surgery or radiation therapy	Cushing's syndrome is caused by chronic exposure to elevated levels of the hormone cortisol. Endogenous Cushing's syndrome is caused by the body's production of high levels of cortisol or a cortisol precursor (adrenocorticotrophic hormone) typically by pituitary, adrenal, or ectopic endocrine tumors. Although some tumors can be successfully treated by surgery or radiation therapy or both, patients who are ineligible for these treatments or who have persistent elevation of cortisol following treatment had no FDA-approved medical options for treatment. Mifepristone (Korlym™) acts to block the cortisol receptor, potentially ameliorating the effects of elevated cortisol levels. In clinical trials, mifepristone taken orally, once daily. Corcept Therapeutics, Menlo Park, CA FDA approved Feb 2012 to control hyperglycemia in adults with endogenous Cushing's syndrome	Ketoconazole (off label) Metyrapone (off label) Mitotane (off label)	Improved symptoms of Cushing's syndrome (e.g., diabetes, glucose intolerance, hypertension)
Prophage series G-200 therapeutic vaccine for gliomas	Patients diagnosed with primary or recurrent brain and central nervous system cancers (gliomas)	Prophage (vitespen and HSPPC-96) is a cancer vaccine that is derived from antigens displayed by the patient's individual tumor. A tumor sample is collected and sent to the laboratory, where workers coimmunoprecipitate the antigens with heat shock protein GP96. These antigens are delivered in weekly/biweekly injections in an attempt to stimulate an immune response against residual cancer cells. Under development for use in both adults and pediatric patients. Agenus, Inc., Lexington, MA Phase II trials ongoing in adults; phase I trial planned for pediatric brain cancers; FDA granted orphan drug status	Bevacizumab Bevacizumab plus irinotecan, BCNU/CCNU, temozolomide Combination PCV (CCNU, procarbazine, and vincristine) Cyclophosphamide Nitrosourea Nitrosourea wafer Platinum-based chemotherapy Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Prostate cancer antigen 3 (Progensa PCA3) assay to determine need for repeat prostate biopsy	Patients undergoing digital rectal examinations for prostate cancer screening	The assay is a urine test that is performed after a digital rectal examination; detects a nonprotein coding messenger RNA, prostate cancer antigen 3, that is highly overexpressed in the "vast majority" of prostate cancers. Assay was developed as a test kit. The FDA indication approved in Feb 2012 is "for use in conjunction with other patient information to aid in the decision for repeat biopsy in men 50 years of age or older who have had 1 or more previous negative prostate biopsies and for whom a repeat biopsy would be recommended by a urologist based on the current standard of care, before consideration of the assay results. A negative Progensa PCA3 assay result is associated with a decreased likelihood of a positive biopsy. A prostate biopsy is required to diagnose cancer." Gen-Probe subsidiary of Hologic, Bedford, MA FDA approved Feb 2012; Conformité Européene (CE) marked in 2006	Digital rectal examination alone Prostate-specific antigen blood test screening	Increased sensitivity and specificity Improved predictive values Avoided unnecessary followup (i.e., biopsy)
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 viral vector vaccine is approved. ProstVac® is a prime-boost immune therapy strategy using fowlpox and vaccinia viral vectors encoding prostate specific antigen and 3 immune costimulatory molecules; the patient's immune system is primed using the vaccinia virus followed by multiple fowlpox vector boosts. Given in 1 prime step and then weekly injections to generate an immune response. BN ImmunoTherapeutics, Mountain View, CA Phase III trial ongoing	Abiraterone Enzalutamide Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life
Protein kinase C-beta inhibitor (enzastaurin) for treatment of diffuse large B-cell lymphoma	Patients with diffuse large B-cell lymphoma (DLBCL) who have achieved complete remission after R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone) chemotherapy	The majority of patients in whom DLBCL is diagnosed achieve complete remission following 1st-line therapy; however, disease recurs in about 25% to 30% of patients. Enzastaurin is a small-molecule inhibitor of protein kinase C beta (PKC-beta) that is being studied as maintenance therapy to prevent DLBCL recurrence. PKC family members play a central role in a diverse range of cellular functions including the passage of signals from receptor tyrosine kinases controlling cell growth, cell survival, and endothelial cell migration. Inhibition of PKC-beta by enzastaurin is hypothesized to limit tumor growth and survival and angiogenesis. In a phase III trial, enzastaurin is being administered in a daily oral dose of 500 mg. Eli Lilly and Co., Indianapolis, IN Phase III trial ongoing	No maintenance therapy is available for DLBCL	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Psilocybin for treatment of anxiety in patients with advanced cancer	Patients with advanced cancer who are not responsive to conventional anxiety and mood therapies	Moderate dose (0.2 mg/kg of body weight) is intended to reduce anxiety and pain for up to 6 months without adverse psychological or physiological events. Various organizations, including New York University and Los Angeles Biomedical Research Institute Trial ongoing and estimated to complete in 2014	Conventional depression/anxiety drug therapy Psychotherapy	Reduced anxiety Reduced need for pain medication Improved quality of life
Radiofrequency ablation of liposomal-encapsulated doxorubicin (ThermoDox) for treatment of hepatocellular carcinoma	Patients in whom hepatocellular carcinoma (HCC) has been diagnosed	ThermoDox™ is a heat-labile liposomal encapsulation of the chemotherapeutic agent doxorubicin. When radiofrequency (RF) energy is applied to the target tissue, it induces local hyperthermia (39.5 to 42 ^{o}C), which releases the agent locally. Celsion Corp., New York, NY Phase III trial ongoing; National Cancer Institute recommended phase III trial as priority for HCC; granted orphan drug status by FDA Mar 2009	RF tumor ablation alone Surgical resection Transcatheter arterial chemoembolization	Decreased need for liver transplantation Reduced side effects Increased overall survival Increased progression-free survival Improved quality of life
Radiolabeled antibody (I-124-cG250, Redectane) for detection of clear cell renal cell carcinoma using positron emission tomography	Patients with uncharacterized renal masses; patients undergoing treatment for renal cell carcinoma	CG250 is a monoclonal antibody specific for carbonic anhydrase IX, a protein that is expressed by the majority of clear cell renal cell carcinomas (ccRCCs) and few normal tissues. Redectane® is a modified version of cG250 that incorporates a radioisotope that can be visualized by positron emission tomography (iodine-124). In combination with computed tomography (CT), imaging using Redectane could potentially be used in the diagnosis of ccRCC and to monitor ccRCC treatment efficacy and screen patients for ccRCC recurrence and metastasis. Redectane is administered by intravenous infusion. Wilex AG, Munich, Germany Phase III trial complete	CT imaging alone	Increased sensitivity and specificity for ccRCC

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Radiopharmaceu-tical (tilmanocept) for sentinel lymph node detection	Selected patients undergoing surgical resection of primary breast, melanoma, or head and neck tumors	The radiopharmaceuticals used to detect tumor-site draining lymph nodes for sentinel lymph node biopsy have several shortcomings, such as slow injection-site clearance, a relatively long half-life, and significant lymph node pass-through. Tilmanocept (Lymphoseek®) is a novel radiopharmaceutical preparation that is intended to improve on these by using a technetium-99 radiolabel. This radiolabel is coupled to a macromolecule that contains multiple units of mannose, which bind to the surface of dendritic cells and macrophages present in lymph nodes. Tilmanocept is administered by injection prior to the procedure. Navidea Biopharmaceuticals (formerly NeoProbe), Dublin, OH Phase III trials complete. In Oct 2011, FDA accepted new drug application for review; in Sept 2012, FDA issued a Complete Response Letter to the company due to manufacturing deficiencies. Company resubmitted the NDA application in Oct 2012. FDA accepted the company's NDA and set a Prescription Drug User Fee Act date of Apr 30, 2013.	Technetium sulfur colloid Vital blue dye (e.g., isosulfan blue)	Increased sentinel node detection sensitivity and specificity Improved patient outcomes Optimized treatment selection
Radium-223 (Alpharadin) for treatment of bone metastases associated with solid tumors	Patients in whom bone metastases associated with advanced hormone-refractory metastatic prostate cancer have been diagnosed	Bone metastases occur in late stages of the majority of solid tumors and are associated with significant morbidity and mortality; however, few treatments specifically targeting bone metastases are available. Alpharadin® is a preparation of radium-223, an alpha particle–emitting isotope that has a natural affinity for bone. It purportedly accumulates in the bone where it preferentially attacks tumors rather than bone marrow because of the short distance over which alpha particles are cytotoxic. Alpharadin is administered in multiple intravenous doses. Algeta ASA, Oslo, Norway, in collaboration with Bayer AG, Leverkusen, Germany Phase III trial complete; new drug application submission for Alpharadin submitted to FDA in Dec 2012; granted fast track status by FDA	Standard therapy plus denosumab or cabozantinib (Cometriq™) Standard therapy with and without Alpharadin	Increased overall survival Increased progression-free survival Increased rate of alkaline phosphatase normalization Reduced pain from bone metastases Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Raman spectroscopy device (Verisante Aura) for melanoma screening	Patients in whom a suspicious skin lesion has been identified	Available methods for melanoma screening have significant false positive rates that lead to a large number of biopsy procedures on benign skin lesions. The Verisante Aura device provides the user with a binary outcome regarding whether an assayed lesion should be biopsied. The device analyses suspicious lesions using a noninvasive method based on Raman spectroscopy, which purportedly detects biochemical differences between benign and malignant lesions. Verisante Technology, Inc., Vancouver, British Columbia, Canada 1,000-lesion clinical trial completed; approved for marketing approval in Canada and EU; company stated plans to pursue FDA approval	Dermatologist visual screening MelaFind computer-aided multispectral dermatoscope	Increased sensitivity and specificity for lesion detection Increased positive and negative predictive values Reduced unnecessary biopsies Improved quality of life
Ramucirumab for treatment of hepatocellular carcinoma	Patients with hepatocellular carcinoma (HCC) whose disease is Barcelona Clinic Liver Cancer stage C or stage B and not amenable to locoregional therapy	No consensus exists on treatment for HCC that has progressed after treatment with sorafenib, and these patients have a poor prognosis. Ramucirumab is a novel monoclonal antibody that binds to the extracellular domain of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2), which is a receptor tyrosine kinase that acts as a central mediator of tumor angiogenesis. Available inhibitors of the VEGF pathway include a monoclonal antibody specific for VEGF and small-molecule inhibitors of the kinase activity of VEGFR2 (and other receptor tyrosine kinases). Therefore, ramucirumab represents a novel mechanism of action for the inhibition of VEGF pathway signaling. In clinical trials for HCC, ramucirumab is administered intravenously, 8 mg/kg of body weight, once every 2 weeks. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing	No consensus on treatment for this patient population	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ramucirumab for treatment of metastatic breast cancer	Patients with metastatic or nonresectable locally advanced HER2-negative breast cancer	Patients with metastatic or nonresectable locally advanced HER2-negative breast cancer have a poor prognosis with current treatment options. Ramucirumab is a novel monoclonal antibody that binds to the extracellular domain of vascular endothelial growth factor (VEGF) receptor 2 (VEFGR2), which is a receptor tyrosine kinase that acts as a central mediator of tumor angiogenesis. Available inhibitors of the VEGF pathway include a monoclonal antibody specific for VEGF and small-molecule inhibitors of the kinase activity of VEGFR2 (and other receptor tyrosine kinases). Therefore, ramucirumab represents a novel mechanism of action for the inhibition of VEGF pathway signaling. In clinical trials for breast cancer, ramucirumab is administered intravenously, 10 mg/kg of body weight, once every 3 weeks. Treatment is intended to be used in the 1st-line setting for metastatic or nonresectable disease. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trial ongoing	Taxane-based (e.g., docetaxel, paclitaxel) therapy) with or without capecitabine or gemcitabine or bevacizumab or anthracycline-based therapy	Increased overall survival Increased progression-free survival Improved quality of life
Ramucirumab for treatment of metastatic colorectal cancer	Patients in whom metastatic colorectal cancer (CRC) has been diagnosed	Current 2nd-line treatments for metastatic CRC are of limited efficacy, and the median overall survival of these patients is less than 1 year. Ramucirumab is a novel monoclonal antibody that binds to the extracellular domain of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2), which is a receptor tyrosine kinase that acts as a central mediator of tumor angiogenesis. Available inhibitors of the VEGF pathway include a monoclonal antibody specific for VEGF and small-molecule inhibitors of the kinase activity of VEGFR2 (and other receptor tyrosine kinases). Therefore, ramucirumab represents a novel mechanism of action for the inhibition of VEGF pathway signaling. In clinical trials for gastric cancer, ramucirumab is intravenously administered at a dose of 8 mg/kg of body weight once every 2 weeks as an adjunct to the standard 2nd-line FOLFIRI (folinic acid [leucovorin], 5-fluorouracil, and irinotecan) regimen. Treatment is intended for patients whose disease has progressed after standard 1st-line chemotherapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trial ongoing	Various FOLFIRI-based therapies with or without cetuximab or panitumumab	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ramucirumab for treatment of metastatic gastric cancer	Patients in whom metastatic gastric cancer has been diagnosed	Patients with gastric cancer that has progressed after 1st-line chemotherapy have a poor prognosis with median survival times of less than 1 year. Ramucirumab is a novel monoclonal antibody that binds to the extracellular domain of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2), which is a receptor tyrosine kinase that acts as a central mediator of tumor angiogenesis. Available inhibitors of the VEGF pathway include a monoclonal antibody specific for VEGF and small-molecule inhibitors of the kinase activity of VEGFR2 (and other receptor tyrosine kinases). Therefore, ramucirumab represents a novel mechanism of action for the inhibition of VEGF pathway signaling. In clinical trials for gastric cancer, ramucirumab is intravenously administered at a dose of 8 mg/kg of body weight, once every 2 weeks. Treatment is intended for disease that has progressed after standard 1st-line platinum-based or fluoropyrimidine-based regimens. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing	Taxane (e.g., docetaxel, paclitaxel) monotherapy Various irinotecan-based single and combination therapies	Increased overall survival Increased progression-free survival Improved quality of life
Ramucirumab for treatment of metastatic nonsmall cell lung cancer	Patients in whom metastatic nonsmall cell lung cancer (NSCLC) has been diagnosed	Patients with metastatic NSCLC whose disease has progressed after 1st-line chemotherapy have few treatment options and a median overall survival of less than 1 year. Ramucirumab is a novel monoclonal antibody that binds to the extracellular domain of vascular endothelial growth factor (VEGF) receptor 2 (VEGFR2), which is a receptor tyrosine kinase that acts as a central mediator of tumor angiogenesis. Available inhibitors of the VEGF pathway include a monoclonal antibody specific for VEGF and small-molecule inhibitors of the kinase activity of VEGFR2 (and other receptor tyrosine kinases). Therefore, ramucirumab represents a novel mechanism of action for the inhibition of VEGF pathway signaling. In clinical trials for NSCLC, ramucirumab is intravenously administered at a dose of 10 mg/kg of body weight, once every 3 weeks as an adjunct to standard 2nd-line chemotherapy with docetaxel. Treatment is intended for patients whose disease has progressed following 1 round of platinum-based chemotherapy. ImClone Systems subsidiary of Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing	Crizotinib Docetaxel Erlotinib Pemetrexed	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Reconstructive laryngeal surgery after treatment of malignancies in the cricoid area	Patients undergoing reconstructive surgery after surgery for cancer in the cricoid cartilage area	Often, malignancies of the cricoid area (i.e., chondrosarcoma) require complete laryngectomy, forcing patients to communicate with voice prostheses or alternative electronic devices. A University of Michigan surgeon has created a surgical procedure that involves resecting the tumor and surrounding cricoid cartilage, harvesting the tip of the patient's shoulder blade (selected for its curvature and blood supply from surrounding muscle), reshaping the bone piece to match the shape of resected cartilage, and transplanting the portion of bone and muscle into the voice box. Dr. Douglas Chepeha, University of Michigan, Ann Arbor 1 case report	Laryngectomy	Preserved larynx and reconstructed cricoid Improved quality of life
Regorafenib (Stivarga) for treatment of gastrointestinal stromal tumors	Patients with advanced/ metastatic gastrointestinal stromal tumors (GIST) that progressed following treatment with imatinib and sunitinib	Patients with GIST whose disease progresses after imatinib and sunitinib therapy have few treatment options and a poor prognosis with approximate progression-free survival and overall survival times of 100 and 300 days, respectively. Regorafenib (Stivarga®) is an inhibitor of multiple tyrosine kinases, including the pro-angiogenic kinases vascular endothelial growth factor receptor 2 and TIE-2 (as well as RAF, RET, and KIT); inhibition of both primary angiogenic kinase pathways is a novel combination in multikinase inhibitor drugs (e.g., imatinib, sunitinib). Bayer AG, Leverkusen, Germany Phase II and phase III trials ongoing; Feb 2011, FDA granted orphan drug status for GIST; in Apr 2012, Bayer announced that regorafenib had improved survival in a phase III trial; in Aug 2012, Bayer announced that a new drug application for this indication had been submitted to FDA	Sorafenib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Regorafenib (Stivarga) for treatment of metastatic colorectal cancer	Patients with metastatic colorectal cancer (CRC) as both a 1st-line treatment in combination with standard cytotoxic chemotherapy (FOLFOX) and as a salvage treatment after all available treatments have been tried	Many treatment options are available for 1st-line treatment of metastatic CRC, but 5-year survival rates are only about 25%. No multikinase inhibitors have been approved for use in metastatic CRC. Regorafenib (Stivarga®) is an inhibitor of multiple tyrosine kinases, including the pro-angiogenic kinases vascular endothelial growth factor receptor 2 and TIE-2 (as well as RAF, RET, and KIT); inhibition of both primary angiogenic kinase pathways is a novel combination in multikinase inhibitor drugs (e.g., sunitinib). Bayer AG, Leverkusen, Germany FDA approved for metastatic CRC Sept 2012	1st-line therapy comparators include: FOLFOX (folinic acid [leucovorin], 5-fluorouracil [5-FU], oxaliplatin) alone FOLFOX plus targeted therapy (e.g., bevacizumab, cetuximab, panitumumab) Other cytotoxic chemotherapy regimens plus or minus targeted therapy (e.g., CapeOX, FOLFIRI, [leucovorin, 5-FU, and irinotecan], 5-FU/leucovorin, capecitabine, FOLFOXIRI [FOLFIRI plus oxaliplatin])	Increased overall survival Increased progression-free survival Improved quality of life
Rigosertib (Estybon) for treatment of myelodysplastic syndrome	Patients with azacitidine- or decitabine-refractory myelodysplastic syndrome with excess blasts	Patients with myelodysplastic syndrome with excess blasts that has not responded to azacitidine or decitabine treatment have a poor prognosis and no standard treatment options. Rigosertib (Estybon®) is a small-molecule, multikinase inhibitor with activity against both the alpha and beta isoforms of the phosphoinositide 3 kinase (PI3K) and polo-like kinase 1 (Plk1). Inhibition of PI3K may disrupt cell signaling that promotes cell growth and survival, and inhibition of Plk1 may disrupt mitosis, leading to cell-cycle arrest. In clinical trials, rigosertib is being administered as a monotherapy in a 72-hour continuous intravenous infusion. Onconova Therapeutics®, Inc., Newtown, PA Phase III trial ongoing	Hematopoietic stem cell transplant Immunosuppressive therapy (e.g., anti-thymocyte globulin plus or minus cyclosporine)	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Routine anal Pap smear screening at HIV clinics to prevent anal cancer	Patients in whom HIV infection has been diagnosed	Patients with HIV have a higher risk of developing anal cancer, yet national or international guidelines do not exist for anal dysplasia screening. Anal Pap (Papanicolaou) screening can be incorporated into routine visits when patients attend HIV clinics for treatment and monitoring, and some clinicians recommend screening regardless of history of anal intercourse. University of Miami Miller School of Medicine, Miami, FL	Anal Pap screening or anoscopy by other physician during regular intervals (after 50 years of age) or during routine gynecologic visits for women	Earlier detection of suspicious polyps Reduced anal cancer incidence in patients with HIV Reduced anal cancer mortality in patients with HIV
Ruxolitinib (Jakafi) for treatment of myelofibrosis	Patients who have myelofibrosis (primary myelofibrosis, post-polycythemia vera myelofibrosis, or post essential thrombocythemia myelofibrosis)	Ruxolitinib is a Janus kinase (JAK) inhibitor (INCB018424, Jakafi™) that inhibits kinase activity of both JAK 2 and JAK 1. Half of myelofibrosis cases bear an activating mutation in JAK 2; therefore, its inhibition is a key target. Incyte Corp., Wilmington, DE, in collaboration with Novartis International AG, Basel, Switzerland FDA approved Nov 2011	None Off-label treatments are only palliative	Increased overall survival Increased progression-free survival Improved quality of life
Small-molecule drug conjugate (vintafolide) for treatment of platinum-resistant ovarian cancer	Patients with platinum-resistant ovarian cancer who have undergone 1 or 2 rounds of platinum-based chemotherapy	Patients in whom platinum-resistant ovarian cancer has been diagnosed have a poor prognosis and few treatment options. Vintafolide (EC145) is a novel, small-molecule drug conjugate that uses a peptide linker to couple a targeting ligand to a cytotoxic agent. In vintafolide, the targeting ligand is specific for the folate receptor, which is expressed on the majority of ovarian cancer cells, but not on cells of normal tissue. Based on this difference, the cytotoxic drug linked to the folate receptor targeting ligand might be preferentially delivered to malignant cells. Vintafolide is administered intravenously and is being studied in combination with pegylated liposomal doxorubicin. Endoctye, Inc., West Lafayette, IN, in collaboration with Merck & Co., Inc., Whitehouse Station, NJ Phase III trial ongoing	Docetaxel Etoposide Gemcitabine Paclitaxel Pegylated liposomal doxorubicin Topotecan	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
SNS01-T for treatment-refractory multiple myeloma	Patients in whom treatment-refractory multiple myeloma has been diagnosed	SNS01-T is a novel therapeutic intended to sensitize cancer cells to apoptotic signals by targeting eukaryotic translation initiation factor 5A1; eIF5A1 functions as a shuttle protein, selectively translocating mRNAs from the nucleus to cytosolic ribosomes for translation. eIF5A1 exists in 2 forms: a pro-apoptotic form and an anti-apoptotic form, which is generated by posttranslational modification. SNS01-T consists of 2 nucleic acid-based molecules: (1) a plasmid that drives expression of a pro-apoptotic form of eIF5A1 that has been modified to prevent its post-translational modification to the antiapoptotic form, and (2) an antisense molecule that inhibits expression of endogenous eIF5A1, which normally serves as the precursor to anti-apoptotic eIF5A1. By altering the balance of pro-apoptotic and anti-apoptotic eIF5A1, SNS01-T purportedly promotes cell death over cell growth and survival. In clinical trials, SNS01-T is administered by intravenous infusion, twice weekly. Senesco Technologies, Inc., New Brunswick, NJ Phase I/II trial ongoing; FDA granted orphan drug status	Various chemotherapeutic regimens, including one or more of the following: Bendamustine Bortezomib Cisplatin Cyclophosphamide Dexamethasone Etoposide Lenalidomide Liposomal doxorubicin Thalidomide	Increased overall survival Increased progression-free survival Improved quality of life
Spicamycin-derived, non-opioid-non-narcotic (KRN5500) for treatment of chronic cancer pain	Patients with chronic cancer pain, especially chemotherapy-induced neuropathic pain	Current pain management medications are not always effective in controlling chronic cancer pain, and their long-term use carries significant side effects (e.g., constipation, nausea, possible opioid addiction, kidney damage, gastrointestinal bleeding associated with nonsteroidal anti-inflammatory drugs [NSAIDs]). KRN5500 is a novel spicamycin derivative that was originally identified as a potential cancer treatment, a compound that could induce differentiation of myeloid leukemia cells. Although KRN5500 did not exhibit efficacy against leukemia, 1 patient with chronic neuropathic pain from previous cancer treatments experienced significant relief from that pain. Additional studies of KRN500 for pain have been undertaken. DARA BioSciences, Inc., Raleigh, NC Phase II trial completed; FDA granted fast track status	NSAIDs Opioid analgesics	Reduced pain Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Stool DNA molecular test (Cologuard) for colorectal cancer screening	All patients undergoing routine colorectal cancer (CRC) screening	A test that obviates the need for the bowel preparation required by current screening methods could improve adherence to recommended CRC screening guidelines. This genetic test (Cologuard™) screens DNA for genetic mutations and epigenetic modifications commonly found in CRCs; 4-gene plus 1 biomarker test performed on stool samples. This test kit is the next generation of the ColoSure™ test, which looked for epigenetic modification in only 1 genetic locus. Exact Sciences Corp., Madison, WI Clinical trial ongoing (phase unstated); first module of a premarket approval application was submitted to FDA in Dec 2012	Colonoscopy Computed tomographic colonography Fecal occult blood testing Sigmoidoscopy	Increased sensitivity and specificity for precancerous lesions and CRC Improved positive and negative predictive values Reduced unnecessary followup for screening
Sunitinib (Sutent) for treatment of pancreatic neuroendocrine tumors	Patients with surgically unresectable pancreatic neuroendocrine tumors (PNETs) that have progressed within the past year	Patients with PNETs have few treatment options, and existing treatments are of limited efficacy. Like many tumors, PNETs depend on receptor tyrosine kinase activity to drive angiogenic and mitogenic processes. PNETs have been shown to express a range of receptor tyrosine kinases that could mediate these processes, such as certain platelet-derived growth factor receptors, vascular endothelial growth factor receptors, and stem-cell factor receptors. Sunitinib (Sutent®) is a small-molecule inhibitor of the kinase activity of these receptors. In clinical trials it was administered orally, at a daily dose of 37.5 mg. Pfizer, Inc., New York, NY FDA approved May 2011 for treating PNETs	5-Fluorouracil Capecitabine Dacarbazine Doxorubicin Everolimus Streptozocin Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life
Tasquinimod for treatment of castration-resistant prostate cancer	Patients in whom castration-resistant prostate cancer (CRPC) has been diagnosed	Median overall survival for patients with CRPC is only about 18 months. Advanced prostate tumors can become resistant to androgen-deprivation therapy; new treatments with novel mechanisms of action are needed to limit the growth of advanced CRPC. Tasquinimod is a novel oral antiangiogenic compound that is intended to restrict blood flow to prostate tumors thus inhibiting growth; tasquinimod which may also exert antitumor effects. Administered at doses of 0.25, 0.5, or 1.0 mg/day. Active Biotech, AB, Lund, Sweden Phase III trial ongoing	Abiraterone Enzalutamide Orteronel (in development) Sipuleucel-T	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Therapeutic vaccine (BiovaxID) for indolent follicular non-Hodgkin's lymphoma	Patients in whom indolent follicular non-Hodgkin's lymphoma has been diagnosed and who are in their 1st complete remission	Personalized cancer vaccine (BiovaxID®) works by producing B-cell hybridomas from the patient's cancer cells. Cancer-specific antibody idiotype is amplified, isolated, and conjugated to an immunostimulant, then readministered with granulocyte macrophage colony-stimulating factor in attempt to induce anti-idiotypic response to the lymphoma tumor. Biovest International, Inc., Tampa, FL Phase III trial complete; FDA granted orphan drug status	Watchful waiting	Increased overall survival Increased progression-free survival Improved quality of life
Therapeutic vaccine (GSK1572932A) for MAGE-A3-positive nonsmall cell lung cancer	Patients with nonsmall cell lung cancer (NSCLC) that expresses the melanoma antigenic epitope (MAGE)-A3 biomarker	MAGE-A3 is an antigen that is expressed by a variety of tumor cells, in particular about 20% of NSCLCs. GSK1572932A is a MAGE-A3 peptide vaccine that is intended to be given to patients who have tumors that express the MAGE-A3 marker as an adjuvant to conventional chemotherapy. GlaxoSmithKline, Middlesex, UK Phase III trial ongoing	Radiation therapy Surgery Various chemotherapies	Increased overall survival Increased progression-free survival Improved quality of life
Therapeutic vaccine (IMA901) for renal cell carcinoma	Patients in whom renal metastatic and/or locally advanced renal cell carcinoma (RCC) has been diagnosed	RCC is typically highly resistant to conventional chemotherapy/radiation therapy, and few treatment options exist for patients with RCC. IMA901 is a rationally designed therapeutic cancer vaccine comprised of 10 different tumor-associated peptides that are found to be highly overexpressed in the majority of patients who have RCC. Immunization is intended to induce cellular immune responses against renal tumors, and IMA901 purportedly has a stable, off-the-shelf formulation. The vaccine is administered intradermally with granulocyte macrophage colony-stimulating factor and sunitinib as a 1st-line therapy. Immatics Biotechnologies GmbH, Tübingen, Germany Phase III trial ongoing	Sunitinib	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Therapeutic vaccine (POL-103A) to prevent melanoma recurrence	Patients at high risk of recurrence after surgical resection of stage IIB, IIC, or III melanoma	After surgical resection of a primary melanotic tumor, disease recurs in many patients, and few adjuvant treatments to prevent recurrence are available. POL-103A is a polyvalent vaccine that is generated by isolating peptides secreted by 3 human melanoma cell lines grown in culture. The vaccine is administered by intradermal injection as adjuvant therapy. Polynoma LLC subsidiary of CK Life Sciences Int'l (Holdings), Inc., Hong Kong Phase III trial ongoing	High-dose interferon	Increased overall survival Increased progression-free survival Improved quality of life
Tivozanib (AV-951) for treatment of advanced renal cell carcinoma	Patients in whom advanced primary renal cell carcinoma has been diagnosed	Tivozanib (AV-951) is a quinoline urea–derived vascular endothelial growth factor (VEGF) receptor (VEGFR) inhibitor that inhibits several tyrosine kinases. The theoretical basis for VEGFR inhibitors in treating solid tumors is that VEGF is a key mediator of normal and tumor-induced angiogenesis, or the proliferation and survival of endothelial cells, and vascular permeability. When VEGFRs are activated by VEGF, endothelial cells migrate and proliferate, resulting in the formation of new tumor vasculature. If the VEGF pathway is disrupted, a tumor can no longer trigger the development of its own blood supply, thereby impeding the tumor's growth and dissemination. It is given orally. AVEO Pharmaceuticals, Inc., Cambridge, MA Phase III trial ongoing; in Jan 2012, the company reported that tivozanib met its primary endpoint of improving progression-free survival; FDA new drug application filed Sept 2012	Axitinib Everolimus Interleukin-2 Pazopanib Sorafenib Sunitinib Temsirolimus	Increased overall survival Increased progression-free survival Improved quality of life
Toll-like receptor 9 agonist (MGN1703) maintenance therapy after 1st-line therapy for metastatic colorectal cancer	Patients with metastatic colorectal cancer (CRC) whose disease has responded to 1st-line chemotherapy	Although many patients with metastatic CRC respond to 1st-line chemotherapy, disease ultimately progresses in the vast majority of patients. MGN1703 is under study as a maintenance therapy intended to prevent or delay disease recurrence. MGN1703 is a DNA molecule that is intended to function as an agonist of toll-like receptor 9 (TLR9). TLR9 signalling is a component of the innate immune system, and agonists of TLR9 purportedly promote immune system activation, possibly through dendritic cell maturation and/or differentiation of B cells into antibody-secreting plasma cells. Immune-response activation by MGN1703 could overcome immune tolerance to tumor associated antigens, potentially leading to an anticancer immune response. MOLOGEN AG, Berlin, Germany Phase II/III trial ongoing	Bevacizumab Chemotherapy-free interval Leucovorin plus 5-fluorouracil	Increased overall survival Increased progression-free survival Improved quality of life

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	Patients with metastatic breast cancer that has progressed on anthracycline-, taxane-, and capecitabine-containing regimens have few treatment options and a poor prognosis. NKTR-102 is a novel formulation of the topoisomerase I inhibitor irinotecan. Although approved for treating colorectal cancer, irinotecan is not indicated for treating breast cancer. NKTR-102 is a modified version of irinotecan in which the drug is linked to a macromolecule core. The linkage purportedly renders the drug inert in the bloodstream and allows the slow release of the drug as the linkages are metabolized in the patient. Slow release extends the time during which the patient's disease is exposed to therapeutic levels of the drug, thus limiting exposure to high levels of the drug at the time of infusion. Additionally, the large drug-polymer conjugate may preferentially accumulate in tumor tissues because of the increased permeability of tumor vasculature. Nektar Therapeutics, San Francisco, CA Phase III trial ongoing	Eribulin Gemcitabine Ixabepilone Pemetrexed Vinorelbine	Increased overall survival Increased progression-free survival Improved quality of life
Trastuzumab emtansine for treatment of breast cancer	Patients in whom metastatic HER2-positive breast cancer has been diagnosed	Trastuzumab emtansine (formerly trastuzumab-DM1) is a combination of a HER2-specific antibody (trastuzumab, Herceptin) and a cytotoxic microtubule inhibitor (DM1, mertansine). This combination is intended to enable preferential delivery of a highly cytotoxic agent to cells expressing HER2 to produce the same (or better) results as HER2 inhibition plus chemotherapy, but with reduced side effects. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials ongoing; company reported that trastuzumab emtansine met its primary endpoint of improving progression-free survival in the 2nd-line setting; full results from this trial anticipated in late 2012; FDA Biologics License Application filed late Aug 2012; FDA decision date set for Feb 26, 2013	Lapatinib-based chemotherapy regimens Trastuzumab-based chemotherapy regimens	Increased overall survival Increased progression-free survival Improved quality of life
Tryptophan hydroxylase inhibitor (telotristat etiprate, LX1032) for treatment of neuroendocrine tumor–associated carcinoid syndrome	Patients in whom metastatic neuroendocrine tumor–associated carcinoid syndrome has been diagnosed	Patients with carcinoid tumors that are not amenable to surgical resection have few treatment options to control disease symptoms, and not all patients respond to current therapies. A hallmark of many carcinoid tumors is the overproduction of serotonin, which leads to complications such as severe diarrhea, flushing, and cardiac damage. Telotristat etiprate (LX1032) is intended to reduce systemic serotonin levels by inhibiting an enzyme involved in the synthesis of serotonin, tryptophan hydroxylase. Lexicon Pharmaceuticals, Inc., The Woodlands, TX Phase II trials completed; FDA granted fast track status	Chemotherapy (e.g., capecitabine, dacarbazine, 5-fluorouracil, temozolomide) Interferon alpha Octreotide	Decreased rate of bowel movements Decreased 5-HIAA levels Decreased rate of flushing episodes Improved quality of life (e.g., less pain, discomfort)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Tumor-treating fields therapy (NovoTTF-100L device) for nonsmall cell lung cancer	Patients in whom stage IIIb–IV nonsmall cell lung cancer has been diagnosed	The NovoTTF-100L system delivers tumor-treating fields (local alternating electrical fields) to the target tumor site. Electrical fields purportedly interfere with charged molecules that are involved cellular mitotic processes. The therapy is delivered in conjunction with chemotherapy. NovoCure Ltd., Haifa, Israel Phase I/II trial complete; company states it is preparing a phase III trial program to obtain FDA approval for investigational device exemption status to conduct the trial	Chemotherapy alone Chemotherapy plus radiation therapy or surgical resection	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	The NovoTTF-100L system delivers tumor-treating fields (local alternating electrical fields) to the target tumor site. Electrical fields purportedly interfere with charged molecules that are involved cellular mitotic processes. The therapy is delivered in conjunction with chemotherapy. NovoCure Ltd., Haifa, Israel FDA approved for recurrent glioblastoma Apr 2011; phase III trial in newly diagnosed glioblastoma ongoing	Bevacizumab Bevacizumab plus irinotecan, BCNU/CCNU, temozolomide Combination PCV (CCNU, procarbazine, and vincristine) Cyclophosphamide Nitrosourea Nitrosourea wafer Platinum-based chemotherapy Temozolomide	Increased overall survival Increased progression-free survival Improved quality of life
Urocidin for treatment of nonmuscle-invasive bladder cancer	Patients in whom nonmuscle-invasive bladder cancer (cancer on the surface of the bladder) has been diagnosed	Urocidin™ is a mycobacterial cell wall/DNA preparation proposed to create a localized immune response. The mechanism of action is unclear. Administered by transurethral catheter directly into the bladder. Bioniche Life Sciences, Inc., Belleville, Ontario, Canada Endo Pharmaceuticals, Chadds Ford, PA (licensee in U.S.) Phase III trial ongoing	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	No treatments are approved for metastatic medullary thyroid cancer, which has a 28% rate of survival for 5 years. Vandetanib (Caprelsa®) is a tyrosine kinase inhibitor with activity against various growth factors: vascular endothelial growth factor receptor, epidermal growth factor receptor, and recombined in transfection (RET); about 25% of medullary thyroid cancer is caused by a mutation in the RET proto-oncogene. Taken orally, once daily. AstraZeneca, London, UK FDA approved Apr 2011	Chemotherapy (off label) Radiotherapy Surgery	Increased overall survival Increased progression-free survival Improved quality of life
Vemurafenib (Zelboraf) for treatment of metastatic melanoma	Patients who have metastatic melanoma with activated *BRAF* mutations	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, BRAF serine/threonine kinase inhibitor. The V600E mutation causes dysregulation of BRAF activity and overstimulation of ERK. This results in spontaneous generation of melanoma and the proliferation of malignant tissue. Vemurafenib a potent inhibitor of BRAF, shuts down the ERK signaling pathway and blocks proliferation of malignant cells carrying the $BRAF^{V600E}$ mutation. It has no effect on tumor cells that lack the V600E mutation. It is administered orally. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Roche Molecular Systems, Inc., Pleasanton, CA First FDA-approved BRAF inhibitor; approved Aug 2011 for treating unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation as detected by the test approved at the same time: cobas® 4800 $BRAF^{V600}$ mutation automated molecular assay	Dacarbazine High-dose interleukin-2 Ipilimumab 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
Vismodegib (Erivedge) for treatment of basal cell carcinoma	Patients in whom advanced/ metastatic basal cell carcinoma has been diagnosed	No systemic treatment was approved for treating basal cell carcinoma before the approval of vismodegib, and patients with advanced/metastatic disease not amenable to surgical resection had few treatment options. Vismodegib (GDC-0449) is an inhibitor of the protein Smoothened, which is essential for transducing hedgehog signaling. 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. It is an oral capsule administered once daily at 150 mg. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland FDA approved Jan 2012, based on phase II results for locally advanced and metastatic cancer; approval includes black box warning of potential risk of death or severe birth defects to unborn fetus	No other approved systemic treatment option available	Increased overall survival Increased progression-free survival Improved quality of life
Vosaroxin for treatment of relapsed or refractory acute myeloid leukemia	Patients in whom acute myeloid leukemia (AML) has been diagnosed	For patients with relapsed AML, the only potentially curative treatment is a hematopoietic stem cell transplant; however, in some patients, disease relapses after transplantation, or they are not candidates or cannot find a suitable donor. Vosaroxin is a 1st-in-class, anticancer quinolone derivative. During normal topoisomerase activity, the enzyme cleaves and then re-ligates double-strand breaks to maintain DNA topology during replication; vosaroxin purportedly intercalates into DNA and inhibits topoisomerase II activity that results in replication-dependent, site-selective double-strand breaks in DNA leading to G2 arrest and apoptosis. Compared with other topoisomerase II inhibitors, vosaroxin is not a P-glycoprotein substrate, evading the most common mechanism for multidrug resistance. It may be used in combination with cytarabine. It is given as an intravenous infusion, 90 mg/m^2 of body surface area for days 1 and 4 for induction and 70 mg/m^2 for all other cycles. Sunesis Pharmaceuticals, Inc., South San Francisco, CA Phase III trial ongoing	Cladribine, cytarabine, and granulocyte colony-stimulating factor (GM-CSF) plus or minus mitoxantrone or idarubicin Clofarabine, cytarabine, and GM-CSF Etoposide and cytarabine plus or minus mitoxantrone Fludarabine, cytarabine, and GM-CSF plus or minus idarubicin High-dose cytarabine and GM-CSF plus or minus anthracycline	Increased overall survival Increased progression-free survival Improved quality of life

Table 3. AHRQ Priority Condition: 03 Cardiovascular Disease: 44 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Adenosine diphosphate receptor antagonist (ticagrelor, Brilinta) for treatment of acute coronary syndrome	Adults in whom acute coronary syndrome has been diagnosed	The efficacy of clopidogrel varies because it is a prodrug. It must be metabolized to become active, which can lead to variable platelet inhibition 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). It is potentially the 1st-in-class reversibly binding oral adenosine diphosphate (ADP) receptor antagonist, and similar to the action of the thienopyridines prasugrel, clopidogrel, and ticlopidine, ticagrelor blocks ADP receptors of subtype P2Y12. It differs from other antiplatelet drugs because it has a different binding site from ADP; it is an allosteric antagonist, and the blockage is reversible. Also, the drug is not activated by the liver, so, researchers believe, it might work better for patients with genetic variants of the enzyme cytochrome P-450 2C19. AstraZeneca, London, UK FDA approved for acute coronary syndrome Jul 2011; approval included labeled warning that states not to take it with a daily aspirin dose of more than 100 mg	Clopidogrel Prasugrel Ticlopidine	Reduced incidence of heart attacks and strokes Increased overall survival Reduced side effects compared with other antiplatelet drugs
Altitude training using a portable altitude simulation chamber for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	Despite medical therapy, many patients with HF often experience suboptimal quality of life, exercise performance, and skeletal-muscle strength. Clinicians use a portable altitude simulation chamber to expose patients to normobaric hypoxia for 10 sessions over several weeks. The machine filters oxygen molecules from the air to mimic the oxygen level at an altitude of 1,500 meters, which is intended to help the body acclimatize, making delivery of oxygen to muscle tissue more efficient. In a pilot clinical trial, researchers used simulators manufactured by Hypoxico, Inc. (New York, NY), which are available for purchase by consumers. Montefiore Medical Center, Bronx, NY Pilot trial complete	High altitude environment Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics)	Improved oxygen-delivery efficiency Improved exercise performance Decreased morbidity and mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anacetrapib for lipid management in coronary artery disease	Patients in whom coronary artery disease has been diagnosed or who are at risk of developing the disease	Cholesterol ester transfer protein inhibitor intended to raise high-density lipoprotein by 100% and reduce low-density lipoprotein, improving lipid profile. Its precursor was torcetrapib; its development was stopped because of high rate of cardiovascular adverse events. Anacetrapib has been reported to not raise blood pressure of subjects in clinical trials thus far. Merck & Co., Inc., Whitehouse Station, NJ Phase III trials ongoing; company anticipated filing new drug application with FDA after 2015	Lifestyle changes Pharmacotherapy (e.g., statins)	Reduced risk of heart attack Improved cardiovascular outcomes
Autologous bone marrow–derived cells (Ixmyelocel-T) for treatment of critical limb ischemia	Patients in whom critical limb ischemia (CLI) has been diagnosed	Outcomes for patients with CLI are poor, and many patients require amputation. This intervention represents a novel treatment modality for this condition. Tissue repair cell (Ixmyelocel-T) technology consists of bone marrow extracted from the patient, expanded over the course of 12 days at the manufacturer's facility using the company's proprietary process, and reinfused into the patient 14 days after extraction. The formulation includes monocytes, macrophages (intended to destroy dead tissue, stimulate regeneration, and reduce inflammation), mesenchymal stem cells (intended to promote angiogenesis), and endothelial progenitor cells (intended to promote blood vessel lining and generate cardiovascular tissue). Aastrom Biosciences, Inc., Ann Arbor, MI Phase III trial ongoing	Percutaneous angioplasty and stenting Pharmacotherapy (e.g., cilostazol and pentoxifylline) Surgery	Tissue regeneration Improved circulation Reduced need for amputation Reduced morbidity and mortality
Bioresorbable vascular scaffold (Absorb) for treatment of critical limb ischemia	Patients in whom below-the-knee critical limb ischemia (CLI) has been diagnosed	Outcomes for patients with CLI are poor, and many patients require amputation. This intervention represents a novel approach to treatment. Absorb bioresorbable vascular scaffold is made of a biocompatible polylactide polymer scaffold that elutes everolimus. It is intended to provide support to the vessel, then dissolve over the course of 2 years. The company purports that because the device is not permanent, natural vessel function may be restored. Abbott Laboratories, Abbott Park, IL U.S. investigational device exemption trial ongoing; approved in Europe in 2011; available also in parts of Asia Pacific and Latin America	Other bioabsorbable scaffolds (in development) Percutaneous angioplasty and stenting Pharmacotherapy (e.g., cilostazol and pentoxifylline) Surgery	Decreased pain Improved circulation and mobility Reduced need for amputation Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cardiac contractility modulation (Optimizer III Implantable Pulse Generator system) for treatment of heart failure	Patients in whom heart failure (HF) has been diagnosed	Optimizer III™ system is a device implant intended to treat patients who have chronic heart failure, are unable to achieve desired goals with optimal medical therapy, and are not candidates for cardiac resynchronization therapy. According to the manufacturer, "it is typically implanted in the right pectoral region and is connected to three standard pacemaker leads that are threaded through veins into the right side of the heart. One lead is used to sense atrial activity, and the other two are used to sense ventricular activity… ." It purportedly delivers nonexcitatory electrical signals during the absolute refractory period (between beats) to purportedly produce more forceful contraction during the heartbeat. It is intended as an adjunct to optimal medical therapy. The system also uses the OMNI Programmer System, a portable programmer intended to enable medical personnel to tailor Optimizer signal parameters to individual patient needs. It uses a battery that can be charged in the patient's home. Impulse Dynamics, N.V., Willemstad, Netherlands Antilles Pivotal investigational device exemption trial completed; FIX-HF-5B confirmatory trial ongoing; Conformité Européene (CE) marked	Implanted pacemakers and/or defibrillators Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics)	Symptom relief Improved 6-minute walk test Fewer hospitalizations Delayed progression of HF Delayed need for ventricular assist devices Improved quality of life
Cardiac pacing system (Revo) for patients who may require future magnetic resonance imaging	Patients with pacemakers who need to undergo MRI scanning	Revo MRI™ SureScan® pacing system is intended for patients who may need to undergo MRI in the future. Pacemaker implants had previously been a contraindication for MRI because of potential risks of malfunction during MRI. Revo includes hardware modifications that are designed to reduce/eliminate pacemaker hazards produced by MRI environment. Pacemaker includes a feature that sets device into appropriate mode for MRI environment. Medtronic, Inc., Minneapolis, MN FDA approved Feb 2011	Other pacemakers might be safe for use with MRI, under certain conditions	Ability for physicians to use MRI for patients who require pacemaker therapy

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Catheter-based renal denervation (Symplicity System) for treatment-resistant hypertension	Patients in whom uncontrolled hypertension has been diagnosed	The Symplicity® catheter system is intended to accomplish renal denervation through a minimally invasive procedure. The device is used to affect the output of the sympathetic nerves outside the renal artery walls. The system consists of a proprietary generator and flexible catheter that is inserted through the femoral artery and threaded into the renal artery near each kidney. Once in place, the catheter tip delivers low-power radiofrequency energy to deactivate surrounding sympathetic nerves. Renal denervation does not involve a permanent implant. Renal sympathetic nerves are believed to often cause chronic hypertension. Medtronic, Inc., Minneapolis, MN Phase III trial SYMPLICITY HTN-3 ongoing	Pharmacotherapy (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers) Renal artery stents	Controlled hypertension without medications Reduced rates of blindness, heart attacks, kidney failure, and stroke
Catheter-based ventricular restoration implant (Parachute) for treatment of heart failure	Patients in whom ischemic heart failure (HF) has been diagnosed	Left ventricular remodeling (enlargement) occurs in many patients who experience a myocardial infarction, resulting in decreased cardiac output, fatigue, and shortness of breath. The unaffected portion of the heart compensates for this output loss and becomes overloaded. Treatment options include medical management and surgical revision. This intervention has the potential to be the 1st minimally invasive, catheter-based treatment for ischemic HF. According to its manufacturer, the Parachute™ Ventricular Partitioning Device is an implant that is deployed in the left ventricle to partition the damaged portion of the heart from the functional heart segment, potentially decreasing the left ventricle's volume and restoring its geometry and function. CardioKinetix, Inc., Menlo Park, CA Phase III clinical trial initiated Dec 2012	Heart transplant Pharmacotherapy (e.g., beta blockers) Surgical ventricular revision	Improved HF symptoms Increased cardiac output Increased survival Reduced left ventricular volume Reduced morbidity
Cholesteryl ester transfer protein inhibitor (evacetrapib) for prevention of cardiovascular events	Patients in whom cardiovascular disease (CVD) has been diagnosed	Despite available treatments, CVD remains the leading cause of mortality worldwide. Evacetrapib is a cholesteryl ester transfer protein (CETP) inhibitor that is intended to raise functional high-density lipoprotein (HDL) by modulating CETP activity through a mechanism that purportedly differs from other CETP inhibitors in development. CETP, also known as LY2484595, is a plasma protein responsible for lipid transport. Eli Lilly and Co., Indianapolis, IN Phase III trial initiated Oct 2012	Pharmacotherapy Sclerotherapy	Improved HDL profile Reduced cardiovascular morbidity and mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Electrical stimulation of carotid baroreceptors (Barostim neo System) for treatment of drug-resistant hypertension	Patients in whom severe, drug-resistant hypertension has been diagnosed	Intervention involves electrical stimulation of the carotid baroreceptors through a pulse generator inserted subcutaneously (CVRx Barostim neo™), which delivers electrical signals to the baroreceptor in the right carotid artery in the neck through a carotid sinus lead. The Barostim neo is a 2nd-generation device that replaces the original Rheos System. CVRx purports that that Barostim neo has a better patient safety profile than the Rheos system. CVRx, Inc., Minneapolis, MN Pivotal trial (phase III) initiated Nov 2012	Pharmacotherapy (e.g., angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers)	Reduced hypertension Reduced stoke incidence Reduced cardiovascular events Improved quality of life
Excimer laser-assisted nonocclusive anastomosis (Elana) procedure for intracranial vascular bypass	Patients older than age of 13 years with an aneurysm or skull base tumor affecting a large (>2.5 mm), intracranial artery that failed balloon test occlusion, cannot be sacrificed, or cannot be treated with conventional means	In some patients, aneurysms or skull base tumors cannot be treated with conventional means (e.g., coiling). For these patients, a surgical bypass of the lesion may be indicated. However, traditional surgical bypass procedures require shutting off blood flow to the target artery, which can put patients at high risk of stroke. The Excimer laser-assisted nonocclusive anastomosis (Elana) procedure purportedly allows clinicians to perform a bypass without shutting off blood flow to the target artery. The system consists of a ring, which is placed around the donor vessel, and a laser catheter system, which is placed through the donor vessel and used to cut holes in the target vessel. One-half of the donor vessel is then sutured to the target vessel, clamped, and eventually attached to the other donor vessel. Elana bv, Utrecht, The Netherlands FDA approved in Mar 2011 under a humanitarian device exemption	Traditional surgical artery bypass grafting	Decreased morbidity Increased survival Reduced stroke incidence

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Extra-aortic balloon counter-pulsation heart assist device (C-Pulse) for treatment of heart failure	Patients with New York Heart Association Class III or ambulatory Class IV heart failure (HF)	Available implanted devices for HF (e.g., intra-aortic balloon pump, left ventricular assist device) come into contact with the patient's blood, leading to a risk of stroke and blood clots, and are intended to be used in patients with more advanced HF. This intervention represents a novel device for treating HF. The C-Pulse® heart-assist system consists of a mechanical balloon cuff that is wrapped around the outside of the aorta during a minimally invasive or full sternotomy procedure and is intended to reduce the workload of the left ventricle. The system's driver sits outside the body. According to the manufacturer, when the balloon is inflated, blood flow to the coronary arteries is increased, potentially providing additional oxygen to the heart. The company claims that during deflation, the workload required by the left ventricle is reduced. The company also states that the balloon counter-pulsation inflation and deflation is synchronized to the patient's electrocardiogram (similar to a pacemaker). Sunshine Heart, Inc., Eden Prairie, MN Feasibility trials completed; pivotal phase III trial initiated Nov 2012	Intra-aortic balloon pumps Left ventricular assist devices	Decreased morbidity Increased cardiac output Increased survival Reduced cardiac workload Reduced risk of stroke or thrombi
Fibrin-specific plasminogen activator (desmoteplase) for treatment of ischemic stroke	Patients in whom acute stroke has been diagnosed	Although stroke is a leading cause of death in the U.S., only 1 drug, tissue plasminogen activator (tPA), is approved for neuroprotection. It is effective only when administered within a narrow window of symptom onset, and only a very small percentage of patients experiencing an acute stroke receive tPA because most do not present for treatment within the necessary time frame. Desmoteplase is a chemical derived from the saliva of vampire bats that catalyzes the conversion of plasminogen to plasmin, the enzyme responsible for breaking down fibrin blood clots. Structurally, the chemical is similar to tPA, but has much higher fibrin selectivity and, therefore, does not cause systemic plasminogen activation and fibrinogen depletion. H. Lundbeck a/s, Valby, Denmark One phase III trial complete; other phase III trials ongoing	tPA therapy	Increased blood flow to the brain Reversed damage Improved stroke-related outcomes
Freedom driver system for Total Artificial Heart as bridge to heart transplantation	Patients with nonreversible biventricular failure who are candidates for heart transplantation	The temporary Total Artificial Heart (TAH) functions in place of ventricles/valves by pumping blood to both the pulmonary and systemic circulation. This TAH is distinguished from prior TAHs by its portable driver (Freedom® driver) that is intended to allow patients to recover and remain at home, rather than remaining hospitalized. SynCardia Systems, Inc., Tucson, AZ TAH was FDA approved in 2004; clinical trial investigating use of Freedom driver system ongoing under FDA investigational device exemption trial status; expected to be complete in Sept 2013	TAH used with in-hospital driver	Restored mobility Possible recovery at home (reduction in hospitalization costs) Extended survival for patients awaiting heart transplantation

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Icatibant (Firazyr) for treatment of acute hereditary angioedema	Patients 18 years of age or older in whom acute hereditary angioedema (HAE) has been diagnosed	HAE is a genetic disorder caused by dysfunction or deficiency of the plasma protein C1 inhibitor (C1INH). C1INH is an inhibitor of the C1 protease that is responsible for activating the complement pathway in the immune system. If C1INH is deficient, the immune system reacts with an inflammatory response that leads to swelling. Unlike bradykinin beta-receptor-1, bradykinin beta-2 receptors do not appear to be involved in chronic inflammatory diseases but may mediate acute inflammatory processes. Icatibant (Firazyr®) is a peptidomimetic drug consisting of 10 amino acids and is a selective and specific antagonist of bradykinin beta-2 receptors. Administered by subcutaneous injection. Shire Pharmaceuticals, plc, Dublin, Ireland FDA approved Aug 2011 for treating acute attacks of HAE	Antihistamines C1-INH (concentrate from donor blood) Fresh-frozen plasma Pain relievers and fluids given intravenously	Faster symptom relief of primary symptom Reduced severity of symptoms Reduced mortality
Imatinib (Gleevec) for treatment of pulmonary artery hypertension	Patients in whom pulmonary artery hypertension (PAH) has been diagnosed	PAH has no cure and can result in heart failure and death. Imatinib (Gleevec®) is a small-molecule, ABL kinase inhibitor that purportedly inhibits cellular processes that are responsible for uncontrolled growth of arterial smooth muscle cells. In clinical trials, imatinib has been administered orally, 200–400 mg, once daily. Novartis International AG, Basel, Switzerland One phase III trial completed; other phase III trials ongoing	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalization
Implantable cardiac monitor for detecting myocardial infarction	Patients at high risk of myocardial infarction (MI)	Implantable electronic device designed to warn patients of an impending MI; measures electrical changes in the heart. Angel Medical Systems, Shrewsbury, NJ Phase III trial ongoing	Conventional, external MI detection technologies Patient report	Earlier detection of impending heart attack Prevention of heart damage Increased overall survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Injectable biopolymer (Algisyl-LVR) for prevention or treatment of heart failure	Patients with an enlarged left ventricle (from mitral valve regurgitation, ischemia, dilated cardiomyopathy and/or other disorders)	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. The material is inert (i.e., does not interact with the human immune system). Cardio Polymers, now part of LoneStar Heart, Inc., Laguna Hills, CA Phase II/III trial ongoing	Drug therapy to prevent HF	Increased left ejection fraction Reduced progression of HF Reduced regression of HF Improved cardiovascular outcomes Improved quality of life
Lomitapide (Juxtapid) for treatment of homozygous familial hypercholesterolemia	Patients in whom homozygous familial hyper-cholesterolemia (HoFH) has been diagnosed	Outcomes with current medication for HoFH are suboptimal. Lomitapide represents a novel class of medication, a microsomal triglyceride transfer protein inhibitor (MTP-I) that is intended to lower both cholesterol and triglycerides. MTP is a lipid transfer protein that is required for moving lipid molecules from their site of synthesis, so inhibiting MTP prevents both hepatic very-low-density lipoproteins and intestinal chylomicron secretion (from food/diet) that, in turn, lowers plasma lipids. Lomitapide is intended to replace statins. Given orally. Aegerion Pharmaceuticals, Inc., Cambridge, MA FDA approved Dec 2012 as “an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH)”	Extracorporeal apheresis Liver transplant Pharmacotherapy (e.g,. statins)	Reduced low-density lipoprotein levels Improved cardiovascular outcomes Improved quality of life Improved long-term health outcomes
Low-dose tPA for treatment of intraventricular hemorrhage	Patients in whom intraventricular hemorrhage has been diagnosed	The agent tissue plasminogen activator (tPA) is a thrombolytic (clot-busting drug) long used for treating stroke; it may be useful to treat intraventricular hemorrhage clots that form once bleeding has been stopped; current strategy is to remove the clots with intraventricular catheter, which can clog and take days. Use of tPA could offer a less invasive, faster treatment option. Johns Hopkins University, Baltimore, MD Phase III trial ongoing	Intraventricular catheter alone	Improved clot evacuation Decreased time to clot evacuation Improved cardiovascular outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mobile phone electrocardiography (iPhoneECG)	Patients in need of an electrocardiogram (ECG) who have access to a mobile device	Access to ECG machines is limited in some rural or emergency rescue locations; patients are required to visit health care facilities for ECG readings, and "portable" ECG machines still require 12 leads. The iPhoneECG is a slim device in a case that fits over an iPhone (also available as the iCard, which sticks to the back of any mobile device, including iPads) and has low-power electrodes on the case that are pressed against the fingers or chest of a patient to display full ECG and heart rate. Device is intended to record and upload the reading onto a server, which converts it to a PDF for analysis by a medical professional; manufacturer intends device to be used to aid diagnosis of heart blockage or unstable heartbeat, or to monitor heart rate during exercise or stress reduction techniques. The manufacturer claims that the device will work in any location with wireless coverage. AliveCor, Seattle, WA Received FDA 510(k) clearance Dec 2012	Standard ECG machines Portable ECG machines	Increased access to ECG technology Reduced morbidity from heart conditions monitored by ECG Reduced health disparities
Off-label minocycline with tPA for treatment of acute ischemic stroke	Patients in whom acute ischemic stroke has been diagnosed	Thrombolysis using tPA during ischemic stroke has been associated with hemorrhage about 7% of the time, and continued bleeding is believed to contribute to poor outcomes in up to 40% of cases. Plasma levels of matrix metalloproteinase (MMP)-9 are known to be amplified by tissue plasminogen activator (tPA) and elevated MMP-9 levels are associated with neurological severity. MMP-9 also is known to predict the risk of tPA-related hemorrhage. Minocycline is known to be a potent MMP inhibitor; thus researchers are investigating whether concomitant administration of minocycline with tPA for treatment of acute ischemic stroke is neuroprotective. Various research institutions Several trials completed	tPA alone	Reduced bleeding in stroke Improved overall outcomes after treatment for acute ischemic stroke
Off-label rituximab for treatment of systemic sclerosis-associated pulmonary artery hypertension	Patients in whom systemic sclerosis-associated pulmonary artery hypertension (SSc-PAH) has been diagnosed	One-year survival for patients with SSc-PAH ranges from 50% to 81%, and treatment is limited to vasodilator therapy. Rituximab, a genetically engineered anti-CD20 antibody for treating B-cell lymphoma, is being investigated for immune mechanisms associated with B-cell dysregulation and pathogenic autoantibody response in SSc-PAH. It is being administered in 2 infusions, 1,000 mg each, 14 days apart. National Institute of Allergy and Infectious Diseases, Bethesda, MD (trial sponsor) Phase II trial ongoing	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalization

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 artery hypertension	Patients in whom pulmonary artery hypertension (PAH) has been diagnosed	PAH has no cure and can result in heart failure and death. No approved oral prostacyclin therapies are available in the U.S.; only intravenous, injected, or inhaled formulations are available. Sustained release oral treprostinil, if approved, could be the 1st oral prostacyclin for PAH and is intended for use early in the PAH disease continuum; treprostinil diethanolamine vasodilates pulmonary and systemic arterial vascular beds and inhibits platelet aggregation. It is intended as an add-on therapy to current oral therapies. United Therapeutics Corp., Silver Spring, MD Phase III trials ongoing	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalization
PCSK9 inhibitor (REGN727/ SAR236553) for treatment of hypercholesterolemia	Patients in whom hypercholesterol-emia has been diagnosed	This drug represents a new mechanism of action for hypercholesterolemia treatment. REGN727/SAR236553 is a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. PCSK9 is a protein involved in regulating circulating low-density lipoprotein (LDL) levels through degradation of the LDL receptor; therefore, pharmacologic inhibition of PCSK9 might decrease circulating LDL levels. Intended to be administered subcutaneously. Sanofi, Paris, France Regeneron Pharmaceuticals, Inc., Tarrytown, NY Phase III trial ongoing	Pharmacotherapy (e.g., statins)	Improved lipid levels Reduced morbidity Reduced mortality
Pediatric ventricular assist device (Excor) for pediatric end-stage heart failure	Pediatric patients in whom heart failure (HF) has been diagnosed who are in need of mechanical support as a bridge to cardiac transplantation	Adult heart-assist devices are too large to be used in children with end-stage HF. While awaiting transplant, the standard of care in this population is extracorporeal membrane oxygenation (ECMO), in which a pump circulates blood through an artificial lung back into the bloodstream. This technique is not approved and is associated with many limitations, including high incidence of complications when used for long-term support, high risk of stroke, and need for anticoagulation therapy. ECMO also requires immobilization of the patient, limiting rehabilitation. The Excor® Pediatric Ventricular Assist Device (VAD) is designed to support pediatric patients (newborns to teenagers) and to bridge patients awaiting heart transplantation for days to several months, until a donor heart becomes available. The device is a paracorporeal, pulsatile VAD, with blood pumps located outside the body and connected to the heart and blood vessels via cannulas. The device can be used for single- or double-ventricle assistance. Berlin Heart GmbH, Berlin, Germany FDA approved Dec 2011; designated an orphan product	ECMO	Increased recovery of native heart (when used as destination therapy) Increased overall survival Reduced adverse events compared with ECMO

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Percutaneous annuloplasty (Carillon Mitral Contour System) for functional mitral valve repair	Patients in whom functional mitral regurgitation has been diagnosed	Percutaneous annuloplasty for functional mitral valve repair is a surgical approach intended to achieve the therapeutic result of open surgical annuloplasty through a less-invasive, catheter-based technique. The Carillon® Mitral Contour System™ comprises a thin, flexible metal bridge or tether with a self-expanding anchor at each end. The device is delivered to the coronary sinus by a catheter inserted in the jugular vein at the neck. This tension around the mitral valve annulus is intended to squeeze the mitral leaflets together to close the gap that may have developed due to heart enlargement. Typically, the entire catheter is removed if the placement of nitinol tension rods does not reduce mitral regurgitation. Cardiac Dimensions, Inc., Kirkland, WA Company lists several trials ongoing; FDA granted investigational device exemption status for clinical trial in 2005; trial ongoing, but not registered with National Clinical Trials database; approved for marketing in Europe in 2009	Optimal medical management Minimally invasive surgery Open surgery	Reduced risk of cardiac events Reduced mitral regurgitation Reduced operative morbidity Reduced mortality Improved quality of life
Percutaneous left atrial appendage occlusion (Watchman) for prevention of atrial fibrillation-associated stroke	Patients with atrial fibrillation who are not good surgical candidates	Intended to block left atrial appendage opening and prevent clots from entering general circulation. Boston Scientific Corp., Natick, MA Phase III trial ongoing	Long-term anticoagulation therapy	Reduction in stroke risk
Phospholipase A2 inhibitor (darapladib) for treatment of atherosclerosis	Patients with atherosclerosis who are at high risk of myocardial infarction	Despite available pharmacotherapy, coronary artery disease remains the leading cause of death in the U.S. This intervention represents a novel mechanism of action for treating atherosclerosis. Darapladib is a lipoprotein-associated phospholipase A2 (LP-PLA2) inhibitor that is being investigated as a treatment for atherosclerosis. LP-PLA2 plays a role in atherosclerotic development and progression. Its levels predict cardiovascular risk, and it has been suggested that it is involved in determining plaque stability. By inhibiting LP-PLA2, this agent may help improve atherosclerosis, stabilize unstable plaques, and reduce cardiovascular risk. GlaxoSmithKline, Middlesex, UK Phase III trials ongoing	Pharmacotherapy (e.g., statins)	Improved plaque stability Reduced atherosclerosis Reduced morbidity and mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pipeline Embolization Device for treatment of brain aneurysms	Patients with giant or wide-necked brain aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments	Pipeline™ Embolization Device is a self-expanding, microcatheter-delivered, cylindrical mesh "flow diversion" device intended to divert blood flow away from the aneurysm sac and assist in reconstruction of the parent artery while leaving the side vessels open. Approved for the "endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments." ev3 Neurovascular, Menlo Park, CA FDA approved Apr 2011; continued followup for 5 years of individuals in the pivotal clinical cohort and continued access cohort required	Endovascular coiling Stent-assisted coiling Surgical clipping or bypass	Prevented rupture of brain aneurysms Reduced mortality form aneurysm
Pneumatic abdominal aortic tourniquet (AAT) for treatment of inguinal hemorrhage on the battlefield	Soldiers on the battlefield with inguinal hemorrhage	For soldiers on the battlefield with inguinal bleeding, no products are available that can effectively stop the blood flow but also remain stable and in place during patient transport. The Institute of Surgical Research has identified this unmet need (uncompressible hemorrhage that is not treatable by a tourniquet in the leg, groin and inguinal region) as its priority for battlefield care because of the extremely high morbidity and mortality associated with this condition. The Abdominal Aortic Tourniquet (AAT™) is a pneumatic circumferential tourniquet that is placed around the body at the navel level, tightened, and inflated into the abdomen until it occludes the aorta and stops the bleeding. The product differs from available options (conventional tourniquets, knee pressing, clamps) because they aren't designed to tighten around a person's midsection, and the aortic artery is located under several inches of flesh, next to the spine. Compression Works, LLC., Birmingham, AL (manufacturer) Speer Operational Technologies, LLC, Greenville, SC (distributor) FDA granted 510(k) clearance Oct 2011, after expedited review	Clamps Conventional tourniquet Knee pressing	Improved bleeding control Reduced morbidity Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Point-of-care genetic testing to determine antiplatelet regimen after percutaneous coronary intervention	Patients undergoing percutaneous coronary intervention (PCI) who will be placed on dual antiplatelet (DAP) therapy	DAP therapy is the standard of care for patients who undergo PCI. The standard regimen consists of aspirin plus the P2Y12 inhibitor clopidogrel. However, a subset of patients who carry a loss-of-function allele of CYP2C19 (CYP2C19*2) are at increased risk of major adverse cardiovascular events when treated with this regimen. The increase is thought to be caused by the failure of CYP2C19*2 to convert clopidogrel (Plavix®) to its active metabolite, lowering the therapeutic concentration of the drug. Prasugrel (Effient®) is an alternative P2Y12 inhibitor that is unaffected by the CYP2C19*2 polymorphism; however, its routine use is precluded because it is associated with an increased rate of bleeding. Therefore, prasugrel is typically reserved for patients who have been shown to harbor the CYP2C19*2 polymorphism. Because many of the adverse cardiovascular events following PCI occur within the 1st few hours of treatment, a need exists for highly accessible, rapid, genetic tests for the CYP2C19 genotype. The Spartan RX CYP2C19 test is a genetic test that could potentially be performed rapidly (about 1 hour), at the bedside, by clinical staff who lack formal clinical laboratory training. Spartan Bioscience, Inc., Ottawa, Ontario, Canada Phase II/III trial complete; Conformité Européene (CE) marked; intending to file for FDA 510(k) clearance	No genetic testing Genetic testing performed in a clinical laboratory	Decreased cardiovascular death Decreased stent thrombosis Decreased nonfatal myocardial infarction Decreased high reactivity on DAP
Polymer strands (cPAX system) for treatment of giant and wide-neck cerebral aneurysms	Patients 22 years of age or older with a wide-necked large and giant sized cerebral aneurysm 10 mm or larger that requires use of adjunctive assist-devices such as stents or balloons	Large, giant and wide-necked 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 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-necked aneurysm than is possible with available platinum coils. Additionally, translucency of its polymeric material allows for noninvasive computed tomography and MRI scans with little or no artifact for more accurate patient assessment and followup. NeuroVasx, Inc., Maple Grove, MN FDA approved under humanitarian device exemption in Apr 2011	Endovascular embolization-detachable coils (spirals of platinum wire) Microvascular clipping (clothespin-like clip on the aneurysm's neck) Occlusion of artery that leads to the aneurysm	Decreased incidence of ruptured aneurysm Reduced incidence of hemorrhagic stroke Reduced short-term and/or permanent brain damage Decreased mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Riociguat (BAY63-2521) for treatment of pulmonary artery hypertension	Patients in whom pulmonary artery hypertension (PAH) has been diagnosed	PAH has no cure and can result in heart failure and death. Riociguat purportedly stimulates the soluble guanylate cyclase pathway that is involved in nitric oxide signaling and vasodilation, which may relieve symptoms of PAH. In ongoing trials, riociguat is administered orally, 1.0, 1.5, 2.0, or 2.5 mg, 3 times daily. Bayer AG, Leverkusen, Germany One phase III trial completed; extension phase III trial ongoing	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalizations
Selective prostacyclin (PGI2) receptor agonist (selexipag) for treatment of pulmonary artery hypertension	Patients in whom pulmonary artery hypertension (PAH) has been diagnosed	PAH has no cure and can result in heart failure and death. Selexipag (ACT-293987) is a 1st-in-class, selective prostacyclin (PGI2) receptor agonist; prostacyclin counteracts the vasoconstrictor and prothrombotic activity of endothelin. Selexipag is an orally available, long-acting, nonprostanoid prostacyclin receptor agonist that mimics the actions of endogenous prostacyclin and exerts vasodilating effects. Selexipag is an oral tablet, taken twice daily. Actelion Pharmaceuticals, Ltd., Allschwil, Switzerland Phase III trials ongoing	Calcium channel blockers Endothelin receptor antagonists Phosphodiesterase type 5 inhibitors Prostanoids	Improved exercise capacity Reduced mortality Reduced hospitalization

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Standardized protocol and integrated system (RACE Project) for treatment and transfer of patients with ST-elevated myocardial infarction	Patients in whom an ST-elevated myocardial infarction (STEMI) has been diagnosed	Current guidelines recommend that patients with STEMI receive fibrinolysis within 30 minutes, and primary percutaneous coronary intervention (PCI) within 90 minutes, of symptom onset, yet fewer than half of patients receive this care within the recommended time frame. Additionally, only 4% of patients who are transferred to a 2nd (PCI-capable) hospital are treated within the 90-minute time frame. Reperfusion of Acute Myocardial Infarction in North Carolina Emergency Departments (RACE) Project: Statewide initiative to identify and overcome barriers to recommended rapid reperfusion times by establishing optimal regional systems of care (with parallels to existing trauma systems). Goal is to improve both the rate and speed of STEMI care through specific interventions with a systemic approach. PCI and non-PCI hospitals are assessed to determine barriers to rapid reperfusion, and customized plans for improvement are developed. Interventions include: educational symposia (on topics such as electrocardiogram (ECG) interpretation, STEMI recognition, treatment options), placing ECG and transmittal equipment on EMS transport vehicles, and establishing a single telephone number to access transfer to a PCI hospital. Transfer-specific interventions include: leaving patient on the original stretcher and creating system-compatible intravenous tubing and pumps, and/or eliminating the need for IV pumps (e.g., through administration of intravenous bolus of unfractionated heparin). Sponsored by North Carolina Chapter of the American College of Cardiology Pilot study with 436 patients at 55 hospitals completed; data available	Current STEMI practices (vary between hospitals)	Reduced door-in-to-door-out time Reduced time to treatment Improved cardiovascular morbidity Improved mortality outcomes
Subcutaneous implantable cardioverter defibrillator (S-ICD System) for treatment of cardiomyopathy	Patients with cardiomyopathy who are at risk of sudden cardiac arrest	This subcutaneous implantable cardioverter defibrillator's (S-ICD®) wires do not connect to the heart and reduce risk of wires bending and causing unnecessary shocks; no imaging equipment required for placement. Boston Scientific Corp., Natick, MA (acquired developer Cameron Health Jun 2012) Premarket approval application submitted to FDA Jan 2012; FDA granted expedited review status; Conformité Européene (CE) marked in 2009. FDA approved Sept 2012 to provide defibrillation therapy for treating life-threatening ventricular tachyarrhythmias in patients who have no symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that can be terminated with anti-tachycardia pacing	Other implantable defibrillators	Quicker recovery after implantation Reduced risk of unnecessary shocks Reduced risk of failures to shock Improved quality of life

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	AS occurs in about 4% to 5% of people aged 75 years or older and an estimated 300,000 people have the condition worldwide. Causes of severe AS include buildup of calcium deposits on the aortic valve, prior radiation therapy, certain medications, and/or a history of rheumatic fever. An estimated 30% of all patients with symptomatic severe AS are not suitable candidates for valve implantation performed as an open-heart surgery procedure. The transcatheter aortic valve (CoreValve®) implantation procedure uses fluoroscopic guidance to replace the native aortic heart valve without open heart surgery; an 18-French diameter catheter is used for delivery of a self-expanding nitinol frame stent with a porcine pericardial tissue valve. Medtronic, Inc., Minneapolis, MN Phase III trials ongoing; Conformité Européene (CE) marked in 2007; available outside U.S. in 34 countries	Open surgery Optimal medical management Other transcatheter aortic valves	Improved cardiac function Increased survival Improved quality of life
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 nonoperable for conventional open-heart valve replacement surgery	AS occurs in about 4% to 5% of people aged 75 years or older and an estimated 300,000 people have the condition worldwide. Causes of severe AS include buildup of calcium deposits on the aortic valve, prior radiation therapy, certain medications, and/or a history of rheumatic fever. An estimated 30% of all patients with symptomatic severe AS are not suitable candidates for valve implantation performed as an open-heart surgery procedure. Sapien transcatheter aortic valve is a tissue valve deployed into the heart using a minimally invasive transcatheter-based procedure (transfemoral or transapical) to try to repair a severely stenotic aortic valve. Edwards Lifesciences Corp., Irvine, CA FDA approved Nov 2011 for “transfemoral delivery in patients with severe symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.” In Oct 2012, expanded approval to include patients with symptomatic severe aortic stenosis who are at high operative risk.	Optimal medical management Open surgery Other transcatheter aortic valves	Accurate valve replacement Avoided open surgery Decreased rehospitalization for heart failure Decreased mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Transcatheter mitral valve repair (MitraClip) for treatment of mitral regurgitation	Patients with degenerative mitral valve disease with prolapse who are not good candidates for open surgical repair	Mitral regurgitation can require invasive surgery when severe. Some patients are not candidates for open surgery and could benefit from a minimally invasive option. The MitraClip® purportedly provides a minimally invasive transcatheter approach that requires a transseptal puncture to access the left heart chambers. In lieu of sutures, a flexible metal clip covered in polyester fabric (MitraClip) is used. The device is intended for patients whose valve disease originates mainly from the center of the valve. Evalve, Inc., Menlo Park, CA (being acquired by Abbott Laboratories, Abbott Park, IL) Phase III trial ongoing; Conformité Européene (CE) marked in 2008	Open surgical mitral valve repair Pharmacotherapy	Improved quality of life for patients who are not good surgical candidates Reduction in mitral regurgitation and associated cardiovascular outcomes Decreased cost because of slowing disease progression Decreased cost compared with open surgery
Ultrasound (ClotBust-ER) for treatment of acute ischemic stroke	Patients in whom acute ischemic stroke has been diagnosed	Transcranial ultrasound is a new treatment for ischemic stroke. However, technical challenges are associated with administration of transcranial ultrasound, and sonographers capable of detecting occluded cerebral artery segments are available only in specialized stroke centers or emergency departments (EDs). An unmet need exists to extend this therapy to smaller EDs. ClotBust™-ER is an ultrasound device that employs multiple transducers operating at 2 MHz, and it is intended to deliver therapeutic ultrasound energy to the vessel occlusion in the brain to treat ischemic stroke in patients eligible for intravenous thrombolytic therapy. The system includes multiple ultrasound transducers, which are mounted on an adjustable head frame to administer therapeutic ultrasound in the principal regions in which the majority of vessel occlusions in the brain occur. Because the transducers self-align based on anthropometric landmarks, they do not need to be aimed by a trained sonographer. Cerevast Therapeutics, Inc., Redmond, WA Phase I/II trial completed; phase III trial registered, but not yet recruiting	Sonographer-administered ultrasound Tissue plasminogen activator therapy	Improved clot lysis Reduced stroke-related morbidity and mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vagus nerve stimulation (CardioFit) for treatment of congestive heart failure	Patients in whom severe congestive heart failure (HF) has been diagnosed	CardioFit® vagus nerve stimulation is an implantable device intended to improve heart-pumping capacity in patients with severe congestive HF. BioControl Medical, Yehud, Israel Phase III trial ongoing	Heart transplantation Minimally invasive heart surgery Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, digoxin, diuretics) Ventricular assist devices	Improved left ventricular ejection fraction Improved 6-minute walk test Reduced need for medication Improved quality of life
Wireless monitoring system (Champion) for management of heart failure	Patients in whom moderately severe heart failure (HF) has been diagnosed	In hospitalized patients, catheters placed temporarily within the heart to monitor left atrial pressure are the gold standard for tracking blood movement (hemodynamics) and worsening HF. However, no devices are available for monitoring ambulatory patients. About 1/3 of patients with HF who have been discharged from the hospital are readmitted within 30 days, usually for worsening signs and symptoms of congestion. This congestion is caused by increases in intracardiac and pulmonary artery pressures, which are apparent several days to weeks before the onset of worsening signs, symptoms, and hospital admission. Thus, researchers suggest, monitoring these pressures might reduce the risk of readmission to hospital. The Champion device is a self-contained, paper-clip-sized device placed in the pulmonary artery during a catheter-based procedure. A patient holds the external electronics module over the chest to wirelessly power the sensor and collect pressure data using radiofrequency energy. The handheld unit then transmits data to the CardioMEMS Champion Web site, which the physician monitors. This device may potentially give clinicians more timely access to changes in symptoms and/or physiologic parameters, allowing them to quickly adjust medications and potentially reduce HF-related hospitalizations. This would be the 1st FDA-approved, permanent monitor implant for this indication. CardioMEMS, Inc., Atlanta, GA Premarket approval application submitted to FDA; Dec 2011 advisory panel voted 6-4 to not recommend approval because of potential bias in the trial design; company is deciding next steps; the technology received the 2012 Intel Innovation Award in Dec.	Weight monitoring (for fluid retention) Symptom monitoring	Improved clinician access to changes in patient symptoms Earlier medical intervention Reduced HF-related hospitalizations Improved morbidity and mortality

Table 4. AHRQ Priority Condition: 04 Dementia (including Alzheimer's: 9 Interventions

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 prodromal Alzheimer's disease	Patients in whom prodromal Alzheimer's disease (AD) has been diagnosed	No approved disease-modifying agents are available for treating AD; available therapy options are limited to symptom management. Gantenerumab is a fully human anti beta-amyloid antibody. It has been shown to pass the blood-brain barrier purportedly with a high capacity to bind to beta-amyloid plaques in the brain. This binding purportedly clears amyloid plaques by a process called phagocytosis. In clinical trials, gantenerumab is given as subcutaneous dose every 4 weeks, for 104 weeks. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trial ongoing	Cholinergic agents (e.g., donepezil, galantamine, tacrine) NMDA inhibitor (e.g., memantine)	Slowed disease progression, or regression Reduced morbidity Improved quality of life
Beta-amyloid monoclonal antibody (solanezumab) for treatment of Alzheimer's disease	Patients in whom mild Alzheimer's disease (AD) has been diagnosed	No approved disease-modifying agents are available for treating AD; available therapy options are limited to symptom management. Solanezumab is a fully humanized anti-beta-amyloid antibody that binds specifically to soluble beta amyloid and is intended to draw the peptide away from the brain through the blood to promote clearance of beta-amyloid protein from damaged sites in the brain. It is intended for mild-to-moderate AD and is administered 400 mg intravenously every 4 weeks for 80 weeks in clinical trials. Eli Lilly and Co., Indianapolis, IN Phase III trials completed (EXPEDITION 1 and 2 trials); EXPEDITION-EXT ongoing; Aug 2012 report of top-line results indicated drug failed to reach its goals in either of 2 phase III studies, but showed improvement in pooled results; new phase III trial in mild AD to begin no later than Sep 2013	Cholinergic agents (e.g., donepezil, galantamine, tacrine) NMDA inhibitor (e.g., memantine)	Decreased beta-amyloid load in brain Slowed or halted disease progression Improved memory and cognition Improved survival Improved quality of life
Beta-amyloid precursor protein site cleaving enzyme inhibitor (MK-8931) for treatment of Alzheimer's disease	Patient in whom Alzheimer's disease (AD) has been diagnosed	No approved disease-modifying agents are available for treating AD; available therapy options are limited to symptom management. MK-8931 is an oral beta-amyloid precursor protein site cleaving enzyme (BACE) inhibitor that is being investigated for treating AD. The company states that the drug is intended to inhibit BACE, an enzyme that is known to play a role in the initiation of synthesis of beta-amyloid peptide. Because abnormal accumulation of beta-amyloid peptide is thought to play a role in AD's progression, the company states, this agent may have the potential to improve outcomes in AD. Merck & Co., Inc., Whitehouse Station, NJ Phase II/III trial ongoing	Cholinergic agents (e.g., donepezil, galantamine, tacrine) NMDA inhibitor (e.g., memantine)	Regressed or slowed disease progression Reduced beta-amyloid load in brain Reduced morbidity and mortality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Florbetapir F18 positron emission tomography imaging agent (Amyvid) for detecting beta-amyloid plaques	Patients suspected of having beta amyloid (a-beta)-associated disease	No definitive method exists for diagnosing AD in a living person. Diagnosis is made on the basis of clinical signs and symptoms, sometimes aided by positron emission tomography (PET) using a contrast agent. Florbetapir F18 (Amyvid™) is a radiopharmaceutical that binds specifically to beta amyloid and is visualized by positron emission tomography (PET) imaging. Contrast agent would be indicated for visualization of beta-amyloid aggregates; a negative result could help to rule out presence of pathologically relevant levels of beta-amyloid plaques. Avid Radiopharmaceuticals subsidiary of Eli Lilly and Co., Indianapolis, IN FDA approved Apr 2012 for detecting beta-amyloid plaques	Blood tests for AD biomarkers Cerebrospinal fluid tests for AD biomarkers Neuropsychological test battery Positron emission tomography scans with beta-amyloid-binding contrast agents	Increased sensitivity and specificity of beta-amyloid plaque detection
Flutemetamol positron emission tomography imaging agent for detecting beta-amyloid plaques	Patients in whom Alzheimer's disease (AD) is suspected	No definitive method exists for diagnosing AD in a living person. Diagnosis is made on the basis of clinical signs and symptoms, sometimes aided by positron emission tomography (PET) using a contrast agent. Flutemetamol is a PET imaging agent intended to detect normal or raised beta-amyloid plaques in the brain to confirm a diagnosis of AD. General Electric Co., Fairfield, CT Phase III trials completed and met primary endpoints; company expected to file new drug application with FDA in 2013	Blood tests for AD biomarkers Cerebrospinal fluid tests for AD biomarkers Neuropsychological test battery PET scans with beta-amyloid-binding contrast agents	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
Handheld event-related potential/ quantitative electroencephalo-graphy system (Cognision) for diagnosis of Alzheimer's disease	Patients in whom a diagnosis of Alzheimer's disease (AD) is suspected	No definitive method exists for diagnosing AD in a living person. Diagnosis is made on the basis of clinical signs and symptoms, sometimes aided by positron emission tomography (PET) using a contrast agent. An unmet need exists for diagnostic/screening tools that can detect the condition before significant loss of memory, cognition, and activities of daily living occur. Cognision™ System is a device intended to provide objective assessment of cognitive function via noninvasive technology using electrodes attached to a hat-like frame, which is placed on the head. The system is designed to measure auditory event-related potentials (ERPs); according to the manufacturer, ERPs are generated in response to auditory stimuli and can accurately measure the cognitive performance of a patient's brain before overt AD symptoms are present. Patient data are located in a central data bank, which analyzes data and classifies the patient's brainwaves based on similarities to known neurologic risk profiles. Neuronetrix, Inc., Louisville, KY Trial ongoing (no phase listed)	Blood tests for AD biomarkers Cerebrospinal fluid tests for AD biomarkers Neuropsychological test battery PET scans with beta-amyloid-binding contrast agents	Improved ability to diagnose, rule out, and/or screen for AD Earlier intervention Improved outcomes Improved quality of life
Intravenous Immunoglobulin for treatment of Alzheimer's disease	Patients in whom mild to moderate AD has been diagnosed	No approved disease-modifying agents are available for treating AD; available therapy options are limited to symptom management. Intravenous immunoglobulin (IVIG) infusion is approved for treating many immune disorders. In patients with AD, IVIG is intended to clear beta amyloid from the brain, thereby blocking beta amyloid's detrimental effects on the brain. Clinical trials are testing low- and high-dose IVIG infusions, given every 2 weeks for 18 months. Baxter International, Inc., Deerfield, IL Several phase III trials ongoing	Cholinergic agents (e.g., donepezil, galantamine, tacrine) NMDA inhibitor (e.g., memantine)	Reduced beta-amyloid 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
Off-label atomoxetine (Strattera) for treatment of mild cognitive impairment	Patients in whom mild cognitive impairment (MCI) has been diagnosed	MCI may be a precursor to Alzheimer's disease (AD). No disease-modifying agents are available for treating AD; available therapy options are limited to symptom management.. Atomoxetine (Strattera®) is a selective norepinephrine reuptake inhibitor (SNRI) that is approved for improving attention span and decreasing impulsiveness and hyperactivity in children and adults with attention-deficit hyperactivity disorder. SNRIs increase brain levels of norepinephrine, which controls behavior. Researchers hypothesize that these properties may have some use in treating MCI. This drug class has been studied in patients with dementia, but not yet in patients with MCI. Taken orally. Eli Lilly and Co., Indianapolis, IN (manufacturer) Emory University, Atlanta, GA, with the National Institute on Aging, Bethesda, MD (investigators) Phase II trial ongoing; it does not appear that Strattera's manufacturer is seeking a labeled indication change	Off-label AD pharmacotherapy; Pharmacotherapies in development	Improved cognitive performance Delayed progression to AD Reduced morbidity
Off-label intranasal insulin for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	No approved disease-modifying agents are available for treating AD; available therapy options are limited to symptom management. This intervention represents a new mechanism of action for treating AD. Insulin is known to play a role in normal brain function, modulating glucose utilization in the hippocampus, facilitating memory at optimal levels, modulating levels of beta amyloid, and providing neuroprotection for synapses against beta amyloid. Patients with AD have reduced levels of insulin and insulin activity. Insulin cannot be delivered peripherally because of the risk of hypoglycemia or induction and/or exacerbation of peripheral insulin resistance. Therefore, researchers have begun delivering insulin intranasally (branded insulin, delivered via a nasal drug delivery device), administered at 20 IU or 40 IU total dose, twice daily. HealthPartners Research Foundation, Minneapolis, MN University of Kansas, Lawrence University of Washington, Seattle Phase II trials ongoing; it does not appear that the insulin manufacturers are pursuing a labeled indication change	Cholinergic agents (e.g., donepezil, galantamine, tacrine) NMDA inhibitor (e.g., memantine)	Slowed disease progression, or regression Improved memory Improved long-term outcomes Improved quality of life

Table 5. AHRQ Priority Condition: 05 Depression and Other Mental Health Disorders: 22 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Amitifadine (EB-1010) for treatment of depression	Patients with major depressive disorder whose disease does not respond adequately to selective serotonin reuptake inhibitors	Despite the many available therapeutic options for major depression, treatment side effects and low remission rates remain an issue. Amitifadine (EB-1010) is a novel, unbalanced, triple serotonin-norepinephrine-dopamine reuptake inhibitor antidepressant that acts simultaneously as a reuptake inhibitor for the 3 monoamines. It demonstrates greatest affinity for transporters that inhibit serotonin reuptake, half as much against norepinephrine reuptake, and 1/8 as much against dopamine reuptake. Euthymics Biosciences, Inc., Cambridge, MA Phase II/III trial ongoing	Pharmacotherapy (e.g., serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants) Psychotherapy	Increased serotonin, norepinephrine, and dopamine neurotransmission Improvement in symptoms, as measured by standard depression rating scales Improved quality of life
Bitopertin (RO4917838) for treatment of negative symptoms of schizophrenia	Patients in whom schizophrenia has been diagnosed	Existing pharmacotherapies for schizophrenia may have limited efficacy and are associated with unwanted side effects in many patients. Additionally, available treatment options inadequately address the negative and cognitive symptoms of schizophrenia. Bitopertin (RG1678, RO4917838) is a glycine transporter type 1 inhibitor. Elevation of extracellular synaptic glycine concentration by blockade of glycine transporter type 1 has been hypothesized to potentiate N-methyl-D-aspartate receptor function. Intended to mediate negative symptoms, which include blank stares, monotone and monosyllabic speech, lack of animation, seeming lack of interest in the world and other people, and inability to feel pleasure. Current treatment focuses on positive symptoms. F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials ongoing	Pharmacotherapy (e.g., atypical antipsychotics)	Symptom improvement Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bright-light adjunctive therapy for nonseasonal major depressive disorder and bipolar major depression	Patients in whom nonseasonal major depressive disorder (MDD) has been diagnosed	Many pharmacologic and psychotherapeutic options are available for major depressive disorder and major depression in bipolar disorder, yet fewer than half of patients achieve remission, and many treatments have undesired side effects 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. Studies have been completed and several are ongoing by various entities using bright light therapy as an adjunct to other treatments, including pharmacotherapy and behavioral therapy. Douglas Mental Health University Institute, Quebec, Canada National Institute of Mental Health, Bethesda, MD New York State Psychiatric Institute, New York, NY University of British Columbia, Canada University of Pittsburgh, PA Trials completed; trials ongoing	Cognitive behavioral therapy Pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants) Psychotherapy	Improved depression rating scale scores Improved sleep patterns Improved quality of life Reduced rate of suicide attempts

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Citizen soldier peer support outreach program (Buddy-to-Buddy) for returning veterans	Returning veterans in whom mental health or substance abuse conditions have been, or may be, diagnosed	25% 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. Available only to veterans in Michigan, but intending to scale up nationally. Developed by Michigan Army National Guard (MI ARNG); Michigan State University, East Lansing; University of Michigan, Ann Arbor; Buddy One funded by MI ARNG and the National Guard Bureau (NGB); Buddy Two funded by Major League Baseball charities, New York, NY; and McCormick Foundation, Chicago, IL Fully implemented in Michigan; outcomes evaluation is ongoing	Peer support group programs (e.g., Vet-to-Vet)	Increased access for veterans to medical and psychological support resources Improved mental health outcomes Improved substance abuse outcomes Improved quality of life
Cortisol antagonist (mifepristone, Korlym) for treatment of psychotic depression	Patients in whom psychotic depression has been diagnosed	No treatments are FDA approved for psychotic depression. This intervention represents a novel mechanism of action for the condition. Mifepristone (Korlym™, previously Corlux) is a cortisol antagonist. Patients with psychotic depression have higher levels of cortisol, a hormone that regulates bodily reactions to stress. Elevated levels of circulating cortisol can produce psychiatric disorders. The drug is intended to be administered orally, in tablet form, once daily. Corcept Therapeutics, Menlo Park, CA Expanded phase III trial ongoing; FDA granted fast track status for this indication; FDA approved for a different indication (Cushing's syndrome) in Feb 2012	Antipsychotics in combination with antidepressants Electroconvulsive therapy	Improvement in psychotic symptoms Reduced suicide rate Improved quality of life

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Dextroamphet-amine prodrug (lisdexamfetamine, Vyvanse) for treatment of binge-eating disorder	Patients in whom binge-eating disorder (BED) has been diagnosed	No pharmacotherapies are approved by FDA for binge-eating disorder, and used off-label pharmacotherapies are associated with limited efficacy, undesirable side effects, and low adherence.. Lisdexamfetamine (Vyvanse®) is a prodrug of dextroamphetamine; it is indicated for treating attention-deficit hyperactivity disorder. The agent is thought to induce the release of dopamine and norepinephrine, which contribute to maintaining alertness, focus, thought, effort, and motivation; however, the company has not yet described the mechanism of action through which this agent is expected to exert its effects in this population. Shire, plc, Dublin, Ireland 1 phase III trial completed, several ongoing	Off-label pharmacotherapies (e.g., antiepileptics, norepinephrine reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors)	Decreased morbidity Fewer binge-eating episodes Improved quality of life
Gamma aminobutyric acid agonist (BL-1020) for treatment of schizophrenia	Patients in whom schizophrenia has been diagnosed	Existing pharmacotherapies for schizophrenia may have limited efficacy and are associated with unwanted side effects in many patients. Additionally, available treatment options inadequately address the negative and cognitive symptoms of schizophrenia. Negative symptoms are an absence of normal responses and include blank stares, monotone and monosyllabic speech, few gestures, and disengagement or disinterest. BL-1020 may address cognitive and negative symptoms of schizophrenia, which can be difficult to recognize and often persist during periods of low (or absent) positive symptoms. BL-1020 has a novel mechanism of action (i.e., 1st in class) as a gamma aminobutyric acid (GABA) ester of perphenazine (Trilafon, typical antipsychotic, no efficacy in negative or cognitive symptoms); it blocks dopamine and serotonin while increasing GABA activity (lowered levels of GABA participate in the pathogenesis of schizophrenia). BioLineRx, Ltd., Jerusalem, Israel Cypress Bioscience, Inc., San Diego, CA Phase II/III trial ongoing	Pharmacotherapy (e.g., atypical antipsychotics)	Improved cognition Decreased negative symptoms Improved social functioning Improved quality of life

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)	Existing pharmacotherapies for schizophrenia may have limited efficacy and are associated with unwanted side effects in many patients. Additionally, available treatment options inadequately address the negative and cognitive symptoms of schizophrenia. RG1678 is a 1st-in-class glycine reuptake inhibitor. It normalizes glutamate neurotransmission by increasing synaptic levels of glycine, an essential cofactor for N-methyl-D-aspartate receptors (NMDARs), which likely have a role in the pathophysiology of schizophrenia; without it, receptor does not work properly. Chugai Pharmaceutical subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Phase III trials ongoing; filing anticipated in 2014	Pharmacotherapy (e.g., atypical antipsychotics)	Meaningful reduction in negative symptoms of schizophrenia, as measured by clinical rating scales (e.g., Positive and Negative Syndrome Scale) Improved personal and social functioning
Lisdexamfetamine (Vyvanse) for treatment of negative symptoms in schizophrenia	Patients in whom schizophrenia has been diagnosed	Existing pharmacotherapies for schizophrenia may have limited efficacy and are associated with unwanted side effects in many patients. Additionally, available treatment options inadequately address the negative and cognitive symptoms of schizophrenia.. Negative symptoms are an absence of normal responses and include blank stares, monotone and monosyllabic speech, few gestures, and disengagement or disinterest. Lisdexamfetamine is a prodrug of dextroamphetamine and induces release of dopamine and norepinephrine, which contribute to maintaining alertness, focus, thought, effort, and motivation. Shire Pharmaceuticals, plc, Dublin, Ireland Phase III trial beginning; lisdexamfetamine is indicated for treating attention-deficit hyperactivity disorder	Pharmacotherapy (e.g., atypical antipsychotics)	Reduced negative symptoms Improved social functioning Improved quality of life
Lisdexamfetamine (Vyvanse) for treatment-resistant major depressive disorder and bipolar depression	Patients in whom treatment-resistant major depressive disorder (MDD) has been diagnosed	Despite the many available therapeutic options for major depression, treatment side effects and low remission rates remain an issue. Available 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. Lisdexamfetamine (Vyvanse®) is a prodrug of dextroamphetamine; induces release of neurotransmitters dopamine and norepinephrine, which are known to contribute to maintaining alertness, focus, thought, effort, and motivation. Shire Pharmaceuticals, plc, Dublin, Ireland Phase III trials ongoing; lisdexamfetamine is indicated for treating attention-deficit hyperactivity disorder	Pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants) Psychotherapy	Improved depression rating scale scores Improved sleep patterns Reduced rate of suicide attempts Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mobile phone psychotherapy applications as alternative care-delivery model for mental health conditions	Patients in whom mental health conditions (e.g., major depressive disorder, anxiety) have been diagnosed	Psychotherapy traditionally involves in-person meetings between a therapist and patient or client. This method has limitations, including lack of intervention at critical moments and an inability to reach individuals who lack the means or willingness to enter a traditional therapeutic relationship. To address these unmet needs, some researchers have created mobile phone applications ("apps") that purport to provide some psychotherapeutic benefit to patients even if they don't attend traditional therapy. These apps range in their capabilities and intended benefits. For example, the Mobilyze app is designed to use data from sensors already embedded in the phone (e.g., GPS, Bluetooth, Wi-Fi, accelerometers) to identify patient states, without requiring patient self-reporting. This automated system for detecting mood-related states is intended to address nonadherence and other treatment difficulties as they occur in real time. For example, if the app detects that an individual is becoming isolated, it will recommend that he or she calls a friend. Another app is intended to decrease social anxiety and excessive worrying by reducing the tendency of anxious people to focus on threatening items around them. The app purports to train people to divert attention away from negative stimuli that appear on the screen. Various research institutions, including Northwestern University, Evanston, IL, and McNally Laboratory at Harvard University, Cambridge, MA Clinical trials ongoing	In-person psychotherapy Internet-delivered (nonmobile phone) psychotherapy	Improved performance on mental health rating scales Reduced morbidity Reduced mortality Improved quality of life
Nicotinic alpha-7 agonist (EVP-6124) for treatment of cognitive symptoms of schizophrenia	Patients in whom schizophrenia has been diagnosed	Existing pharmacotherapies for schizophrenia may have limited efficacy and are associated with unwanted side effects in many patients. Additionally, available treatment options inadequately address the negative and cognitive symptoms of schizophrenia. EVP-6124 is a selective, potent compound that is intended to enhance synaptic transmission in the brain and act as a co-agonist in combination with acetylcholine (ACh) to enhance cognition. According to the manufacturer, the agent sensitizes the alpha-7 receptor, thereby allowing smaller amounts of naturally occurring ACh to be effective in activating the alpha-7 receptor. The company purports that 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. Given orally/ EnVivo Pharmaceuticals, Watertown, MA Phase III trial registered, not yet recruiting	Pharmacotherapy (e.g., atypical antipsychotics)	Improved cognitive symptoms Improved social functioning Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label armodafinil (Nuvigil) for treatment of binge-eating disorder	Patients in whom binge-eating disorder has been diagnosed	No pharmacotherapies are approved by FDA for binge-eating disorder, and used off-label pharmacotherapies are associated with limited efficacy, undesirable side effects, and low adherence. Armodafinil (Nuvigil®) is a wakefulness-promoting drug with an unknown mechanism of action; it was approved in 2007 for treating excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift work disorder. Some investigators have suggested that binge-eating disorder may mediate the relationship between narcolepsy and obesity, so researchers are investigating the off-label use of armodafinil in patients with binge-eating disorder. In a clinical trial, the drug is being dosed in oral form, at a variable dosage of 150–250 mg/day. Cephalon, Inc., acquired by Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, in Oct 2011 (manufacturer) Lindner Center of Hope, Mason, OH (investigator) Phase III trial ongoing	Off-label pharmacotherapies (e.g., antiepileptics, norepinephrine reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors)	Improved symptoms of binge eating Reduced morbidity Reduced mortality
Off-label ketamine for treatment-resistant severe depression	Patients in whom treatment-resistant major depressive disorder (MDD) or bipolar depression has been diagnosed	Despite the many available therapeutic options for MDD, treatment side effects and low remission rates remain an issue. Available options for treatment-resistant MDD (e.g., deep brain stimulation [DBS], vagus nerve stimulation [VNS], transcranial magnetic stimulation, or repetitive transcranial magnetic stimulation [rTMS]) are surgically invasive and must be performed in a hospital setting. Oral N-methyl-D-aspartate (NMDA; ketamine, a recreational drug) for rapid (within 40 minutes) relief of severe treatment-resistant depression. National Institutes of Health, Bethesda, MD Phase II-IV trials ongoing	DBS Electroconvulsive therapy Pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants) Psychotherapy Transcranial magnetic stimulation VNS	Rapid response Improved treatment adherence Reduced symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label oxytocin for treatment of social cognition deficits associated with schizophrenia	Patients in whom schizophrenia has been diagnosed	Existing pharmacotherapies for schizophrenia may have limited efficacy and are associated with unwanted side effects in many patients. Additionally, available treatment options inadequately address the negative and cognitive symptoms of schizophrenia. Psychotherapeutic interventions are limited by suboptimal efficacy and availability. Release of oxytocin is associated with social bonding, empathy, and trust. Given oxytocin's importance in social behavior, researchers purport it may have utility in improving social cognition deficits in patients with schizophrenia. Researchers have administered this agent intranasally over varying periods of time. Several institutions, including University of California, Los Angeles, and University of North Carolina, Chapel Hill Clinical trials ongoing	Psychotherapy	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	Despite the many available therapeutic options for major depression, treatment side effects and low remission rates remain an issue. Available options for treatment-resistant MDD (e.g., deep brain stimulation [DBS], vagus nerve stimulation [VNS], transcranial magnetic stimulation, or repetitive transcranial magnetic stimulation [rTMS]) are surgically invasive and must be performed in a hospital setting.. The mechanism of action of riluzole (Rilutek®) would be novel for this disease state. Riluzole is a glutamatergic modulator FDA approved for treating amyotrophic lateral sclerosis; glutamate is the primary excitatory neurotransmitter in the brain, and the glutamatergic system plays a major role in MDD. Riluzole has been shown to inhibit glutamate release, enhance glutamate reuptake, and protect glial cells against glutamate excitotoxicity. Sanofi, Paris, France (manufacturer) National Institute of Mental Health, Bethesda, MD (investigator) Phase II trials ongoing; 1 phase II trial completed	DBS Electroconvulsive therapy Pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants) 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 venlafaxine (Effexor) for treatment of compulsive hoarding	Patients with compulsive hoarding habits who have no other identified psychiatric morbidity	Compulsive hoarding affects an estimated 2% to 5% of individuals in the U.S. The condition can be difficult to treat, and only 1 study has been conducted to determine whether pharmacotherapy is an effective treatment. Selective serotonin reuptake inhibitors (SSRIs) have been used in this population, but they are associated with side effects and suboptimal efficacy, especially in older adults. Extended-release venlafaxine (Effexor XR®) is a selective norepinephrine reuptake inhibitor that is indicated in the U.S. for treating depression, generalized anxiety disorder, social anxiety disorder, and panic disorder. Because this agent is better tolerated and more effective in treating patients with obsessive-compulsive disorder (often associated with hoarding), researchers hypothesize that it may have utility in patients in whom compulsive hoarding has been diagnosed. In trials, the drug was administered orally, once daily. Pfizer, Inc., New York, NY (manufacturer) University of California, San Diego (investigator) Clinical trial completed; it does not appear that Effexor's manufacturer is seeking a labeled indication change	Psychotherapy Selective serotonin reuptake inhibitors	Improved scores on hoarding rating scales Reduced morbidity Reduced mortality Improved quality of life
Text-messaging therapy for bulimia nervosa	Patients in whom bulimia nervosa has been diagnosed	Feelings of shame affect willingness to undergo treatment, and access to treatment and duration of treatment are significant issues with eating disorders because of their chronic nature. New behavioral therapy approaches are needed that engage participant. With this text-messaging approach, participants send a nightly text message to clinicians to report the number of binge-eating and purging episodes and rate their urges to binge and purge. Participants receive automatic feedback message tailored to their self-reported symptoms. This approach is being studied in conjunction with a cognitive behavior therapy program to keep patients engaged in therapy. University of North Carolina at Chapel Hill Trial completed (phase not reported)	Antidepressants Nutritional counseling Psychological counseling	Reduced number of binge eating and purging episodes Improved symptoms of depression, eating disorder, and night eating Enhanced self-monitoring and treatment, leading to improved attendance, adherence, and engagement in treatment Increased remission

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vortioxetine (Lu AA21004) for treatment of major depressive disorder	Patients in whom major depressive disorder (MDD) has been diagnosed	Despite the many available therapeutic options for major depression, treatment side effects and low remission rates remain an issue. Lu AA21004 is a 5-HT3 and 5-HT7 receptor antagonist, 5-HT1A receptor agonist, 5-HT1B receptor partial agonist, and 5-HT transporter inhibitor that has been shown to increase brain levels of serotonin, noradrenaline, dopamine, acetylcholine, and histamine. Clinical trials have suggested that the drug may be associated with low (similar to placebo) rates of sexual dysfunction, compared with available products. Planned oral dosages include 10, 15, and 20 mg. Takeda Pharmaceutical Co., Ltd., Osaka, Japan, jointly with H. Lundbeck a/s, Valby, Denmark Phase III trials completed; new drug application submitted Oct 2012	Pharmacotherapy (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants) Psychotherapy	Improved depression rating scale scores Improved sleep patterns Improved quality of life Reduced rate of suicide attempts

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
AFQ056 for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	No cure exists for FXS; medications and behavioral interventions alleviate individual symptoms but do not address the cause of FXS. Individuals with FXS have DNA mutations in the *FMR1* gene that basically turn off the gene; it is the most common known heritable cause of cognitive and behavioral disability. Normal *FMR1* gene produces a protein that controls the synthesis of proteins at synapses that are stimulated via metabotropic glutamate receptors (mGluRs); without this control provided by the FMR1 protein, synaptic protein synthesis is excessive and connections do not develop normally. AFQ056, a selective, noncompetitive antagonist of the metabotropic glutamate receptor 5 (mGluR5), may potentially normalize the excessive protein synthesis and control symptoms associated with FXS. Dose range will be 25, 50, or 150 mg twice a day. Novartis International AG, Basel, Switzerland Phase II/III trials ongoing in adults and adolescents; company plans new drug application filing in 2013; drug is also under study for treating Parkinson's disease and Huntington's disease	Physical and behavioral interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Pharmacotherapy (e.g. antipsychotics. central nervous system stimulants, clonidine [Catapres®], folic acid, selective serotonin reuptake inhibitors, melatonin)	Change from 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
Off-label donepezil (Aricept) for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	No cure exists for FXS; medications and behavioral interventions alleviate individual symptoms but do not address the cause of FXS. FXS is a neurodevelopmental disorder caused by mutations of the *FMR1* gene; it is the most common known heritable cause of cognitive and behavioral disability. Abnormalities of cholinergic pathway function and neurochemistry observed with functional magnetic resonance imaging (fMRI) in FXS patients make 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; it may potentially augment the cholinergic system in adolescents affected by FXS. Under study by Autism Speaks, New York, NY; National Institute of Mental Health, Rockville, MD; and Stanford University, CA Phase II trial ongoing; approved to treat mild, moderate, and severe Alzheimer's disease and under study for various other types of cognitive impairment, including Down syndrome	Behavioral and physical interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Central nervous system pharmacology Melatonin Selective gamma aminobutyric acid type B receptor agonist (in development)	Improvements in specific measures of behavior and cognition Improved scores on behavior assessments Improved scores on working-memory tests

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label intranasal oxytocin (Syntocin) for treatment of social dysfunction in autism spectrum disorders	Patients in whom autistic spectrum disorder (ASD) or Asperger's syndrome has been diagnosed	Most individuals with ASD are treated through highly structured behavioral programs to try to improve social cognition and functioning, Pharmacologic therapies address symptoms of hyperactivity and depression, but pharmacologic treatments for social deficits in individuals with ASD are lacking. A pharmacologic treatment targeted at the core social deficits of ASD in early childhood could affect developmental pathways to make other psychosocial interventions possible. Oxytocin acts on smooth muscle cells (causes uterine contractions and milk ejection); it also can influence activity in brain amygdala, an area involved in social and emotional processing. Oxytocin may increase visual contact to eye region of human faces, increase memory for faces, and improve the ability of people to infer the mental states of others, which are challenges associated with autism. Potential improvements in social function and quality of life and reductions in certain types of repetitive behaviors may be realized with oxytocin therapy. This treatment is administered intranasally at a 12-unit puff per nostril, twice daily, totaling 48 IU daily. Children's Hospital of Pennsylvania, PA Mount Sinai School of Medicine, New York, NY Montefiore Medical Center, Bronx, NY Stanford University School of Medicine, CA University of Illinois at Chicago, IL Phase II trials ongoing	Behavioral and physical interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Central nervous system pharmacology Melatonin Selective gamma aminobutyric acid type B receptor agonist (in development)	Improved Diagnostic Analysis of Nonverbal Accuracy results Improved Social Responsivity Scale scores Improved Clinical Global Impressions Scale - Improvement scores

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label minocycline for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	Medications and behavioral interventions alleviate individual symptoms but do not address the cause of FXS. Individuals with FXS have DNA mutations in the *FMR1* gene that basically turn off the gene; it is the most common known heritable cause of cognitive and behavioral disability. In FXS, synaptic protein synthesis is excessive and connections do not develop normally. Minocycline is an antibiotic used in children for infection and is being investigated for treating FXS; minocycline lowers matrix metalloproteinase 9 levels, which are high in FXS, and it also strengthens brain connections according to animal models of FXS. Administered orally, once a day, for 3 months. University of California, Davis; FRAXA Research Foundation (in collaboration with Fragile X Foundation of Canada), Toronto, Ontario, Canada Pilot trial ongoing; unphased trial completed	Behavioral and physical interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Central nervous system pharmacology Melatonin Selective gamma aminobutyric acid type B receptor agonist (in development)	Improved behavior, perceptual and cognitive development Improved daily living skills Improved gross motor skill development Increased sociability and communication Improved speech and language
Off-label N-acetylcysteine for treatment of autism	Children in whom autism has been diagnosed	According to the U.S. Centers for Disease Control and Prevention, autism spectrum disorders are diagnosed in about 9 of 1,000 people in the U.S. Current therapies include behavioral programs, devices, and pharmacotherapies. N-acetylcysteine (NAC) is a glutamate modulator and antioxidant known to increase glutathione in children who have autism. For children with autism, In 1 study, NAC is being administered orally, 900 mg twice daily, or 900 mg 3 times daily;; in another study evaluating NAC for treating autism spectrum disorders, NAC is being administered orally, 600 mg, 3 times daily, with a maximum dose of 4,200 mg/day. Stanford University School of Medicine, Stanford, CA, and Indiana University School of Medicine, Indianapolis, in collaboration with National Alliance for Autism Research, Princeton, NJ Stanford University School of Medicine: phase II trial completed Indiana University School of Medicine: phase II trial completed	Behavioral and physical interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Central nervous system pharmacology Melatonin Selective gamma aminobutyric acid type B receptor agonist (in development)	Improved Clinical Global Rating Scale results Improved Repetitive Behavioral Scale score Improved social responsiveness Improved speech and language Improved metabolic measures Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
STX209 (arbaclofen) for treatment of fragile X syndrome	Patients in whom fragile X syndrome (FXS) has been diagnosed	No cure exists for FXS; medications and behavioral interventions alleviate some individual symptoms, but do not address the underlying cause of FXS. Individuals with FXS have DNA mutations in the *FMR1* gene that basically turn off the gene; it is the most common known heritable cause of cognitive and behavioral disability. Pharmacologic treatments that address FXS social deficits are needed because impairments in social function are a core feature of FXS. Research suggests that individuals with FXS have abnormalities in synaptic transmission. STX209 (arbaclofen) is a selective gamma aminobutyric acid type B (GABA-B) receptor agonist; through the GABA-B receptor, STX209 may serve to restore the normal balance at the synapse and correct abnormalities associated with FXS. Seaside Therapeutics, Inc., Cambridge, MA Phase III trials ongoing	Behavioral and physical interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Central nervous system pharmacology Melatonin Selective gamma aminobutyric acid type B receptor agonist (in development)	Improved behavioral and cognitive measures Increased sociability and communication
STX209 (arbaclofen) for treatment of social withdrawal in autism spectrum disorder	Patients in whom an autism spectrum disorder (ASD) has been diagnosed	Most individuals with ASD are treated through highly structured behavioral programs to try to improve social cognition and functioning; pharmacologic treatments to address ASD-related social deficits are lacking (existing pharmacologic treatments address symptoms such as hyperactivity, irritability, anxiety, or depression, not social deficits). A pharmacologic treatment targeted at the core social deficits in areas of communication or repetitive behaviors and restricted interests is needed. Research suggests an imbalance in gamma aminobutyric acid (GABA)/glutamate transmission underlies behavioral deficits of ASD; arbaclofen is intended to improve synaptic functioning by regulating glutamate and increasing GABA (the main inhibitory neurotransmitter in the central nervous system), an inhibitory transmitter, which counteracts the over-excitability of cells. STX209, a GABA-B agonist, has been proposed as a treatment to normalize this deficiency. Clinical trials dosage: disintegrating tablet 5 or 10 mg, twice a day; 10 or 15 mg, 3 times a day. Seaside Therapeutics, Inc., Cambridge, MA Phase III trial ongoing	Off-label pharmacotherapy (e.g., acetylcholinesterase inhibitors, alpha-2 adrenergic agonists, carnitine) Physical and behavioral interventions including speech and language, behavior, cognitive development, sensory integration, gross motor development, and activities of daily living Pharmacotherapy (e.g., risperidone, anti-inflammatories, melatonin, naltrexone, oxytocin, tetrahydrobiopterin)	Improvement in Aberrant Behavior Checklist-Social Withdrawal Subscale

Table 7. AHRQ Priority Condition: 07 Diabetes Mellitus: 19 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Allogeneic fecal enema for treatment of metabolic syndrome in obese patients	Obese patients with metabolic syndrome (at least 3 of 5 National Cholesterol Education Project metabolic syndrome criteria)	The prevalence of metabolic syndrome is increasing in the U.S., warranting the need for effective therapies aimed to reduce coronary artery disease, stroke, and diabetes mellitus. Fecal matter is harvested from healthy, lean donors, processed, and transferred into obese patients who have metabolic syndrome in an effort to treat insulin resistance and obesity by populating the lower intestinal tract with the flora of a healthy, lean person. Academic Medical Center/University of Amsterdam, the Netherlands Pilot trial completed	Antiobesity pharmacotherapy Dietary and behavioral modifications Surgical intervention (e.g., bariatric surgery)	Improved fecal flora composition Weight loss Resolution of metabolic syndrome
Alpha-1 antitrypsin for treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus (T1DM) has been diagnosed	Current therapies for T1DM have had variable results, and other therapies are needed to more effectively treat and slow progression of T1DM. Alpha-1 antitrypsin (AAT) has shown anti-inflammatory properties, and although the level of AAT in diabetes patients is normal, its activity appears to be significantly lower. These anti-inflammatory properties are believed to have potential to interfere with or even prevent autoimmune destruction of beta cells in the pancreas. AAT is administered intravenously at 40, 60, or 80 mg per dose, in 4-week intervals. Kamada, Ltd., Ness Ziona, Israel National Institute of Allergy and Infectious Disease, Bethesda, MD University of Colorado, Denver, in collaboration with Omni Bio Pharmaceuticals, Inc., Greenwood Village, CO Phase I/II trial and phase II trials ongoing; FDA granted orphan drug designation Aug 2011	Insulin modifications Islet cell transplantation Pancreas transplantation	Reduced daily insulin usage Improved glycosylated hemoglobin (HbA_{1c}) levels Reduced complications of diabetes Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anakinra interleukin-1 receptor antagonist for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	Research has implicated inflammation in the development of insulin resistance associated with T2DM; however, no anti-inflammatory treatments are approved for treating T2DM. Anakinra is a recombinant protein inhibitor of interleukin-1 (IL-1) receptors that has been approved since 2001 for treating rheumatoid arthritis. IL-1 is a proinflammatory cytokine that has been observed in pancreatic sections obtained from patients with T2DM and may play a role in the inflammatory process leading to T2DM progression. Amgen, Inc., Thousand Oaks, CA (manufacturer) Radboud University Nijmegen, the Netherlands; University Hospital, Zurich, Switzerland; and Steno Diabetes Center, Gentofte, Denmark (investigators) Phase II/III trials completed.	Dietary and lifestyle modifications Exenatide Insulin sensitizers (pioglitazone, rosiglitazone) Insulin Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Achieved target glycosylated hemoglobin (HbA_{1c}) levels Desired fasting glucose level control Resolved insulin sensitivity
Artificial pancreas device system for treatment of diabetes	Patients with type 1 or type 2 diabetes mellitus who require insulin and are highly motivated to use the system and monitor its function	Artificial pancreas is a closed-loop system consisting of an insulin pump, a real-time glucose monitor, and a sensor to detect glucose levels. Various manufacturers have made components required for the artificial pancreas; however, no single manufacturer has created a total closed loop system. Sixteen systems are in early-phase trials. Various manufacturers Early phase trials completed and ongoing; Dec 2011, FDA issued a 2nd guidance document for artificial pancreas systems to facilitate clinical development of the fully closed-loop system	Insulin modifications Islet cell transplantation Pancreas transplantation	Reliable glycemic control at desired levels Reduced risk of acute and nighttime hypoglycemia Reduction in postprandial (after meal) hyperglycemia Halted or delayed progression of secondary complications Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Buccal insulin (Oral-lyn) for treatment of type 1 or type 2 diabetes	Individuals with type 1 diabetes mellitus (T1DM) or uncontrolled type 2 diabetes mellitus (T2DM) who require insulin	Buccal insulin (Oral-lyn™ delivered via RapidMist™ device) is a fast-acting insulin that is sprayed in aerosol form on the inside of the cheek (buccal mucosa) to allow rapid absorption into bloodstream; short duration of activity. It is intended for dosing before and after meals and is intended for use adjunctively with long-acting, injectable or infused insulin and as a substitute for injectable short-acting insulin. It is not intended to reach the lungs and may pose less risk of respiratory or pulmonary complications associated with inhaled insulin. Generex Biotechnology Corp., Toronto, Ontario, Canada Phase III trial completed; FDA approved in 2009 a treatment investigational new drug program for the product that allows Generex to provide early access to people with serious or life-threatening T1DM or T2DM who have no satisfactory alternative treatments and who are not eligible for participation in the company's ongoing phase III clinical trial of the drug	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sodium glucose co-transporter 1 and/or 2 inhibitors (in development) Sulfonylurea drugs (glimepiride)	Achieved target glycosylated hemoglobin (HbA_{1c}) levels Reduced glycemic excursions related to meals Prevented onset of T2DM in prediabetic individuals Delayed insulin dependence in T2DM Improved quality of life
Canakinumab interleukin-1 inhibitor for treatment of type 2 diabetes	Patients in whom impaired glucose tolerance or type 2 diabetes mellitus (T2DM) has been diagnosed	Research has implicated inflammation in the development of insulin resistance associated with T2DM; however, no approved anti-inflammatory treatments are available 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. Novartis International AG, Basel, Switzerland Phase II/III trial completed	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sodium glucose co-transporter 1 and/or 2 inhibitors (in development) Sulfonylurea drugs (glimepiride)	Glycosylated hemoglobin (HbA_{1c}) level control 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
C-peptide replacement therapy (Ersatta) for treatment of diabetic peripheral neuropathy	Patients in whom diabetic peripheral neuropathy has been diagnosed	Current treatments for diabetic peripheral neuropathy involve control of secondary symptoms (i.e., pain management). In the body, C-peptide is generated during insulin processing and is secreted along with insulin; until recently, C-peptide was not thought to possess biologic activity and was used as a biomarker, However, recent studies suggest that a lack of C-peptide (which is not provided by exogenous insulin administration) may contribute to various secondary complications of diabetes. Ersatta™ is an extended-release formulation of C-peptide, which is being studied in treating of various secondary complications of diabetes. Cebix, Inc., La Jolla, CA Phase II trial ongoing; FDA has granted fast track status for diabetic peripheral neuropathy	Analgesics Antiepileptics Duloxetine (antidepressant), Lidocaine patches Pregabalin (anticonvulsant) Selective serotonin reuptake inhibitors Serotonin-norepinephrine reuptake inhibitors Tricyclic antidepressants	Reduced patient-reported pain on visual analog scale Improved quality of life
Exenatide (Byetta) continuous subcutaneous (Duros, or ITCA 650 pump) delivery for treatment of type 2 diabetes	Patients with type 2 diabetes mellitus who have not achieved desired blood glucose goals with metformin	Exenatide (Byetta®) is a glucagon-like peptide-1 (GLP1) mimetic delivered continuously with an implantable pump, using Duros® technology; device can be inserted under the skin in a few minutes; intended to improve glucose control and result in less nausea than observed with injected exenatide. Amylin Pharmaceuticals, Inc., San Diego, CA (drug) Intarcia Therapeutics, Inc., Hayward, CA (device) Phase II trial completed and phase III trials ongoing; Duros technology is FDA approved for drug delivery; exenatide formulation for use with pump is under study; in Nov 2011, Eli Lily and Co. returned all development rights of exenatide to Amylin	Dietary and lifestyle modifications Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sodium glucose co-transporter 1 and/or 2 inhibitors (in development) Sulfonylurea drugs (glimepiride)	Improved glycosylated hemoglobin (HbA_{1c}) levels Weight loss Reduced side effects (nausea)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Exenatide extended-release (Bydureon) for treatment of diabetes	Patients with type 2 diabetes mellitus (T2DM) who take oral agents for control	Extended-release exenatide (Bydureon™), a version of Byetta (approved in 2005) is taken by injection, once a week. Amylin Pharmaceuticals, Inc., San Diego, CA Alkermes, Inc., Waltham, MA FDA approved Jan 2012 with black box warning; FDA requested several studies to examine C-cell hyperplasia and compare glucagon-like peptide-1 receptor expression on human, rat, and mouse thyroid C-cells. The company must also maintain a 15-year case series registry to monitor the incidence of medullary thyroid carcinoma and its association, if any, to Bydureon. FDA also required company to conduct a double-blind, placebo-controlled trail to evaluate the effects of Bydureon on the incidence of major adverse cardiovascular events in T2DM patients; medullary thyroid carcinoma biomarkers; and long-term effects on specific disorders of the thyroid and pancreas. The approval also included a Risk Evaluation and Mitigation Strategy plan.	Dietary and lifestyle modifications Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sodium glucose co-transporter 1 and/or 2 inhibitors (in development) Sulfonylurea drugs (glimepiride)	Blood sugar control Cardiovascular changes (QTc segment prolongation arrhythmias)
Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema	Patients in whom diabetic macular edema (DME) has been diagnosed	DME affects an estimated 560,000 patients in the United States. Only 1 FDA-approved drug therapy (Ranibizumab) is available for treating DME. Iluvien® is a tube-shaped implant that releases a steady flow of the corticosteroid fluocinolone acetonide (FAc) into the ocular space for up to 3 years. FAc is a corticosteroid that has both anti-inflammatory and anti-VEGF (vascular endothelial growth factor) activity and has a history of effectiveness in treating ocular disorders. Alimera Sciences, Inc., Alpharetta, GA Phase III trials completed; new drug application (NDA) submitted 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; it received marketing approval in several EU countries	Intravitreal triamcinolone acetonide with or without laser photocoagulation Laser photocoagulation Pharmacotherapy (e.g., vascular endothelial growth factor antagonists)	Increased visual acuity Increased contrast sensitivity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Inhaled insulin (Afrezza) for treatment of diabetes	Patients with type 1 or diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) who require insulin injections	Inhaled insulin (Afrezza®) to control blood glucose levels. Afrezza is categorized as an ultra-rapid-acting insulin therapy to be taken at mealtime by individuals with T1DM or T2DM who require exogenous insulin. This combination drug-device product uses a proprietary inhalation powder that has been metered into single-use dose cartridges. The inhaler device is small and fits within the palm of the user's hand. MannKind Corp., Valencia, CA Phase III trials ongoing; in Mar 2010, FDA issued a complete response letter questioning whether the inhaler used in mid-phase trials was comparable to a new-generation inhaler that the company wants to market with the drug. In Jan 2011, company received a 2nd response letter outlining additional trials needed for approval; Aug 2011, 2 phase III trials were planned after manufacturer met with FDA; Oct 2012, manufacturer stated that enrollment has been completed for 2 phase III trials. These trials are not yet registered on National Clinical Trials database	Dietary and lifestyle modifications Exenatide Insulin modifications Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sodium glucose co-transporter 1 and/or 2 inhibitors (in development) Sulfonylurea drugs (glimepiride)	Decreased blood glucose levels Better glycemic control Delayed or halted progression of complications Improved patient acceptance Improved quality of life
Metabolic surgery for resolution of diabetes in obese and nonobese patients	Obese and nonobese patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	Metabolic surgery (i.e., gastric bypass, lap banding, sleeve gastrectomy) has been observed to restore metabolic imbalances in morbidly obese patients who have undergone bariatric surgery for weight loss. This led to interest in the surgery for patients with diabetes who are overweight and obese as well as nonobese patients because researchers have observed that weight is not the only factor contributing to the metabolic abnormalities observed in patients with T2DM. Some researchers suggest that metabolic surgery could be used to possibly "cure" T2DM regardless of body mass index and independent of weight loss. Multiple U.S. academic research centers Mid-to-late phase trials completed and ongoing	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sodium glucose co-transporter 1 and/or 2 inhibitors (in development) Sulfonylurea drugs (glimepiride)	Resolution of T2DM

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Noninvasive skin measurement test (Scout DS) for screening for type 2 diabetes	Patients at risk of type 2 diabetes mellitus (T2DM)	About 7 million of the 25.8 million people in the U.S. with diabetes have not been screened and had the disease diagnosed. Late detection typically leads to secondary complications (e.g., cardiovascular disease, nephropathy, neuropathy) that could be prevented or delayed with earlier diagnosis. Late diagnosis may occur for many reasons, including patient nonadherence with recommended screening (blood draw). The Scout DS® is a portable tabletop unit that measures skin fluorescence to detect biologic markers associated with cumulative glycemic exposure, oxidative stress, and microvascular changes. Using an algorithm that adjusts for skin-tone variations, the skin fluorescence measurement is said to be converted into a Scout Diabetes Score in less than 4 minutes. This device is intended for individuals 18 years or older who are at risk of prediabetes and/or T2DM. VeraLight, Inc., Albuquerque, NM Late-phase testing completed on 5,000 patients; U.S. testing ongoing in 3,500 patients; company expected to file for FDA approval by end of 2012; has Conformité Européene (CE) mark and Health Canada License approval	Standard blood glucose testing	Delayed or prevented secondary complications Increased screening adherence Increased rate of early diagnosis Improved quality of life
Off-label salsalate for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	Research has demonstrated a link between T2DM progression and inflammation. Salsalate is a widely available anti-inflammatory derivative of salicylic acid; although salicylic acid has been known for many years to aid in control of blood glucose levels, concerns regarding gastrointestinal (GI) side effects have prevented its use; salsalate may avoid these GI side effects while maintaining anti-inflammatory activity. Joslin Diabetes Center, Boston, MA; various academic research centers Phase II/III trial completed; other phase II/III trials ongoing	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sodium glucose co-transporter 1 and/or 2 inhibitors (in development) Sulfonylurea drugs (glimepiride)	Achieved target glycosylated hemoglobin (HbA_{1c}) levels Desired fasting glucose level control Resolved insulin sensitivity

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Peptide immune modulator (DiaPep277) for treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus (T1DM) has recently been diagnosed	No current treatments for T1DM are curative or address the underlying cause and dysfunction. DiaPep277® has a novel mechanism of action and is an immune-modulating therapy intended to dampen the immune system's activity against beta-islet cells, thereby promoting their survival and preserving function of the pancreas; therapy consists of a peptide derived from heat shock protein 60, which is 1 of the main antigens on beta-islet cells recognized by cytotoxic T cells; DiaPep277 is designed to interact with both the T cell receptor and TLR2, which has the effect of downregulating the inflammatory response induced by T helper cells. Would be delivered as a vaccine in a physician's office rather than as a self-administered drug (or self-administered insulin). Andromeda Biotech, Ltd., Yavne, Israel Phase III trials complete	Insulin modifications Islet cell transplantation Pancreas transplantation	Improved beta-cell function (measured as change from baseline in stimulated C-peptide secretion during a mixed-meal tolerance test) Increased glycemic control
Pulsed acoustic pressure device (dermaPACE) for treatment of diabetes-related foot ulcers	Patients in whom diabetic foot ulcers have been diagnosed	About 3 million patients a year develop diabetic foot ulcers; current treatments achieve complete healing less than 30% of cases; therefore, effective treatments are intended to accelerate and complete wound healing. The dermaPACE® device is intended to work by use of acoustic pressure waves that are purported to initiate a biologic response at the cellular level to try to stimulate production of angiogenic growth factors, including vascular endothelial growth factor, endothelial nitric oxide synthase, and proliferating cell nuclear antigen. This is asserted to lead to growth of newly formed vessels and increased cellular proliferation and tissue regeneration needed to heal a wound. Sanuwave, Inc., Alpharetta, GA In May 2012, company received conditional approval from FDA for an investigational device exemption supplement for an additional clinical trial of dermaPACE® for this indication	Acellular wound matrices Cellular wound matrices Hyperbaric oxygen therapy Negative pressure wound therapy	Increased percentage of ulcers healed Shortened time to complete healing Reduced ulcer size Reduced incidence of gangrene Reduced incidence of amputation

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pyridoxamine (Pyridorin, BST-4001, K-163) for treatment of diabetic nephropathy	Patients with type 2 diabetes mellitus who have been given a diagnosis of diabetic nephropathy	Although a variety of treatments exist to manage symptoms of diabetic neuropathy, none of these address the underlying cause, and few can slow disease progression. Pyridorin™ is an oral pharmaceutical that targets pathogenic oxidative chemistries, including advanced glycation end-products, toxic carbonyls, and reactive oxygen species, which develop in patients with diabetes and are considered a principal causative factor in the development of diabetic microvascular disease. NephroGenex, Inc., Research Triangle Park, NC Company seeking partner for phase III; Nov 2011, NephroGenex and FDA agreed on phase III trial design; FDA granted drug fast track status	Dialysis (end-stage renal failure) Kidney transplantation (end-stage renal failure) Pharmacotherapy (e.g., angiotensin-converting enzyme inhibitors)	Reduced disease progression (as measured by serum creatinine and biomarkers) Improved renal function Reduced complications of diabetic nephropathy Increased survival Improved quality of life
Ranibizumab (Lucentis) for treatment of diabetic macular edema	Patients in whom clinically significant diabetic macular edema (DME) has been diagnosed	DME affects an estimated 560,000 patients in the United States. 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 has been studied for DME (a new indication) and was the first medication approved by FDA for DME. The approved dosage is 0.3 mg, once monthly, administered by injection into the eye. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland Novartis International AG, Basel, Switzerland FDA approved Aug 2012 for treatment of DME	Intravitreal triamcinolone acetonide with or without laser photocoagulation Laser photocoagulation Pharmacotherapy (e.g., vascular endothelial growth factor antagonists)	Improved vision Stabilized vision Reduced side effects of existing treatment Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ultra-long-acting insulin (Tresiba, degludec; Ryzodeg degludec plus aspart) for treatment of type 1 or 2 diabetes	Patients with type 1 or 2 diabetes mellitus who require insulin or insulin and oral medication	Degludec (Tresiba®) is an ultra-long-acting insulin that releases over several days—its action extends beyond 42 hours, according to the company. The flexible dosing regimen allows 8–40 hours between dosing, which could lead to thrice-weekly dosing, or dosing once in the evening. Novo Nordisk a/s, Bagsvaerd, Denmark Phase III trials completed for degludec and degludec plus aspart; Nov 2012, FDA advisory committee voted 8-4 to recommend approval of both formulations; FDA panel unanimously also recommended a cardiovascular outcomes trial be conducted; approved Sept 2012 in Japan; submitted for approval in Europe. Another formulation is also in development that combines degludec with insulin aspart (Ryzodeg®).	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sodium glucose co-transporter 1 and/or 2 inhibitors (in development) Sulfonylurea drugs (glimepiride)	Achieved target glycosylated hemoglobin (HbA_{1c}) levels Reduced progression of complications Improved quality of life

Table 8. AHRQ Priority Condition: 08 Functional Limitations and Disability: 77 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Adenosine 2A antagonist (SYN115) for treatment of Parkinson's disease	Patients in whom Parkinson's disease (PD) has been diagnosed	Patients with PD experience “on” times when medication reduces symptoms and “off” times when medication becomes ineffective and symptoms worsen before the next dose of medication can be administered. Treatments that can increase the “on” time could improve quality of life and management of the disease. SYN115 is an oral, adenosine 2A (A2A) receptor antagonist intended to increase “on” time for patients taking levodopa; the striatopallidal output pathway synthesizes gamma aminobutyric acid (GABA) and enkephalin as neurotransmitters and expresses the A2A subtype of adenosine receptors. Pharmacologic inhibition of A2A adenosine receptors may inhibit the overactive striatal GABAergic blocking of neurons associated with PD. Biotie Therapies Corp., Turku, Finland Phase II/III trial ongoing	Adenosine A2A receptor antagonist (in development) Dopamine agonists Glutamate receptor 5 modulators (in development) Levodopa/carbidopa Monoamine oxidase-B inhibitors Nicotinic receptor agonist (in development)	Improved motor skills Improved symptoms Reduced disease progression Reduced incidence/severity of levodopa-induced dyskinesia Improved quality of life
Alemtuzumab (Lemtrada) for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	Alemtuzumab (Lemtrada™) represents a new mechanism of action for RRMS. Alemtuzumab is a humanized monoclonal antibody targeted to the CD52 antigen (expressed on both T and B lymphocytes, monocytes, macrophages, and eosinophils); intended to target antigen-carrying cells, thereby rapidly removing T cells from blood, bone marrow, and organs; T-cell depletion claimed to last for more than 1 year; once-yearly treatment regimen (once a day for 5 days) via intravenous administration. The drug is FDA approved for treating refractory chronic lymphocytic leukemia. Genzyme Corp., Cambridge, MA Phase III trial ongoing; FDA accepted the company’s new drug application filing Jan 28, 2013 (after having issued the company a refusal-to-file letter in Aug 2012 requesting data reorganization)	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Reduced frequency of relapse Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Amygdala retraining program for treatment of chronic fatigue syndrome	Patients in whom chronic fatigue syndrome (CFS) has been diagnosed	CFS has no cure, and no single therapy provides symptom relief in all patients; new therapies are needed. The amygdala retraining program (ARP) is based on the hypothesis that following a traumatic event involving acute psychological stress, the brain's amygdala may become conditioned to be chronically sensitized to signals arising in the body (i.e., physiological, chemical, dietary stressors). This conditioned response leads to overstimulation of the sympathetic nervous system eventually resulting in chronic fatigue; it is purported that the development of neuronal pathways from the medial prefrontal cortex to the amygdala in the brain can extinguish this fear response. The ARP attempts to develop these "safety neurons" by a program tailored to the patient consisting of holistic dietary, lifestyle, stress management, and self-awareness treatments. Stress tools and techniques are performed for a minimum of 30 minutes a day in 1 sitting (meditation, "soften and flow," alternate nostril breathing), along with some neurolinguistic-programming, 30-2nd tools used throughout the day when required. The intent of these techniques is to recognize and interrupt fearful responses, replacing them with a relaxation response. Ashok Gupta, holistic medicine practitioner, London, UK Ann Vincent, M.D., Mayo Clinic, Rochester, MN Trial completed (unphased); sold as a proprietary program; clinically implementable	Behavioral and lifestyle modifications Psychotherapy Pharmacotherapy (e.g., antidepressants, sleeping aids)	Improved ability to perform daily activities Reduced symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Amygdala retraining program for treatment of fibromyalgia	Patients in whom fibromyalgia has been diagnosed	Fibromyalgia is poorly understood and lacking effective treatment options for many patients. The amygdala retraining program (ARP) is based on the hypothesis that following a traumatic event involving acute psychological stress, the brain's amygdala may become conditioned to be chronically sensitized to signals arising in the body (i.e., physiological, chemical, dietary stressors). This conditioned response leads to overstimulation of the sympathetic nervous system eventually resulting in neurologic disorders such as fibromyalgia; it is purported that the development of neuronal pathways from the medial prefrontal cortex to the amygdala in the brain can extinguish this fear response. The ARP attempts to develop these "safety neurons" by a program tailored to the patient consisting of holistic dietary, lifestyle, stress management, and self-awareness treatments. Stress tools and techniques are performed for a minimum of 30 minutes a day in 1 sitting (meditation, "soften and flow," alternate nostril breathing), along with some neurolinguistic-programming, 30-second tools used throughout the day when required. The intent of these techniques is to recognize and interrupt fearful responses, replacing them with a relaxation response. Ashok Gupta, holistic medicine practitioner, London, UK Ann Vincent, M.D., Mayo Clinic, Rochester, MN Trial completed (unphased); sold as a proprietary program; clinically implementable	Pharmacotherapy (e.g., duloxetine, fluoxetine, gabapentin, lorazepam, milnacipran, pregabalin, tricyclic antidepressants) Behavioral and lifestyle modification	Improved ability to perform daily activities Reduced symptoms Improved quality of life
Autologous knee bone and cartilage transfer for surgical treatment of wrist injuries	Patients with wrist fractures, chronic wrist pain, and ligament tears that require surgical intervention	About 1/6 of fractures evaluated in U.S. emergency rooms are wrist fractures. Some wrist injuries are unstable, with ligament tears and dissociation of the wrist bones. Conventional ligament reconstruction surgery often does not alleviate pain, warranting the need for better surgical procedures. Knee bone and cartilage transfer represents an innovative surgical procedure that involves resecting, shaping, and transferring the patient's own cartilage-bearing bone from the knee to the wrist, with the intent of eliminating the previously existing gap caused by the torn ligament(s). Union Memorial Hospital's Curtis National Hand Center, Baltimore, MD First reported procedure completed Aug 2011	Conventional ligament reconstruction surgery	Decreased wrist pain Decreased risk of wrist arthritis Improved wrist function Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Balloon angioplasty and/or stenting of azygos and internal jugular vein for treatment of multiple sclerosis	Patients with multiple sclerosis (MS) who exhibit evidence of chronic cerebrospinal venous insufficiency (CCSVI)	No effective treatments for MS exist; therapies providing relief of symptoms are needed. CCSVI, in particular stenotic and occlusive lesions in the azygos and internal jugular vein, is hypothesized to play a role in the etiology, disease progression, and/or pathogenesis of MS. Image-guided interventional endovascular management is a procedure in which an interventional radiologist performs percutaneous transluminal angioplasty using either an angioplasty balloon and/or stent to improve circulation/reduce hypoperfusion of brain parenchyma to relieve MS symptoms. Procedure uses existing technologies and is in early diffusion in Europe and U.S.; first reported by University of Ferrara, Italy Clinical trials under way to further assess validity	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Improved cognitive and motor function Reduced relapse Reduced lesions on imaging Improved quality of life
Bioartificial liver system (Extracorporeal Liver Assist Device) as bridge to liver transplantation	Patients in whom acute liver failure has been diagnosed	Extracorporeal bioartificial liver support system (Extracorporeal Liver Assist Device [ELAD®]) is intended to replace lost liver functions, such as synthesis of metabolic enzymes and key proteins. The cell-based liver support system adds a “bioreactor” filter to standard liver dialysis systems that temporarily remove blood from the body to remove circulating toxins. ELAD incorporates cultured human hepatocytes in bioreactor cartridges as part of a dialysis-like system. It functions as bridge while a transplant candidate awaits a donor liver. The device is regulated as a combination biologic by FDA’s Division of Cellular, Tissue and Gene Therapy in the Center for Biologics Evaluation and Research. Vital Therapies, Inc., San Diego, CA Phase II/III trial completed; phase III pivotal trial being planned	Pharmacotherapy (e.g., antibiotics and lactulose) Liver transplantation	Improved rate of 30-day transplant-free survival
BioErodible MucoAdhesive (BEMA) delivery of buprenorphine for treatment of moderate to severe chronic pain	Patients in whom moderate to severe chronic pain has been diagnosed	Buprenorphine is an opioid that is used in current formulations for treating opioid addiction or management of moderate pain. BEMA™ (BioErodible MucoAdhesive) is drug delivery technology used to deliver opioids and other drugs by encapsulating the drug in a dissolvable polymer film used on the inside of the check for buccal delivery. BioDelivery Sciences International, Raleigh, NC Phase III trial completed; 2nd phase III trial enrolling; company anticipated filing new drug application in 1st half of 2012. The technology was FDA approved for use with fentanyl and is under development for delivery of buprenorphine.	Pharmacotherapy (e.g., COX-2 inhibitors, Buprenex, nonsteroidal anti-inflammatory drugs, opioids)	Reduced pain Reduced risk of addiction

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
BreathID test to monitor liver function	Patients at risk of or in liver failure	Breath test (BreathID®) is intended to monitor liver function; theory is that breath test could give additional liver function assessment not available with blood tests. The company purports to provide a novel diagnostic option in patients with impaired liver function. The test requires a patient to breathe into a device and is administered in the physician's office. Exalenz Bioscience, Inc., Modi'in, Israel Phase III trials ongoing in Israel; approved to detect *Helicobacter pylori* infection	Liver function blood tests	Improved patient comfort Increased adherence with liver function testing Earlier detection of liver function problems
Collagenase clostridium histolyticum (Xiaflex) for treatment of Peyronie's disease	Men in whom Peyronie's disease has been diagnosed	Peyronie's disease is the development of a collagen plaque that causes the penis to curve while erect; treatments for Peyronie's disease are experimental or require surgical correction. Collagenase clostridium histolyticum (Xiaflex®) is a locally injected protein mixture that is intended to disrupt the collagen plaques. Auxilium Pharmaceuticals, Inc., Malvern, PA Phase III trial completed. Xiaflex is FDA approved for treating the hand disorder Dupuytren's contracture.	Surgical therapy Interferon local injections Verapamil local injections	Change in penile curvature from baseline Improved Peyronie's Disease Questionnaire (PDQ) score
Corneal collagen cross-linking for treatment of progressive keratoconus	Patients in whom progressive keratoconus has been diagnosed	Keratoconus is a degenerative disease of the eye and is the leading cause of corneal transplants in the U.S. Progressive keratoconus requires invasive interventions, such as corneal transplants and insertion of corneal rings. These invasive surgical interventions may present unfavorable complications, such as graft rejection, persistent visual problems, permanent vision loss, and prolonged surgical recovery. If accepted, corneal collagen-crosslinking (CCL) would provide a procedure that is less invasive, requires a shorter recovery time, and generates more optimal clinical outcomes to improve patient quality of life. CCL is a procedure performed by removing the corneal epithelium and applying riboflavin drops to the eye; the eye is then exposed to ultraviolet light, interacting with the riboflavin. The interaction produces reactive oxygen molecules that cause the formation of chemical bonds between and within the corneal collagen fibrils, making them stiffer. Avedro, Inc., Waltham, MA Phase III trial completed; Conformité Européene (CE) marked	Corneal ring segment inserts Surgical therapy	Improved corneal structure Improved vision Improved quality of life

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	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 by subcutaneous injection, 150 mg, once every 4 weeks. Biogen Idec International GmbH, Zug, Switzerland Abbott Laboratories, Abbott Park, IL Phase III trials ongoing; data expected in late 2012; FDA granted fast track status	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Delayed disease progression Decreased demyelination Fewer relapses Improved quality of life
Davunetide for treatment of progressive supranuclear palsy	Patients in whom progressive supranuclear palsy (PSP) has been diagnosed	No treatments exist for PSP, a rare condition; anticholinergic medications for Parkinson's disease are used to control symptoms. Davunetide, also known as AL-108, is a 1st-in-class agent intended to target tau tangles, 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. It is derived from naturally occurring activity-dependent neuroprotective protein. Administered intranasally, 30 mg twice a day. Allon Therapeutics, Inc., Vancouver, British Columbia, Canada Phase II/III trial ongoing; FDA granted orphan drug status in Jan 2010	Pharmacotherapy (e.g., anticholinergic medications, antidepressants) Botulinum toxin type A (Botox®) injection	Improved symptom control Delayed or halted disease progression Improved quality of life
Deferiprone (Ferriprox) for treatment of contrast-induced acute kidney injury	Patients in whom contrast-induced acute kidney injury (CI-AKI) has been diagnosed	The only current standard treatment for CI-AKI in high risk patients with chronic kidney disease (CKD) is hydration and avoidance of nephrotoxic drugs. Deferiprone (Ferriprox®) is an orally active hydroxypyridin-4-one iron chelator that binds iron and removes excess iron from the body. If proven effective, deferiprone could become the 1st therapeutic drug to prevent CI-AKI in CKD. Deferiprone 900 mg is administered orally, 1 immediate release tablet and 2 extended-release tablets, 1–3 hours before angiography, and then every 12 hours for 8 days. CorMedix, Inc., Bridgewater, NJ Phase III trial registered but not yet open for participant recruitment.	Pharmacotherapy (e.g., deferoxamine) Hydration	Reduced occurrence and complications of CI-AKI Reduced incidence of CI-AKI in high risk patients with CKD

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Dimethyl fumarate (BG-12, Panaclar) for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis has been diagnosed	Available treatments provide unsatisfactory efficacy for many patients. Dimethyl fumarate (BG-12, Panaclar®) is a fumaric acid ester (FAE) which purportedly reduces peripheral CD4+ and CD8+ T lymphocytes because FAE can induce apoptosis. Dimethyl fumarate purportedly represents a novel mechanism of action through modulating the Nrf-2 pathway, mediating neuroprotective and anti-inflammatory effects, Safety profile may allow combination dosing. Administered orally, 240 mg, twice daily. Biogen Idec International GmbH, Zug, Switzerland Phase III trial completed; FDA granted fast track status in 2008; in May 2012, FDA accepted new drug application for review; FDA delayed the anticipated late 2012 decision date to 2013	Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Reduced frequency of relapse Reduced symptom severity Slowed disease progression Improved quality of life
Dopamine stabilizer pridopidine (ACR16, Huntexil) for treatment of Huntington's disease	Patients in whom Huntington's disease (HD) has been diagnosed	No cure exists for HD, and current therapies only help to manage emotional and motor symptoms associated with the disease. Pridopidine (ACR16, Huntexil®) is a small-molecule, dopamine stabilizer that purportedly increases or decreases dopamine to healthy levels in patients with HD. Pridopidine purportedly contrasts with neuroleptics that reduce dopamine activity regardless of baseline level. Administered orally, at doses of 45 or 67.5 mg, twice daily. Teva Pharmaceutical Ltd., Ballerup, Denmark Phase III trials completed	Pharmacotherapy (e.g., tetrabenazine, antidepressants, antipsychotics)	Improved clinical global impression of change, cognitive function, behavior, and symptoms of depression and anxiety Improved voluntary motor function
Droxidopa (Northera) for treatment of symptomatic neurogenic orthostatic hypotension	Patients with Parkinson's disease, multiple system atrophy, and/or pure autonomic failure who are at risk of neurogenic orthostatic hypotension	Current treatment options for symptomatic neurogenic orthostatic hypotension include pharmacotherapy but do not achieve an adequate response in many patients; more effective treatment options are needed to address the underlying cause. Droxidopa (Northera™) is a norepinephrine precursor; allows for reuptake of norepinephrine into peripheral nervous system neurons, stimulating receptors for vasoconstriction and providing physiological improvement in symptomatic neurogenic orthostatic hypotension. Administered orally, up to 3 times daily. Chelsea Therapeutics, Inc., Charlotte, NC Phase III trials completed; FDA granted orphan drug and fast track status; in Feb 2012, FDA Cardiovascular and Renal Drugs Advisory Committee voted 7-4 with 1 abstention and 1 nonvote recommending approval; in Mar 2012, FDA issued a complete response letter (CRL) requesting additional efficacy data; in Jul 2012, it issued a CRL calling for an additional trial to demonstrate a significant and persistent effect of Northera	Dietary and lifestyle modifications Pharmacotherapy (e.g., midodrine hydrochloride)	Decreased orthostatic hypotension Decreased risk of falling Decreased confusion from reduced cerebral circulation

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Dual orexin receptor antagonists (MK-6096 and MK-4305) for treatment of primary insomnia	Patients in whom primary insomnia has been diagnosed	Insomnia is a common sleep problem that may stem from factors including stress, poor sleeping habits, depression, and chronic pain. Primary insomnia is known as the inability to sleep that is not attributed to any medical, psychological, or environmental factor. Current pharmacotherapies for this indication may come with unwanted adverse events and have limited efficacy. Dual orexin receptor antagonists act by inhibiting the binding of neuropeptide orexin to its receptor, known to regulate the sleep-wake cycle through control of downstream pathways that involve histaminergic, dopaminergic, and cholinergic activity. MK-6096 is administered orally, 2.5, 5, 10, or 20 mg per dose before bedtime; MK-4305 is administered orally, 15, 20, 30, or 40 mg per dose. Merck & Co., Inc., Whitehouse Station, NJ MK-6096: phase II trial completed MK-4305: phase III trials completed	Pharmacotherapy (e.g., Ambien®) Lifestyle and behavior modifications	Improved sleep cycle Improved quality of life
Enzyme replacement therapy (ENB-0040) for treatment of hypophosphatasia in infants and children	Infants and children receiving a diagnosis of hypophospha-tasia	Hypophosphatasia is a rare metabolic disorder caused by deficiency of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP). No other pharmacologic therapy is available. TNSALP is a phosphomonoesterase that plays a key role in regulation of bone mineralization. Alterations in the *TNSALP* gene results in extracellular accumulation of inorganic pyrophosphate, leading to inhibition of bone mineralization and resultant rickets, osteomalacia, or both. Incidence has been estimated at 1 per 100,000 births. ENB-0040 is an enzyme that is a form of recombinant human TNSALP. This enzyme is fused to the Fc portion of human immunoglobulin G and attaches to a deca-aspartate bone-targeting peptide derived from osteopontin and bone sialoprotein. This enzyme has a high affinity for bone, allowing it to exert its effects with limited systemic effect and at a half-life 30% longer in bone, compared with serum. Alexion Pharmaceuticals, Inc., Cheshire, CT Phase II trials ongoing; phase II/III trial ongoing; 1 phase II study withdrawn "pending further review of clinical design"; FDA granted fast track and orphan drug status	Pharmacotherapy (e.g., cortisone) Vitamin supplementation (e.g., magnesium, vitamin B_6, zinc)	Restoration of bone mineralization Decreased risk of rickets and osteomalacia Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Enzyme replacement therapy (SBC-102) for treatment of late-onset lysosomal acid lipase deficiency	Patients in whom late-onset lysosomal acid lipase (LAL) deficiency has been diagnosed	LAL deficiency is a rare genetic syndrome for which no treatment is FDA approved. LAL is an enzyme breaks down cholesteryl esters and triglycerides; when it is lacking, these materials build up in the liver, the gut, other organs, and blood vessel walls. The deficiency occurs less often in infants than in children, adolescents, or adults. The early onset form is also known as Wolman disease, and is rapidly fatal, usually within the 1st year. Late-onset LAL is also known as cholesteryl ester storage disease (CESD), and can lead to liver fibrosis, cirrhosis, liver failure, cardiovascular events, and premature death. No FDA-approved treatment is available. SBC-102 is a recombinant protein intended to be used as enzyme replacement therapy for this disease; if approved it would be the first treatment approved for LAL deficiency. In ongoing trials, SBC-102 has been given in 4 once-weekly infusions (0.35, 1 or 3 mg/kg of body weight), followed by an infusion every other week (1 or 3 mg/kg) as part of a long-term open-label extension study. Synageva BioPharma Corp., Lexington, MA Phase II trial ongoing with open-label extension; FDA granted orphan drug status; Synageva plans to start an international randomized double-blind controlled trial in early 2013	Palliative treatments	Improved cholesteryl ester and triglyceride levels Improved quality of life
Eprodisate disodium (Kiacta) for treatment of amyloid A amyloidosis	Patients at risk of amyloid A amyloidosis, especially those in whom rheumatoid arthritis or chronic infection is present	No curative treatment for AA amyloidosis is available. Eprodisate disodium (Kiacta™) is designed to interfere with the formation of amyloid A fibrils that can accumulate in organs and tissues. Orally administered capsules. Bellus Health, Inc. (formerly Neurochem), Laval, Quebec, Canada Celtic Therapeutics Management LLP, St. Thomas, U.S. Virgin Islands Phase III trial ongoing; new drug application submitted to FDA in 2006, but FDA requested more data before approval; company initiated phase III confirmatory trial in 2010 to address this concern	Biologics (e.g., tumor necrosis factor-alpha inhibitors and interleukin-1-receptor antagonists) Supportive care Immunosuppressants (e.g., chlorambucil, cyclophosphamide, melphalan methotrexate) Surgical excision of infected tissue and antibiotics for chronic infection Kidney transplantation for kidney failure Colchicine for familial Mediterranean fever	Reduced risk of organ failure (especially kidneys, liver, spleen) Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Erythropoiesis-stimulating agent (peginesatide, Omontys) for treatment of anemia from chronic renal failure	Patients with chronic kidney disease (CKD) who are on dialysis and in whom anemia has been diagnosed	Anemia is a common consequence of chronic renal failure, affecting more than 90% of patients with chronic renal failure stage 5. Erythropoiesis stimulating agents (ESAs) have been established as a treatment for anemia in chronic renal failure subjects and have improved the management of anemia over alternatives such as transfusion. Peginesatide (Omontys®) is a long-acting, parenteral formulation being developed for treating anemia in patients on dialysis (i.e., with CKD). It binds to and activates the human erythropoietin receptor (on bone marrow cells) and stimulates erythropoiesis in human red cell precursors in a manner similar to other known ESAs. Peginesatide is administered once monthly, by subcutaneous or intravenous injection, 0.04–0.16 mg/kg of body weight per dose. It is not intended for use in patients with CKD who are not on dialysis or for use in patients with anemia from other conditions, such as cancer. Affymax, Inc., Palo Alto, CA, in collaboration with Takeda Pharmaceutical Co., Ltd., Osaka, Japan FDA approved Mar 2012 with a Risk Evaluation and Mitigation Strategy for treating anemia in adults on dialysis; it is the 1st agent approved for this condition since 2001. The labeling includes a warning that states**:** **"**ESAs increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence."	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride) Renal transplantation	Reduced frequency of drug administration Resolution of anemia Improved quality of life
Exon-skipping agent (eteplirsen) for treatment of Duchenne muscular dystrophy	Patients in whom Duchenne muscular dystrophy (DMD) has been diagnosed	Current treatments for DMD address symptoms only; additionally, patients who receive available treatment still have a reduced lifespan and require additional support from devices. Eteplirsen is intended for patients in whom DMD has been diagnosed who have a mutation in the dystrophin gene. The 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 form of dystrophin that is not perfect, but functional. It is administered once weekly, by intravenous infusion. AVI BioPharma, Inc., Bothell, WA, now Sarepta Therapeutics, Inc., Cambridge, MA Phase IIb trial completed; phase III trial planned; FDA granted orphan drug status in 2007	Symptom control using corticosteroids and $beta_2$ agonists Physical therapy Orthopedics Respiratory support (respirator/ ventilators)	Delayed or halted muscle degeneration Reduced symptoms Increased survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Extended-release cysteamine bitartrate (RP103) for treatment of nephropathic cystinosis	Patients in whom nephropathic cystinosis has been diagnosed	Nephropathic cystinosis is a disease characterized by the abnormal transport of cystine out of lysosomes, which leads to renal failure, growth failure, rickets and fractures, photophobia, and blindness. Poor patient adherence with conventional treatment because of dosing frequency (4 times a day) and side effects has led to complications for patients. RP103 is an enteric-coated, delayed-release, microbead formulation of cysteamine bitartrate that is intended to reduce gastrointestinal adverse events associated with immediate-release cysteamine bitartrate. It requires half the number of daily doses compared with existing medical treatment. Cysteamine bitartrate converts cystine to cysteine and cysteamine-mixed disulfide, preventing resultant organ damage. RP103 is administered orally, 75 mg, twice daily. Raptor Pharmaceutical Corp., Novato, CA Phase III trial completed; extension phase III trial ongoing; Mar 2012, company submitted new drug application to FDA; FDA granted orphan drug status	Growth hormone therapy Pharmacotherapy (e.g., Cystagon®, indomethacin) Renal transplantation Urinary loss supplementation	Improved glomerular function Reduced morbidity and mortality Improved quality of life
Ezogabine (Potiga) for treatment of partial onset seizures in epilepsy	Patients in whom epilepsy has been diagnosed	Treatment options for partial onset seizures, the most common form of seizure in epilepsy, include pharmacotherapy; but are limited in efficacy for some patients. Ezogabine (Potiga™) is a drug with a new mechanism of action intended for treating partial epileptic seizures. As a potassium channel opener, it stabilizes neuronal potassium channels in the open position with the intention of modifying ion channels so they modify neuronal hyperexcitability, and thus reduce seizures. The drug is available in tablet form in 50, 200, 300, and 400 mg sizes. Valeant Pharmaceuticals International, Inc., Mississauga, Ontario, Canada GlaxoSmithKline, Middlesex, UK FDA approved Jun 2011	Pharmacotherapy (e.g., lamotrigine, levetiracetam, tiagabine, tricyclics, valproate)	Reduced frequency of partial seizures Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Glycogen synthase kinase-3 enzyme inhibitor (tideglusib; Zentylor) for treatment of progressive supranuclear palsy	Patients in whom progressive supranuclear palsy (PSP) has been diagnosed	No treatments exist for PSP. Tideglusib (Zentylor™) represents a novel drug class for this indication as a glycogen synthase kinase 3 (GSK-3) inhibitor for treating PSP. In patients with PSP, hyperphosphorylation of the tau protein occurs and contributes to microtubule destabilization and axonal transport dysfunction. GSK-3 is believed to be the major enzyme responsible for the abnormal hyperphosphorylation of tau; it may also be involved in the formation of the beta-amyloid peptide. It is a disease-modifying drug. Noscira, S.A., Madrid, Spain Phase II trial completed; FDA granted orphan drug and fast track status; has orphan drug status in EU	Anticholinergic medications	Improved symptom control Delayed or halted disease progression Improved quality of life
GSK-2402968 (PRO-051) for treatment of Duchenne muscular dystrophy	Ambulatory patients 5 years of age or older who have Duchenne muscular dystrophy (DMD) and have a dystrophin gene mutation including deletions of exon 50, exon 52, exons 45–50, exons 48–50, and exons 49–50	Current treatments for DMD are limited to reducing symptoms without addressing their underlying cause. Patients experience a shortened lifespan and require additional support from devices. GSK2402968 is an antisense oligonucleotide that induces exon skipping of exon 51; technology uses small pieces of DNA called antisense oligonucleotides to skip a defective exon (small sequences of genetic code that codes for sections of protein) to correct the reading frame and allow a normal protein to be produced. This RNA therapeutic is given by injection. GlaxoSmithKline, Middlesex, UK, in partnership with Prosensa, Leiden, The Netherlands Phase III trial ongoing; FDA granted orphan drug status	Pharmacotherapy (e.g., corticosteroids, $beta_2$ agonists) Physical therapy Orthopedics Respiratory support (respirator/ ventilators)	Decreased muscle degeneration Improved symptoms Decreased need for supportive devices Increased survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Handheld intracranial scanner (Infrascanner, Model 1000) for detection of intracranial hematomas	Patients at risk of intracranial hematoma	About 1.7 million people sustain a traumatic brain injury (TBI) each year with direct and indirect costs such as lost productivity attributed to TBI reaching about $76.5 billion in the U.S. in 2000. An increase in improvised explosive device use in war has increased blast-induced TBI among U.S. soldiers, and intracranial hematomas can be particularly life threatening. These traumatic injuries can have occult signs, making them difficult to diagnose, particularly without the use of expensive, sophisticated equipment. The Infrascanner™ Model 1000 is a handheld near-infrared spectroscopy device that directs near-infrared light into the skull, where the light is absorbed by the blood from the intracranial hematoma. Because the blood from a hematoma absorbs light differently from vascular blood, the scanner can detect differences in optical density; it wirelessly transmits the results to a handheld computer. InfraScan Inc., Philadelphia, PA, in collaboration with the Office of Naval Research, Arlington, VA FDA approved Dec 2011	Automated Neuropsychological Assessment Metrics (computerized cognitive test) Computed tomography scans MRI studies Onsite neurophysical exam	Reduced morbidity Reduced mortality Improved quality of life
Helminthic therapy (pig whipworm) for treatment of multiple sclerosis	Patients in whom multiple sclerosis (MS) has been diagnosed	Current treatments for MS may slow disease progression, but the disease has no cure. Effective treatments are needed. Autoimmune diseases such as MS are less common in parts of the world where helminthic exposure and infestations are common. Exposure to helminths purportedly promotes production of regulatory T cells and immunomodulatory cytokines that dampen autoimmune responses. Changes in the patient's cytokine balance in response to the infestation are intended to lead to reduced MS symptoms. Patients orally ingest 2,500 *Trichuris suis* ova (TSO; pig whipworm eggs) at home, every 2 weeks. Coronado Biosciences, Inc., Burlington, MA Copenhagen University, Copenhagen, Denmark Phase II trial recruiting	Dimethyl fumarate Fingolimod Glatiramer Interferon beta-1a Natalizumab Oral immunomodulators (in development)	Reduced brain tissue loss/atrophy Reduced frequency of relapse Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Human spinal cord–derived neural stem cells (NSI-566RSC) for treatment of amyotrophic lateral sclerosis	Patients who have received a diagnosis of amyotrophic lateral sclerosis (ALS)	Only 1 agent (riluzole) is FDA approved for treating ALS, and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function; novel therapies for ALS are urgently needed. Stem cell therapy may potentially repair neurologic damage. NSI-566RSC was developed from human spinal cord–derived neural stem cells; this neural stem cell product is injected into the lumbar spinal cord. Neuralstem, Inc., Rockville, MD Phase I trial ongoing on 12 patients; FDA granted orphan drug designation for ALS treatment; May 2012, FDA granted approval to advance the trial enabling administration of a 2nd dose in the cervical spine of 3 patients	Riluzole Supportive care	Slowed or halted progression of ALS Reduced symptoms Improved quality of life
Intranasal gel (Compleo TRT) for treatment of hypogonadism	Patients in whom hypogonadism has been diagnosed	About 13 million American men are affected by low testosterone levels, and as many as 90% go untreated. Treatment guidelines focus on restoring physiologic testosterone levels through exogenous testosterone preparations. Compleo TRT™ is a bioadhesive intranasal gel formulation of testosterone applied to the interior lateral wall of the nasal cavity, where absorption into the nasal mucosa occurs in 10–15 minutes. It is purported this targeted delivery area to the nasal mucosa will avoid skin-to-skin transference to others, an issue seen with existing topical testosterone gel preparations. Additionally, the drug-delivery system could mitigate adverse events from 1st-pass metabolism on the liver. Trimel Pharmaceuticals Corp., Mississauga, Ontario, Canada Phase III trial ongoing	Various formulations of testosterone	Increased testosterone levels Reduced adverse events
KIT tyrosine kinase inhibitor (masitinib) for treatment of multiple sclerosis	Patients in whom multiple sclerosis (MS) has been diagnosed	Current treatments for MS may slow disease progression, but they are not effective in all patients, and the disease has no cure. Masitinib is a tyrosine kinase inhibitor purported to target the activity of mast cells, which are involved in triggering local inflammatory reactions in tissues. Masitinib purportedly selectively inhibits KIT, platelet-derived growth factor receptor, Lyn, and to a lesser extent, fibroblast growth factor receptor 3. In clinical trials, masitinib is being administered orally, 6 mg/kg of body weight, daily. AB Science S.A., Paris, France Phase IIb/III trial ongoing	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Delayed disease progression Reduced symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Laser surgery for treatment of epilepsy	Patients in whom epilepsy has been diagnosed	An estimated 3 million people in the U.S. have some form of epilepsy, with about 1 million cases resistant to medical therapy. Pharmacological therapies have helped treat epilepsy, but recurrence may commonly occur. Surgical procedures such as craniotomy may be performed, but they may leave the brain susceptible to unintended injury and resultant neurological complications. If accepted, laser therapy would provide a minimally invasive, potentially curative therapy for patients receiving a diagnosis of epilepsy. Laser surgery involves use of MRI-guided laser technology to ablate lesions in specific and nearly inaccessible regions of the brain. The laser probe is inserted through a hole (diameter of a pen) created in the skull to map the brain and then ablate the confirmed affected area. To protect surrounding neurological tissue, an automatic system shuts the laser down when approaching such areas. Laser therapy is for patients in whom definable lesions causing epilepsy have been detected by MRI. Texas Children's Hospital, Houston, TX Pilot trial completed	Pharmacotherapy (e.g., lamotrigine, levetiracetam, tiagabine, tricyclics, valproate)	Reduction or elimination of seizures
Letermovir (AIC246) for prevention of human cytomegalovirus reactivation after organ transplantation	Patients undergoing organ transplantation who could be at risk of reactivation of human cytomegalovirus (HCMV)	HCMV is the primary cause of morbidity and mortality during the 1st 6 months after a patient receives an organ transplant. Ganciclovir is considered expensive and not appropriate or effective in preventing HCMV reactivation in many patients. Letermovir is a quinazoline purported to target the HCMV terminase enzyme. The terminase enzyme is crucial for concatemeric HCMV DNA cleavage during the replication process and its subsequent packaging into the HCMV virions. This is purported to be a novel mechanism of action that should remain effective against strains resistant to current therapy targeting the HCMV DNA polymerase. In a clinical trial, letermovir was administered orally, 120 or 240 mg, once daily. AiCuris GmbH & Co. KG, Wuppertal, Germany Phase II trial complete; FDA granted orphan drug status and fast track designation	Ganciclovir	Decreased rate of organ rejection Increased time to organ rejection Reduced HCMV load

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Levadex (MAP-0004) orally inhaled for treatment of migraine headaches	Patients in whom migraine headaches have been diagnosed	A derivative (Levadex™ [MAP-0004]) of the available dihydroergotamine; intended to alleviate migraine headache symptoms quickly through oral inhalation using the company's Tempo inhaler. MAP Pharmaceuticals, Inc., Mountain View, CA In Jan 2011, company partnered with Allergan Inc., Irvine, CA, for Levadex commercialization Positive phase III results reported; new drug application accepted by FDA in Aug 2011; Mar 2012, FDA issued a complete response letter citing chemistry, manufacturing, and control issues, but did not request additional efficacy or safety information	Pharmacotherapy (e.g., pain relievers, triptans, ergot, anti-nauseates, opiates, dexamethasone)	Quicker reduction in pain and light/noise sensitivity Reduced recurrence of symptoms Reduced side effects
Macrophage regulator (NP001) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	Only 1 agent (riluzole) is FDA approved for treating ALS, and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function; novel therapies for ALS are urgently needed. NP001 is a small-molecule regulator of macrophage activation; aberrant macrophage activation believed to be a primary contributor to the pathology underlying ALS and other neurodegenerative diseases. NP001 is intended to restore normal functioning of macrophages in central nervous system, reducing inflammation and normalizing the cellular environment. Administered intravenously. Neuraltus Pharmaceuticals, Inc., Palo Alto, CA Phase II trial ongoing; FDA granted fast track and orphan drug status Aug 2011	Riluzole Supportive care	Improved biomarker levels Restoration of macrophages to their neuroprotective state Improved activities of daily living Delayed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Intraoral Tongue-Drive Computerized System to Maneuver Electrically-Powered Wheelchairs	Patients with spinal cord paralysis, particularly from the neck down	The Tongue Drive System is a computerized, tongue-operated, assistive neurotechnology. It consists of a lentil-sized magnetic tracer/stud that is embedded in a dental retainer worn in the mouth with the tracer affixed to the tongue, most commonly by piercing. The magnetic tracer/stud creates a magnetic field around the pierced glossal area, where magnetic sensors located on a wireless headset/headphones communicate with a wheelchair. In spinal cord injuries and neuromuscular diseases, the tongue is generally spared from injury, because it is innervated by nerves from the brain and not the spinal cord. The tongue is also strong and does not fatigue easily, designating it the target of choice for the magnetic pierced-tongue mobility aid. The change in magnetic field (prompted by tongue movement) in the mouth is detected by the magnetic sensors on the headset, transmitting information wirelessly to a smartphone carried by the patient. The smartphone can then transmit information to a wheelchair or computer, commanding these devices to perform tasks such as wheelchair movement or daily computer tasks (e.g., email). This system can be recharged via USB after 2 days of continuous use. A standby mechanism for the TDS allows patients to perform daily tasks such as eating, sleeping, and conversing without unnecessary TDS use. According to the registered clinical trial protocol description, the TDS requires that the patient's teeth are brushed, the oral surface sterilized with chlorhexidine mouthwash, and local anesthetics applied on the tongue before clinicians pierce it with a titanium magnetic stud. Patients must undergo computer training with the TDS for the computer program to appropriately interpret and calibrate tongue movement. This will allow for proper control of the patient wheelchair and computer device. Georgia Institute of Technology, Atlanta Pilot trial and unphased trials completed	Comparators depend on severity of spinal cord paralysis Chin control wheelchair Head control wheelchair "Sip and puff" wheelchair Speech control wheelchair Tongue keyboard controller wheelchair	Improved wheelchair function and control Improved aesthetics of device Improved mobility Improved quality of life
Mecobalamin (E-0302) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	Only 1 agent (riluzole) is FDA approved for treating ALS, and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function; novel therapies for ALS are urgently needed. Mecobalamin (E-0302) is a methylated form of vitamin B_{12} proposed for parenteral therapy for ALS. Eisai Co., Ltd., Tokyo, Japan Phase II/III trials ongoing in Japan	Pharmacotherapy (e.g., riluzole) Supportive care	Increased survival rate Improved functional rating scale Increased safety Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mesenchymal stem cells (remestemcel-L, Prochymal) for treatment of acute graft-versus-host disease	Pediatric patients with treatment-refractory, acute graft-versus-host disease (GVHD)	GVHD is a relatively rare condition that most often occurs when donor cells in an allogeneic hematopoietic stem cell transplant mount an immune response against recipient tissues. Patients with acute GVHD typically exhibit damage to the skin, liver, and gastrointestinal tract, and GVHD is lethal in up to 80% of patients with severe forms of the disease. Remestemcel-L (Prochymal®) is an off-the-shelf preparation of mesenchymal stem cells expanded from allogeneic donors. Mesenchymal stem cells are purported to have immunomodulatory effects that may downregulate the antirecipient immune response that underlies GVHD. In clinical trials, remestemcel-L was administered by intravenous injection, twice weekly, for 4 weeks. Osiris Therapeutics, Inc., Columbia, MD Phase III trials complete; FDA granted orphan drug and fast track status; available under expanded access program since 2008; Health Canada gave approval in 2012	Anti-thymocyte globulin Corticosteroids Methotrexate and cyclosporine Mycophenolate mofetil Other immunosuppressants Photopheresis	Increased overall survival Improved quality of life
Micro-bypass implant (iStent Trabecular Micro-Bypass Stent System) for treatment of glaucoma	Patients undergoing cataract surgery who are also at risk of developing glaucoma due to uncontrolled elevated reduce intraocular pressure (IOP)	iStent Trabecular Micro-Bypass Stent System is intended for implantation during cataract surgery in patients with or at risk of developing open-angle glaucoma. iStent is designed to increase aqueous outflow by shunting aqueous humor from the anterior chamber to the Schlemm's canal, bypassing the trabecular meshwork. Use of the procedure avoids having to move the iris, conjunctiva, or sclera and preserves other surgical and medical options for treating glaucoma. Glaukos Corp., Laguna Hills, CA FDA approved Jul 2012 approved "for use in combination with cataract surgery to reduce pressure inside the eye (intraocular pressure) in adult patients with mild or moderate open-angle glaucoma and a cataract who are being treated with medication to reduce intraocular pressure." Conformité Européene (CE) marked in select countries in Europe; approved in Canada	Pharmacotherapy (e.g., eye drops) Surgical therapy Trabectome (device)	Preserved vision Reduced elevated or uncontrolled IOP

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Migalastat hydrochloride (AT1001) for treatment of Fabry disease	Patients with Fabry disease who have either migalastat-responsive mutations in alpha-galactosidase A or who are receiving enzyme replacement therapy	Current enzyme replacement therapies for Fabry disease are expensive to produce and have been subject to recent shortages. AT1001 is a small-molecule drug that acts as a molecular chaperone that enhances the activity of alpha-galactosidase A, the enzyme that is deficient in Fabry disease. The drug could be used to enhance the activity of exogenously provided enzyme replacement therapy or used to enhance the endogenous activity of certain alpha-galactosidase mutant isoforms that have been shown to be responsive to it. In trials, it is being tested as monotherapy and in combination with enzyme replacement therapy. Amicus Therapeutics, Inc., Cranbury, NJ Phase III trial ongoing	Enzyme replacement therapy Palliative treatment	Increased GL-3 levels (urine, kidney biopsy) Improved renal function (e.g., glomerular filtration rate) Improved quality of life
Nabiximols oromucosal spray (Sativex) for treatment of multiple sclerosis spasticity and neuropathic pain	Patients in whom multiple sclerosis (MS) has been diagnosed	Few effective treatment options are available for patients with MS. Sativex® is a whole plant medicinal cannabis extract that contains Tetranabinex® and Nabidiolex® (cannabidiol) as its main component. Delta-9-tetrahydrocannabinol (THC) in the extract acts as a partial agonist at both cannabinoid receptors, CB1 and CB2, mimicking the effects of the endocannabinoids, which may modulate the effects of neurotransmitters (e.g., reduce effects of excitatory neurotransmitters such as glutamate) to improve symptoms. Sativex is sprayed under the tongue, 100 mcL/dose, which contains 2.5 mg cannabidiol and 2.7 mg THC. Sativex is intended to be an add-on treatment to current MS therapies. GW Pharmaceuticals, plc, Salisbury, UK Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan Phase III trial ongoing; approved in New Zealand and Canada for treating MS spasticity; approved in Canada for relief of MS-related neuropathic pain	Pharmacotherapy (e.g., opioids, nonsteroidal anti-inflammatory drugs)	Reduced pain Reduced spasticity Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
N-acetylgalactos-amine 6-sulfatase (GALNS) for treatment of Morquio syndrome	Patients in whom the genetic disorder Morquio syndrome type A has been diagnosed	Morquio syndrome type A is a rare autosomal recessive genetic disorder resulting from a deficiency in N-acetylgalactosamine-6-sulfate sulfatase activity, which leads to the accumulation of keratan sulfate and various developmental defects. No treatments exist to address the underlying cause of the disease; only palliative treatments are available. N-acetylgalactosamine 6-sulfatase (BMN-110) is an enzyme replacement therapy intended to treat the underlying disorder. BioMarin Pharmaceutical, Inc., Novato, CA Phase III trial ongoing	No current treatments are available to resolve the underlying disease.	Disease regression Improved bone growth as measured by radiograph Improved activities of daily living Increased physical endurance (6-minute walk test) Improved respiratory function Reduced urine keratan sulfate levels
Nonnucleoside NS5B polymerase inhibitor (setrobuvir) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Current standard of care for HCV infection is generally ineffective in more than half of infected patients. Effective treatments are needed. Setrobuvir is a HCV nonnucleoside, NS5B polymerase inhibitor intended to limit viral replication when used in combination with pegylated interferon plus ribavirin (IFN/RBV) for both treatment-naive patients and patients whose HCV infection has failed to respond to a prior course of therapy with IFN/RBV. Administered orally, 200–400 mg. Anadys Pharmaceuticals, Inc., San Diego, CA Phase II trial ongoing; FDA granted fast track status	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nonsurgical, removable dental hearing device (SoundBite) for treatment of single-sided deafness	Patients in whom single-sided deafness has been diagnosed	Hearing loss affects more than 28 million people in the U.S., prompting use of hearing devices. Available hearing aids may not provide optimal quality for patients, and surgical interventions or bone anchored implants may be too invasive and expensive. The nonsurgical, removable dental hearing device (SoundBite™) consists of a behind-the-ear (BTE) microphone unit which houses the receiver, a wireless transmitter, an attached microphone, and a discreet, removable in-the-mouth (ITM) hearing device. The BTE unit transmits sound to the ITM device, which then is intended to produce imperceptible sound vibrations via the teeth through bones and to both cochleae. The ITM device is custom molded to the teeth without surgery or alterations to tooth structure. Sonitus Medical, Inc., San Mateo, CA FDA 510(k) clearance granted 2011	Bone anchored implants Hearing aid devices (BTE, in-the-ear devices, canal aids)	Improved hearing Improved quality of life
Ocrelizumab for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	Current therapy for RRMS provides unsatisfactory results for many patients. Ocrelizumab represents a novel mechanism of action for this disease state. It is a human monoclonal antibody intended to target CD20-positive B cells (believed to play a role in multiple sclerosis), then interact with immune system to eliminate these CD20-positive B cells. Administered via infusion, once every 6 months. F. Hoffman-La Roche, Ltd., Basel, Switzerland Biogen Idec International GmbH, Zug, Switzerland Phase III trials ongoing	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Decreased frequency of relapse Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label bevacizumab for treatment of retinopathy of prematurity	Infants weighing 1,500 grams or less at birth and at 30 weeks' or less gestation in whom stage 3 retinopathy of prematurity (ROP) in zone I or posterior zone II has been diagnosed	ROP occurs in many infants who are born before 31 weeks' gestation; it can result in alternating episodes of tissue hyperoxia and hypoxia and induction of vascular endothelial growth factors (VEGFs), which can lead to development of abnormal retinal fibrovascular tissue and cause blindness, ROP in premature infants is an acute condition with a time frame measured in days and weeks. Current standard therapy (peripheral retinal ablation) for ROP is known to work, but does not prevent all vision loss and recurrence of VEGF can be as high as 40% in treated infants; off-label use of bevacizumab is injected into the infant's vitreous to reduce incidence of blindness by suppressing VEGF. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland (manufacturer) BEAT-ROP cooperative (trial sponsor) Postmarket trial of off-label use completed; manufacturer is not pursuing a labeled indication	Peripheral retinal ablation with lasers (e.g., xenon, argon, diode)	Prevented recurrence of neovascularization arising from the retinal vessels Improved visual acuity
Off-label etanercept (Enbrel) for treatment of Kawasaki disease	Patients in whom Kawasaki disease (KD) has been diagnosed	KD is the most common cause of acquired heart disease in U.S. children. In many patients, the disease is refractory to current standard of care; new treatment options are needed for patients whose disease is refractory to treatment. Etanercept (Enbrel®) is a dimeric soluble form of the p75 tumor necrosis factor (TNF) receptor purported to bind TNF alpha and beta molecules, thus inhibiting the binding of TNF molecules to cell surface receptors and preventing inflammation associated with KD. Etanercept may be administered immediately after intravenous immunoglobulin (IVIG) infusion, 0.8 mg/kg of body weight per dose, 2 times weekly. Amgen, Inc., Thousand Oaks, CA Phase II trial ongoing; FDA approved in 1998 for moderate to severe rheumatoid arthritis and other inflammatory conditions	Corticosteroids High-dose aspirin IVIG	Improved survival Prevented increase in coronary artery diameter Prevented new coronary artery dilation/cardiac dysfunction Reduced fever

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label fingolimod (Gilenya) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	Only 1 agent (riluzole) is approved for treating ALS (Lou Gehrig's disease), and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function. Novel therapies are urgently needed. Fingolimod (Gilenya®) purportedly an agonist to sphingosine 1-phosphate receptors on the surface of thymocytes and lymphocytes. This mechanism of action purportedly reduces the number of circulating lymphocytes available to cause autoimmune reactions and destroy nerve tissue. Reduced inflammatory reactions against peripheral nerves could reduce ALS symptoms. Administered orally, 0.5 mg, daily. ALS Therapy Development Institute, Cambridge, MA Phase II trial planned; FDA approved for treating relapsing-remitting multiple sclerosis	Physical and speech therapy Medications for symptom management (muscle cramps, constipation, fatigue, excessive salivation, excessive phlegm, pain, depression) Riluzole (Rilutek®)	Increased survival Reduced symptoms Slowed or halted disease progression Improved quality of life
Off-label naltrexone for treatment of fibromyalgia	Patients in whom fibromyalgia has been diagnosed	Fibromyalgia is poorly understood and effective treatment options are not available for many patients. Naltrexone is an opiate antagonist purported to block the inflammatory effects of the toll-like receptor 4 (TLR-4) on glial cells. TLR-4 is purported by the investigators to be involved in pain felt by patients with fibromyalgia. Administered orally, 3.0–4.5 mg, once daily. Stanford University, Stanford, CA Pilot study completed	Behavior and lifestyle modification Pharmacotherapy (e.g., duloxetine, fluoxetine, gabapentin, lorazepam, milnacipran, pregabalin, tricyclic antidepressants)	Improved ability to perform daily activities Reduced symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label neurokinin-1 receptor antagonist aprepitant (Emend) for treatment of HIV infection	Patients in whom HIV infection has been diagnosed	HIV infection remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments. HIV drug resistance, poor tolerance to existing treatments, and high lifelong cost of therapy continue to suggest that improved therapeutic options be pursued to treat patients. Additionally, patients with successfully managed HIV infection frequently develop neurocognitive impairment that is associated with residual chronic inflammation. Aprepitant (Emend®), a drug already approved for treating chemotherapy-induced nausea and vomiting (CINV), is purported to have immunomodulator and antiviral activity. That activity is intended to target residual inflammation by acting on host cells and not the virus, thus leading to prevention of inflammatory and neurocognitive events associated with HIV infection. Aprepitant is purported to be a neurokinin-1 receptor antagonist, inhibiting HIV replication in macrophages by decreasing expression of the chemokine receptor type 5 coreceptor which is needed for HIV to infect cells and possibly other mechanisms. Aprepitant is also purported to improve natural killer cell function, which may help patients better control the virus. Aprepitant is purported to act synergistically with HIV protease inhibitors. In trials, aprepitant was administered orally, 125 or 250 mg, once daily. Merck & Co., Inc., Whitehouse Station, NJ (manufacturer) University of Pennsylvania, Philadelphia, and National Institute of Mental Health, Bethesda, MD (trial sponsors) Phase I trial ongoing for HIV-1 treatment; FDA approved in 2003 for preventing acute and delayed CINV and preventing postoperative nausea and vomiting	Antiretroviral therapy Therapeutic vaccines (investigational)	Delayed onset of AIDS Increased T-cell counts Reduced cognitive impairment Reduced viral load
Off-label rifampicin for treatment of multiple system atrophy	Patients in whom multiple system atrophy (MSA) has been diagnosed	MSA is a progressive neurodegenerative disorder characterized by cytoplasmic inclusions containing abnormally aggregated alpha-synuclein proteins, which are purported to be associated with the neurodegeneration observed in MSA. Current MSA treatments are aimed at controlling symptoms rather than treating the underlying cause of neurodegeneration. The antibiotic rifampicin purportedly reduces the aggregation of alpha-synuclein and the associated neurodegeneration in a preclinical models as well as disaggregate preformed alpha-synuclein fibrils. Mayo Clinic, Rochester, MN Phase III trial ongoing	Pharmacotherapy (e.g., anticholinergics, beta blockers, monoamine oxidase inhibitors, vasoconstrictors)	Improved symptoms based on Unified Multiple System Atrophy Rating Scale Reduced neurodegeneration Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oral estriol (Trimesta) for treatment of multiple sclerosis	Female patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	Current treatments for RRMS can slow disease progression, but the disease has no cure and more effective treatments are needed. Estriol is an estrogen that is produced in the placenta during pregnancy and is thought to be involved in maintaining maternal immune tolerance for the fetus. Estriol purportedly induces spontaneous remission of helper T-cell, type-1-mediated autoimmune responses and may have other beneficial immunomodulatory effects in women with MS during pregnancy. Oral administration of exogenous estriol (Trimesta™) is postulated by the manufacturer to improve MS symptoms. Administered orally, 8 mg, daily. Synthetic Biologics, Inc., Ann Arbor, MI Phase II/III trial ongoing	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Reduced frequency of relapse Slowed disease progression Improved quality of life
Oral short-chain fatty acid derivative compound (HQK-1001) for treatment of sickle cell disease	Patients in whom sickle cell disease (SCD) has been diagnosed	SCD is an autosomal recessive disorder that affects about 100,000 people in the U.S. and Europe. An increased prevalence of disease is seen in people of African and Mediterranean descent; about 1 in 500 African-American children born have sickle cell anemia. Despite advancements in management of complications of SCD (i.e., pain crises), the only drug FDA approved for treatment is hydroxyurea. HQK-1001 is a short chain fatty acid derivative (SCFAD) compound that purportedly reduces the frequency of pain crises and hospitalizations related to SCD. SCFAD has been shown to stimulate expression of fetal hemoglobin and production of red blood cells. HQK-1001 is administered orally at 10, 20 or 30 mg/kg of body weight, once a day (on dosing days). HemaQuest Pharmaceuticals, Inc., San Diego, CA Phase I/II trial completed; phase II trial ongoing; FDA granted orphan drug status	Allogeneic hematopoietic stem cell transplantation Antioxidant therapy Azacitidine Decitabine butyrate Gardos channel inhibition Gene therapy Hydroxyurea Lenalidomide Nitrous oxide and vasodilators Statins	Reduced severity and duration of vaso-occlusive crises Reduced health disparities (African Americans) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pasireotide (SOM230) for treatment of gastrointestinal injuries from acute radiation exposure	Patients with gastrointestinal (GI) injuries from acute radiation syndrome (ARS)	ARS is a disease caused by harmful exposure to high doses of ionizing radiation, resulting in bone marrow, cardiovascular, GI, respiratory, and skin complications. Although few treatments exist for irradiated bone marrow, none exist for irradiated GI organs. Additionally, no treatments are FDA approved for use as medical radiation countermeasures for preventing or treating ARS. Pasireotide is a cyclohexapeptide engineered to bind to multiple somatostatin receptor subtypes to mimic the actions of natural somatostatin. For ARS, pasireotide is intended to reduce pancreatic secretions known to invade the irradiated intestinal wall and induce an inflammatory response. Novartis International AG, Basel, Switzerland (manufacturer) University of Arkansas for Medical Sciences, Little Rock (investigator) Clinical trial phase not reported; in Sept 2011, the U.S. Department of Health and Human Services' Biomedical Advanced Research and Development Authority (BARDA) awarded $56.3 million in grants to 4 companies and the University of Arkansas to develop ARS treatments. Novartis is providing the drug to the university for this 2-year study; data generated are intended to form the basis for a new drug application that Novartis will submit to FDA	Pharmacotherapy (e.g., antibiotics, hematopoiesis-stimulating agents) Stem cell therapy	Prevented or reduced GI flora Decreased mortality
Pegylated recombinant phenylalanine ammonia lyase (PEG-PAL) enzyme replacement therapy for treatment of phenylketonuria	Individuals in whom phenylketonuria has been diagnosed	Pegylated recombinant phenylalanine ammonia lyase (PEG-PAL); phenylketonuria is an inherited disorder in which an enzyme that is needed to break down essential amino acid phenylalanine is missing. The drug is intended to reduce levels of phenylalanine in patients unresponsive to Kuvan®. Administered by injection, 1–3 times a week. BioMarin Pharma, Inc., Novato, CA Phase II trials ongoing; FDA granted orphan drug status	Kuvan (tetrahydrobiopterin or BH4)	Decreased phenylalanine levels Fewer diet restrictions Improved quality of life Injection site inflammation is most common adverse event (43%)

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Perampanel (Fycompa) for treatment of partial-onset epilepsy	Patients aged 12 or older in whom partial-onset epilepsy has been diagnosed	Some patients with partial-onset epilepsy do not respond to current therapy. Perampanel (Fycompa®) represents a new mechanism of action/class of drugs for this disease state. It is a highly selective, noncompetitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptor antagonist; AMPA receptors (located in excitatory neurons) transmit signals stimulated by glutamate and are believed to play a role in diseases characterized by excess neuroexcitatory signaling, such as epilepsy. The drug is taken as an oral tablet, once daily, in 8 or 12 mg doses. Eisai Co., Ltd., Tokyo, Japan Phase III trials completed; FDA approved Oct 2012 as adjunctive treatment of partial-onset seizures with or without secondarily generalized partial-onset seizures in patients with epilepsy aged 12 years or older. FDA stated the approval includes a warning “to alert prescribers and patients about the risk of serious neuropsychiatric events, including irritability, aggression, anger, anxiety, paranoia, euphoric mood, agitation, and mental status changes.” FDA recommended that the drug be classified by the U.S. Drug Enforcement Administration as a scheduled drug; DEA will review the recommendation and determine the final scheduling designation. The drug was approved by the European Medicines Agency in Jul 2012.	Pharmacotherapy (e.g., lamotrigine, levetiracetam, tiagabine, tricyclics, valproate)	Reduced frequency of partial seizures Improved quality of life
PET/MRI integrated imaging system (Biograph mMR) for diagnosis of neurologic conditions	Patients who require morphologic, functional, and metabolic imaging exams for neurologic indications	Imaging exams (Biograph mMR™) that combine positron emission tomography (PET) with MRI; intended to provide simultaneous acquisition of morphologic, functional, and metabolic imaging data; exam intended to take 30 minutes compared with 1 hour or more for sequential PET and MRI exams. Siemens AG, Munich, Germany FDA 510(k) clearance granted Jun 2011	Stand-alone PET and MRI exams	More efficient imaging for patient Improved diagnosis from combined morphologic, functional, and metabolic imaging Improved treatment planning
Preladenant for treatment of moderate to severe Parkinson's disease	Patients in whom moderate to severe Parkinson’s disease (PD) has been diagnosed	Current treatments for PD address symptoms rather than underlying cause, and the patient eventually plateaus or ceases to respond to them; new interventions are needed. Preladenant acts as a potent and selective antagonist at the adenosine A2A receptor; unlike L-dopa, effects do not appear to decrease over time and it appears to have fewer side effects. Merck & Co., Inc. (Schering-Plough), Whitehouse Station, NJ Phase III trials ongoing	Levodopa/carbidopa MOA-B inhibitors	Improved symptoms (motor function) Slowed disease progression Preserved independence Delayed need for assisted care

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Prosthetic arm to restore natural arm functions	Patients with trauma-induced amputations of the upper limbs	Advanced prosthetic arm technology comprises 2 major components, a prosthetic arm and body-machine interfaces. The prosthetic arm is intended to produce near-normal movement, dexterity and function; provide effortless and intuitive function via simple thoughts; and restore tactile sensation. Body-machine interfaces are designed to improve the number of control sites available to manipulate the arms. Techniques under clinical evaluation include implantable myoelectric sensors, peripheral nerve interface electrodes, and targeted muscle reinnervation (surgery). U.S. Defense Advanced Research Projects Agency, Arlington, VA (commissioned and funded research) U.S. Department of Defense, Washington, DC, and U.S. Department of Veterans Affairs, Washington, DC (conducting clinical testing); several U.S. and international research partners participating Early phase trials ongoing in 2011; FDA is piloting a new regulatory pathway for this technology, the innovative device pathway, which is intended to move innovative devices to market within 4 years of start of trials	Conventional prosthetic arms	Significant restoration of limb function compared with current prosthetic devices

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Reciprocating gait orthoses (ReWalk and Ekso exoskeleton systems) for independent mobility after spinal cord injury	Patients with spinal cord injury resulting in paraplegia and need for wheelchair use	Currently, conventional manual and powered wheelchairs are the primary assistive devices to restore some degree of mobility in people with paraplegia. However, these devices do not assist users in walking or climbing stairs. Two reciprocating gait orthosis systems in development, the ReWalk-I™ system could provide greater mobility and freedom to persons with paraplegia from spinal cord injury. The ReWalk system comprises a set of computer-controlled, motorized leg braces that restore the ability to walk with crutches to patients with paraplegia who retain the ability to use their hands and shoulders to walk with crutches and who have good bone density and cardiovascular health. The Ekso system is a described by the manufacturer as a ready-to-wear, battery-powered exoskeleton worn over the user's clothing. The device weighs 45 lb. but purportedly transfers its load to the ground so the patient doesn't bear the weight. The system is adjustable to fit people weighing 220 pounds or less with a height between 5 feet, 2 inches, and 6 feet, 2 inches, and with partial upper body strength. The system has 3 walk modes. The patient provides the balance and proper body positioning. Argo Medical Technologies, Ltd., Yokneam Illit, Israel (ReWalk system) distributed in the U.S. by Bionics Research, Inc., Mt. Laurel, NJ Ekso Bionics, Richmond, CA (Ekso system) The ReWalk-I (institutional use) system is FDA-listed for institutional use only. The company registered the ReWalk-P system for personal use with FDA for routine use outside of institutions and it became available in late 2012. The Ekso system was available through 16 U.S. rehabilitation centers as of Aug 2012.	Wheelchairs	Improved mobility Improved independence Improved quality of life
Ocriplasmin (Jetrea) treatment for symptomatic vitreomacular adhesion including macular hole	Patients in whom focal vitreomacular adhesion (VMA) of the eye has been diagnosed	Focal VMA is a condition in which the vitreous gel, in the center of the eye, has an unusually strong adhesion to the macula, the center of the retina at the back of the eye. VMA is believed to play a key role in several back-of-the-eye conditions, such as macular hole and some forms of macular edema. A microplasmin molecule similar to human plasmin is thought to have potential to break down fibrin clots (fibrinolysis) that adhere the vitreous gel to the macula; thus, intravitreal injection of ocriplasmin (Jetrea®) is a potential nonsurgical treatment for VMA. The recommended dose is 0.125mg (0.1mL) of the diluted solution given by intravitreal injection to the affected eye once as a single injection. ThromboGenics NV, Heverlee, Belgium FDA approved Oct 2012 for the treatment of symptomatic VMA	Pharmacotherapy (e.g., Macugen®) Surgical therapy	Preserved vision Reduced complications associated with surgical treatment Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Recombinant porcine factor VIII (OBI-1) for treatment of acquired hemophilia	Individuals with acquired hemophilia A who develop immune reaction to human factor VIII	About 15% to 30% of patients with acquired hemophilia develop immune reaction to recombinant human coagulation factor VIII. Recombinant porcine factor VIII (OBI-1) is considered to be a physiologic replacement therapy that activates the natural hemostatic pathway. Administered as intravenous infusion every 2–3 hours for the 1st 24 hours of treatment. Inspiration Biopharmaceuticals, Inc., Laguna Niguel, CA Phase II/III and III trials ongoing	Human coagulation factor VIIa	Adequate control of bleeding episodes
RenalGuard for prevention of contrast-induced nephropathy	Patients at risk of contrast-induced nephropathy (CIN)	The only standard treatment for CIN in high-risk patients with chronic kidney disease (CKD) is hydration and avoidance of nephrotoxic drugs. The RenalGuard System™ is a closed loop, single-use, software-controlled console that automatically matches fluid loss and replacement to minimize overhydration or dehydration in patients during medical procedures in which creating and maintaining high urine output is essential. The single-use urine collection set is connected to a Foley catheter and an infusion set is connected to a standard intravenous catheter. The console is managed by monitoring software that measures urine volume in the collection set and matches patient urine output with an equal volume of hydration fluid. PLC Systems, Inc., Milford, MA Pivotal trial completed	Pharmacotherapy (e.g. deferoxamine) Hydration	Reduced occurrence and complications of CIN Reduced incidence of CIN in high-risk patients with CKD Improved quality of life
Retinal prosthesis system (Argus II) for treatment of retinitis pigmentosa	Patients with retinitis pigmentosa (RP) and a functioning optic nerve	No medications or devices are available to restore lost vision or halt progression of vision loss that occurs with the inherited disorder RP. The Argus™ II implant consists of an array of electrodes that is surgically inserted into the retina of 1 eye and used in conjunction with an external camera and video processing system to provide a rudimentary form of sight. By electrically stimulating the retina, visual perception is enabled for blind persons with severe to profound RP. The device is intended to restore a level of vision that is sufficient to improve patients' ability to function more independently. Second Sight, Inc., Sylmar, CA Sept 2012 FDA Advisory Panel recommended approval; Conformité Européene (CE) marked in 2011	Standard of care No other treatments available	Improved visual acuity Improved quality of life and independence

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Rituximab (Rituxan) for treatment of Wegener's granulomatosis and microscopic polyangiitis	Patients in whom Wegener's granulomatosis has been diagnosed	Wegener's granulomatosis and microscopic polyangiitis can cause vasculitis, which can be fatal within months. Immunosuppressive therapies for the disease have many side effects, and better treatments are needed. Rituximab (Rituxan®), a genetically engineered anti-CD20 antibody approved for treating B-cell lymphoma, purportedly reduces the antibody production that leads to the inflammation associated with Wegener's granulomatosis and microscopic polyangiitis. The treatment is intended to be used with glucocorticoids. Genentech subsidiary of F. Hoffmann-La Roche, Ltd., Basel, Switzerland FDA approved Apr 2011 for this indication	Pharmacotherapy (e.g., Imuran®, Cytoxan®, methotrexate, prednisone)	Disease remission
Robotic navigation aid (Guide Vest) to assist visually impaired persons	Patients with visual impairment	Current assistive devices and measures, such as long canes and guide dogs, have limitations that subject patients to injuries that affect quality of life. The guide vest robotic navigation aid is a head-mounted camera/vest combination that allows the head camera to capture images wirelessly through the simultaneous localization and mapping software to build maps of the patient's environment. This allows the technology to accurately identify a safety path devoid of obstacles. The safety route is communicated to the patient through micro motors in the shoulder and waist that vibrate in the event that the route is obstructed. Vibrations to the shoulders are intended to indicate a higher object (i.e. left shoulder vibration for higher left obstacle) and vibrations to the waist indicate a lower object. If adopted, the guide vest may serve as a 1st-line assistive technology device for individuals in whom visual impairment has been identified. University of Southern California Keck School of Medicine's Doheny Eye Institute and Viterbi School of Engineering, Los Angeles Pilot study completed at Braille Institute	Long canes Remote Infrared Audible Signage (RIAS) "Sighted" wheelchair	Decreased risk of falls and injury Improved mobility Increased independence
Smartpatch stimulator for treatment of poststroke pain	Patients in whom stroke has been diagnosed	Approximately 10% of stroke survivors experience mild to severe pain after the stroke. It can be acute or chronic. The Smartpatch peripheral nerve stimulation system is proposed as a minimally invasive therapy during which a fine wire from the patch is placed through the skin near the selected nerves to relieve pain. It purportedly differs from existing electrical stimulation modalities for treating pain because it is not an implanted stimulator device and is placed near nerves rather than touching them. SPR Therapeutics, LLC, Cleveland, OH Phase III trial ongoing	Anticonvulsants Antidepressants Corticosteroids Nonsteroidal anti-inflammatory drugs	Reduced pain Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
SOLX gold shunt for treatment-refractory glaucoma	Patients in whom treatment-refractory glaucoma has been diagnosed	Investigators have not found a cure for glaucoma, and if untreated or refractory to treatment, it leads to blindness. The SOLX® Gold Shunt is gold implant uses the eye's natural pressure differential to reduce intraocular pressure (IOP). The device is a flat, perforated, rectangular-shaped implant inserted between choroid layer and sclera in the trabecular meshwork area. It is differentiated from other surgical glaucoma options because it purportedly reduces IOP without creating a bleb, which is a source of serious complications. SOLX, Inc., Waltham, MA Phase III trials ongoing; approved in Canada and parts of Europe	Pharmacotherapy (e.g., eye drops) Surgical therapy Trabectome (device)	Reduced IOP Preserved vision
Somatostatin analog (pasireotide) for treatment of Cushing's disease	Patients who have Cushing's disease caused by an adreno-corticotropic hormone (ACTH)-secreting pituitary tumor	The majority of Cushing's disease cases are caused by benign pituitary tumors that generate elevated levels of ACTH. ACTH stimulates the production and release of the stress hormone cortisol. Too much ACTH results in too much cortisol, which controls the body's use of carbohydrates, fats, and proteins and helps reduce inflammatory responses. No medical treatments directly targeting ACTH-secreting pituitary tumors are available, and not all patients respond to surgical or radiotherapy treatment. Pasireotide is a subcutaneously administered somatostatin analog that activates a wide range of somatostatin receptors and has demonstrated the ability to inhibit ACTH secretion. Novartis International AG, Basel, Switzerland Phase III trial ongoing	Pharmacotherapy (e.g., ketoconazole, metyrapone, mitotane) Radiation therapy Surgical therapy	Reduced ACTH levels Reduced morbidity from excess cortisol Improved quality of life
Subepidermal moisture scanner (SEM) for prevention and early detection of decubitus ulcers	Patients at risk of developing decubitus ulcers	According to The Joint Commission, about 2.5 million patients are treated for pressure ulcers in acute-care hospitals each year, and the incidence is growing at a significant rate. Prevention and early diagnosis remain a challenge; visual assessment is the current standard of detection. The Sub-Epidermal Moisture (SEM) scanner is a handheld device intended to measure a tissue's dielectric properties and estimate the subepidermal moisture to detect potential decubitus ulcer formation before it becomes visible. This device can transmit data wirelessly to a storage system for analysis. Bruin Biometrics, LLC, Los Angeles, CA Pilot trial completed; other trials ongoing	Visual assessment	Prevention or early treatment of decubitus ulcers Reduced morbidity and mortality from complications

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Subretinal transplantation of human embryonic stem cell-derived retinal pigment epithelium cells for treatment of Stargardt macular dystrophy	Patients in whom Stargardt macular dystrophy has been diagnosed	Stargardt macular degeneration is a genetic eye disorder affecting the retina and it causes progressive vision loss. The macular degeneration affects a small area near the center of the retina called the macula. The disease prevalence is an estimated 1 in 8,000 to 10,000 individuals and no treatment is available. Subretinal transplantation of retinal pigment epithelial cells derived from human embryonic stem cells is under study to determine its safety and tolerability for halting or preventing the disease. Treatment is administered by subretinal injection of 50,000, 100,000, 150,000 or 200,000 cells Advanced Cell Technology, Inc., Santa Monica, CA Phase I/II trials ongoing; FDA and EU granted orphan drug status	No treatment is available	Improved vision Reversed loss of central vision Improved functional status Improved quality of life
Terlipressin for reversal of hepatorenal syndrome type 1	Patients in whom hepatorenal syndrome (HRS) type 1 has been diagnosed	HRS is a rapid, progressive renal impairment with more than 80% mortality within 3 months. Terlipressin is a synthetic vasopressin analog that acts as a systemic vasoconstrictor, mainly in abdominal circulation, which may improve renal blood flow and renal function in patients with HRS. No U.S.-approved drugs for HRS are available. Given intravenously, in combination with albumin. Ikaria Holdings, Inc., Clinton, NJ Phase III and II/III trials ongoing	Liver transplantation Pharmacotherapy (e.g., dopamine, misoprostol, vasoconstrictors)	Confirmed HRS reversal Increased survival to time of transplantation Increased rates of transplant-free survival up to 90 days
Transthyretin stabilizer (tafamidis, Vyndaqel) for treatment of transthyretin familial amyloid polyneuropathy	Patients in whom transthyretin familial amyloid polyneuropathy (TTR-FAP) has been diagnosed	TTR-FAP is a genetic neurodegenerative disease that can also affect the heart and kidneys. The disease is usually fatal within a decade in the absence of a liver transplant. Transthyretin (TTR) is a transport protein for thyroxine and retinol. It can be amyloidogenic: mutation of the TTR gene can lead to the development of unstable TTR, which forms amyloid fibrils that are deposited in various organs. Tafamidis (Vyndaqel®) purportedly is a transthyretin stabilizer intended to treat TTR-FAP. Tafamidis purportedly binds to the TTR protein to promote the stabilization of functional tetrameric molecules, slowing the formation of misfolded amyloid fibrils. Pfizer, Inc., New York, NY Phase III trials ongoing; FDA granted orphan drug status; new drug application submitted to FDA Apr 2011; FDA issued a refusal to accept letter in Jun 2012 and asked the company to conduct another trial	Supportive therapy	Improved Neuropathy Impairment Score TTR stabilization

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vesicular monoamine transporter type 2 inhibitor (NBI-98854) for treatment of tardive dyskinesia	Patients with schizophrenia who have been given a diagnosis of tardive dyskinesia	Only 1 treatment is approved for this condition, and the development of the disease is not yet well understood. More and better treatment is needed. NBI-98854 is a vesicular monoamine transporter type 2 inhibitor that regulates the levels of dopamine release during nerve communication while reducing the likelihood of "off-target" side effects. This compound provides sustained plasma and brain concentrations of the active drug to minimize side effects associated with excessive dopamine depletion. Neurocrine Biosciences, Inc., San Diego, CA Phase II trials completed; FDA granted fast track status Jan 2012	Pharmacotherapy (e.g., benzodiazepines, Cogentin®, omega-3 fatty acids, Mirapex®, Tarvil®, tetrabenazine)	Reduced abnormal involuntary movements
Video game therapy for stroke rehabilitation	Patients who are recovering from mild to moderate ischemic or hemorrhagic strokes	Wii is a video gaming system. A motion-detection system allows patients to see their actions on a television screen with real-time sensory feedback; Wii tennis and Wii Cooking Mama, which uses movements that simulate cutting a potato, peeling an onion, and shredding cheese, are being used in stroke rehabilitation, intended to improve motor skills and speed. Heart and Stroke Foundation, Ottawa, Ontario, Canada Ontario Stroke System, Toronto, Ontario, Canada Phase I trial completed	Standard physical therapy Standard occupational therapy Robot-assisted rehabilitative therapy	Improved motor function Improved strength Improved quality of life
Wearable artificial kidney (WAKs) for end-stage kidney failure	Patients with advanced kidney failure	In current peritoneal dialysis (dialysate) is infused into the abdomen through a permanent indwelling catheter to remove toxins. Peritoneal lining acts as a filter. Spent dialysate solution is drained from peritoneal cavity. With WAKs, dialysate is cleaned and reinfused through external pumps and filtration components that are attached to the front of a vest or waist belt worn by the patient. AWAK Technologies, Inc., Burbank, CA FDA selected this technology in Apr 2012 as 1 of 3 technologies to be piloted for its new innovation pathway designation. Phase I study completed by developers Royal Free London NHS Foundation Trust (formerly Royal Free Hampstead NHS Trust) and Xcorporeal, Inc. (purchased by Fresenius Medical Care Holdings AG & Co. KGaA), in the United Kingdom; 5 randomized controlled trials planned, but none registered at National Clinical Trials database of Jan 2013	Conventional home dialysis systems Kidney transplantation	Adequate filtration of toxins from kidneys Improved mobility Improved quality of life

Table 9. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 37 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Anthrax antitoxin monoclonal antibody raxibacumab (ABthrax) for treatment of inhalation anthrax	Patients suspected to have inhaled anthrax spores	Patients can be unaware that they have inhaled anthrax spores, leading to late treatment that may render antibiotics ineffective; treatments for later stage inhalation anthrax are needed. Raxibacumab (ABthrax™) is a fully human, antitoxin monoclonal antibody purported to treat inhalation anthrax by inhibiting the activity of the protective antigen of anthrax toxin, inhibiting the protein's ability to facilitate pathogenesis. Human Genome Sciences, Rockville, MD FDA approved Dec 2012 for treating adult and pediatric patients with inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterials and for prevention of inhalational anthrax when other therapies are not available or not appropriate	Anthrax vaccine Antibiotics	Protection against inhalation anthrax Rapid resolution of symptoms
AVI-6002 for treatment of Ebola virus exposure	Patients who have been exposed to Ebola virus	Ebola infection has an 80% mortality rate with no effective treatments. AVI-6002 is a drug that uses phosphorodiamidate morpholino oligomer (PMO) antisense technology; PMOs are synthetic structures modeled after RNA, but with modifications purported to improve pharmacologic properties. PMOs have the same nucleic acid bases found in RNA or DNA, but they are bound to morpholine rings instead of ribose rings and are linked through phosphorodiamidate rather than phosphodiester or phosphorothioate groups, which purportedly 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 purportedly improves 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) time frame. AVI BioPharma, Inc., Bothell, WA, now Sarepta Therapeutics, Inc., Cambridge, MA Phase I trial completed; manufacturer to file for FDA approval through the animal efficacy rule after completing studies in healthy human subjects	Supportive care	Increased symptom resolution Reduced mortality

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
AVI-6003 for treatment of Marburg virus	Patients who have been exposed to Marburg virus	Marburg infection has an 80% mortality rate with no effective treatments. AVI-6003 uses phosphorodiamidate morpholino oligomer (PMO) antisense technology. PMOs are synthetic structures modeled after RNA, but with modifications purported to improve pharmacologic properties. PMOs have the same nucleic acid bases found in RNA or DNA, but they are bound to morpholine rings instead of ribose rings and are linked through phosphorodiamidate rather than phosphodiester or phosphorothioate groups, the purportedly 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 purportedly improves targeted cell penetration to improve efficacy in the presence of viral mutations. PMOs could be created in a very short (i.e., days or weeks) timeframe. AVI BioPharma, Inc., Bothell, WA (now Sarepta Therapeutics, Inc., Cambridge, MA), with support from the U.S. Army Medical Research Institute for Infectious Diseases, Frederick, MD Phase I trial completed; manufacturer to file for approval through the animal efficacy rule after completing studies in healthy human subjects	Supportive care	Improved symptom resolution Reduced mortality
Bedaquiline (Sirturo) for treatment of drug-resistant tuberculosis	Patients in whom drug-resistant tuberculosis (TB) is inspected	TB has developed resistance to existing antibiotic therapies and treatment is further complicated by a lengthy regimen. Treatments that can improve outcomes in antibiotic-resistant infections and shorten treatment duration are needed. Bedaquiline (Sirturo™) is a diarylquinoline antituberculosis drug that is intended to achieve clinical response rates twice as fast as standard treatment. The dosage on the approved product labeling is 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks with food. Janssen Therapeutics, Division of Janssen Products, LP, Titusville, NJ FDA approved Dec 28, 2012 for treating pulmonary, multidrug-resistant tuberculosis (MDR-TB) in adults as part of combination therapy when other alternatives are not available. The drug carries a boxed warning alerting patients and health care professionals that the drug can affect the heart (i.e., QT prolongation), which could lead to an abnormal and potentially fatal heart rhythm.	Ethionamide Ethambutol Isoniazid Kanamycin Ofloxacin Pyrazinamide Rifampicin	Resolution of active TB infection Reduced time to clinical response Improved patient adherence with therapy Reduced spread of infection Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Boceprevir (Victrelis) for treatment of hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) genotype 1 infection has been diagnosed	Current standard of care for HCV infection is generally ineffective in more than half of infected patients; effective treatments that improve clinical outcome in a shorter period of time are needed. Boceprevir (Victrelis™) is a NS3/4 protease inhibitor intended to block the activity of HCV protease, preventing the cleavage and maturation of functional viral particles. Administered orally, 800 mg, 3 times daily, in combination with pegylated interferon and ribavirin (IFN/RBV). Merck & Co., Inc., Whitehouse Station, NJ FDA approved May 2011	IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Collaborative care model (HITIDES) for treatment of depression secondary to HIV	Patients in whom depression secondary to HIV has been diagnosed	HIV Translating Initiatives for Depression Into Effective Solutions (HITIDES) is a collaborative care model to support HIV and mental health clinicians in delivering evidence-based depression treatment. Depression care team (registered nurse depression care manager, a clinical pharmacist, and a psychiatrist) works with treating (for HIV) clinicians, delivering the following components: participant education and activation, assessment of treatment barriers and possible resolutions, depression symptom and treatment monitoring, substance abuse monitoring, and instruction in self-management (e.g., encouraging patients to exercise and participate in social activities). Veterans Affairs Medical Centers Trial completed	Usual HIV care without depression care team	Depression improvement Improved care-implementation process Improved quality of care Improved health status Decreased HIV symptom severity Improved HIV medication and antidepressant adherence Improved patient satisfaction Improved health-related quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Copper surfaces in the intensive care unit for prevention of hospital-acquired infections	Patients admitted to an intensive care unit (ICU)	Health care–acquired infections (HAIs) are the 4th leading cause of death in the U.S. behind heart disease, stroke, and cancer; nearly 1 in every 20 hospitalized U.S. patients acquires an HAI, resulting in 100,000 deaths each year. Bacteria on surfaces in ICUs are said to be responsible for 35% to 80% of patient infections. Replacing the most heavily contaminated touch surfaces in ICUs with antimicrobial copper purportedly controls bacterial growth and lowers the rates of infections acquired in the ICU. Bacterial reduction rates are intended to achieve the same outcome as current "terminal cleaning" practices. International Copper Association, New York, NY Commercially available; studies at hospitals ongoing	Terminal cleaning of standard surfaces	Reduced costs associated with HAIs Reduced infection rates Reduced bacteria isolated from surfaces Reduced morbidity and mortality from HAIs
Crofelemer (Fulyzaq) for treatment of HIV-1-associated diarrhea	Patients on HIV antiretroviral therapy with chronic diarrhea	About 40% of patients in the U.S. with HIV-1 infections have chronic diarrhea, which can reduce adherence to antiretroviral regimens. Effective antidiarrheals that do not cause adverse reactions with antiretrovirals are needed. Crofelemer (Fulyzaq™) treats diarrhea by inhibiting the cystic fibrosis transmembrane conductance regulator ion channel, which is responsible for transporting chloride ions into the intestinal lumen, which subsequently draws water into the bowel. Thus, it is thought to work by blocking chloride secretion, thereby reducing the high volume water loss seen in HIV-associated diarrhea. The drug is a delayed release formulation, and the dosage in the approved product labeling is 125 mg, twice daily. Salix Pharmaceuticals, Ltd., Raleigh NC (distributor) Napo Pharmaceuticals, Inc., San Francisco, CA (licenser) FDA approved Dec 28, 2012 for "symptomatic relief of non-infectious diarrhea in adult patients with human immunodeficiency virus (HIV)/ acquired immune deficiency syndrome (AIDS) on anti-retroviral therapy (ART)."	Absorbents containing attapulgite or polycarbophil Antibiotics Diphenoxylate Loperamide	Reduced number of watery bowel movements Relief of diarrhea

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Cyclophilin inhibitor alisporivir for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Current HCV treatment options are not effective in all patients, even with the newly approved agents of telaprevir and boceprevir. Treatment options are also associated with frequent adverse events and a long duration of therapy; effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. Cyclophilin A is a host cell protein involved in protein folding and transport, and it has been shown to be essential in HCV replication; cyclosporine A inhibits cyclophilin activity but is immunosuppressive; alisporivir (Debio-025) is an oral modified form of cyclosporin A, that purportedly acts as a host-targeted antiviral with enhanced cyclophilin binding but no immunosuppressive activity, which might be due to the inability of the alisporivir-cyclophilin complex to bind calcineurin which modulates proinflammatory lymphocyte signaling. Debiopharm, S.A., Lausanne, Switzerland Novartis International AG, Basel, Switzerland Phase III trials ongoing; FDA granted fast track status	Boceprevir Pegylated interferon plus ribavirin Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Extracorporeal membrane oxygenation for treatment of serious influenza infections	Patients in whom serious influenza infection has been diagnosed	Influenza continues to cause significant morbidity and mortality in susceptible patients; better treatments are needed. Extracorporeal membrane oxygenation (ECMO) has been contraindicated in patients with serious infections; however, recent trials in patients with H1N1 influenza suggested some utility for the procedure. ECMO involves cannulas placed in large blood vessels to provide access to the patient's blood. The ECMO machine continuously pumps blood from the patient through a membrane oxygenator that imitates the gas exchange process of the lungs. Oxygenated blood is then returned to circulation. Management of the ECMO circuit requires a specially trained team. Far Eastern Memorial Hospital, Taipei, Taiwan, and National Taiwan University Hospital, Taipei Could be implemented readily	Ventilation support Treatment of comorbidities	Reduced morbidity Reduced mortality
Fecal microbiota transplantation for treatment of recurrent *Clostridium difficile* infection	Patients with recurrent *Clostridium difficile* infection (CDI)	Because of antibiotic resistance, new options are needed that can improve clinical cure rates and reduce CDI recurrence. Fecal matter from a healthy donor is collected and mixed with a saline solution and transplanted into the recipient in 1 of several ways (e.g., colonoscopy, nasogastric tube) with the intended purpose of introducing healthy flora to the intestinal tract to prevent recurrence of CDI. Multiple trials ongoing at various U.S. medical centers	Fidaxomicin Metronidazole Vancomycin	Reduced diarrhea Reduced dehydration Reduced reinfection

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fidaxomicin (Dificid) for treatment of *Clostridium difficile* infection	Patients in whom *Clostridium difficile*–associated diarrhea has been diagnosed	Because of antibiotic resistance, new antibacterials that can improve clinical cure rates and reduce *Clostridium difficile* infection (CDI) recurrence are needed. Fidaxomicin (Dificid®) is an antibiotic that is 1st in a new class, called macrocyclics, that inhibit bacterial RNA polymerase, resulting in rapid killing. Fidaxomicin has a narrow spectrum and selectively eradicates CDI with minimal disruption to the normal intestinal flora, which may lower recurrence rates. Administered orally, 200 mg, twice a day. Optimer Pharmaceuticals, Inc., San Diego, CA FDA approved May 2011	Fecal microbiota transplant Metronidazole Vancomycin	Increased clinical cure rates Reduced CDI recurrence
Nitazoxanide for treatment of influenza	Patients in whom viral influenza has been diagnosed	New influenza treatments are needed because of the development of resistance to existing agents. Nitazoxanide is a thiazolide with a broad spectrum of anti-infective activity. It may interfere with protease activity and the maturation and intracellular transport of the viral hemagglutinin protein (other drugs inhibit neuraminidase), leading to a reduction in viral replication. In trials drug is administered orally, 300 mg, twice a day. Romark Laboratories, L.C., Tampa, FL Phase II/III trial completed; phase III trial planned	Oseltamivir (Tamiflu®) Zanamivir (Relenza®)	Reduced complications of influenza infection Shorter duration of symptoms
Nitro-dihydro-imidazooxazole (delamanid) for treatment of tuberculosis	Patients in whom tuberculosis (TB) has been diagnosed	TB has developed resistance to existing antibiotic therapies and treatment is further complicated by a lengthy regimen. Treatments that can improve outcomes in antibiotic-resistant infections and shorten treatment duration are needed. Delamanid purportedly addresses these unmet needs. As a nitro-dihydro-imidazooxazole derivative, it purportedly inhibits the synthesis of mycolic acid, which is a component of the TB bacteria cell wall. Delamanid is administered orally, 100 mg, twice daily, or 200 mg, once daily, besides standard TB regimens. Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan Phase III trial ongoing	Bedaquiline, a diarylquinoline (in development) Ethionamide (Trecator®) Kanamycin Ofloxacin (Floxin®) PA-824, a nitroimidazole (in development) Pyrazinamide	Improved patient adherence with therapy Reduced spread of infection Reduced time to clinical response Resolution of active TB infection Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nitroimidazole (PA-824) for treatment of pulmonary tuberculosis	Patients in whom multidrug-resistant/drug susceptible tuberculosis has been diagnosed	TB has developed resistance to existing antibiotic therapies and treatment is further complicated by a lengthy regimen. Treatments that can improve outcomes in antibiotic-resistant infections and shorten treatment duration are needed. PA-824 is a nitroimidazole, a class of antibacterial agents that has activity in vitro against all tested drug-resistant clinical isolates. It is intended to shorten treatment time and simplify treatment. Taken orally. Novartis International AG, Basel, Switzerland Bayer AG, Leverkusen, Germany Phase II trials ongoing; FDA granted orphan drug and fast track status for treating tuberculosis	Ethambutol Ethionamide Isoniazid Kanamycin Ofloxacin Pyrazinamide Rifampicin	Shorter duration of therapy Simpler dosing Improved adherence Safer method of action Lower cost of overall treatment
Nonnucleoside polymerase inhibitor (ABT-333) for treatment of chronic hepatitis C infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	HCV treatment options are not effective in all patients, are associated with frequent adverse events, a long duration of therapy, and low patient adherence. Effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. ABT-333 is a nonnucleoside NS5B polymerase inhibitor intended to bind HCV RNA-dependent RNA polymerase and inhibit replication of the viral genome. It could be used in combination with ABT450/r and ribavirin in an interferon (IFN)-free regimen. Administered orally, once daily. Abbott Laboratories, Abbott Park, IL Phase III trial ongoing	Boceprevir NS5A inhibitors (in development) Nonnucleoside polymerase inhibitors (in development) Nucleoside polymerase inhibitors (in development) Telaprevir	Decreased need for liver transplant Slowed or halted disease progression Sustained virologic response (defined as undetectable virus at 24 weeks) Improved quality of life
NS3 protease inhibitor (asunaprevir) for treatment of chronic hepatitis C virus infection	Patients in whom chronic infection with hepatitis C virus (HCV) has been diagnosed	HCV treatment options are not effective in all patients, are associated with frequent adverse events, a long duration of therapy, and low patient adherence. Effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. Asunaprevir is an NS3 protease inhibitor intended to block the activity of HCV protease preventing the cleavage and maturation of functional viral particles. Administered orally, 200 mg, twice daily, in combination with NS5A inhibitor BMS-914143 with or without the standard-of-care pegylated interferon plus ribavirin (IFN/RBV). Bristol-Myers Squibb, New York, NY Phase III trial ongoing	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
NS3 protease inhibitor (sovaprevir) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	Current standard of care for HCV infection is not effective in all patients seeking treatment and is poorly tolerated in many patients; effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. Sovaprevir is a NS3 protease inhibitor intended to block the activity of HCV protease, preventing the cleavage and maturation of functional viral particles; sovaprevir is purported to have broad genotypic coverage and to induce high rates of rapid virologic responses irrespective of interleukin-28 genotype; intended to be used in combination with standard-of-care pegylated interferon plus ribavirin (IFN/RBV). Administered orally, 200–800 mg, once daily. Achillion Pharmaceuticals, Inc., New Haven, CT Phase II trial ongoing; FDA granted fast track status for treating chronic HCV	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
NS3/4 protease inhibitor (faldaprevir) for treatment of chronic hepatitis C virus infection	Patients in whom chronic infection with hepatitis C virus (HCV) has been diagnosed	HCV treatment options are not effective in all patients, are associated with frequent adverse events, a long duration of therapy, and low patient adherence. Effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. Faldaprevir is a NS3/4 protease inhibitor intended to block the activity of HCV protease preventing 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 the polymerase inhibitor BI-207127. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials ongoing; granted FDA fast track status in combination with standard of care and in IFN-free combination with BI-207127	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
NS3/4A protease inhibitor and ritonavir (ABT-450/ritonavir) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	HCV treatment options are not effective in all patients, and are associated with frequent adverse events and a long duration of therapy. Effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. ABT-450/r is an NS3/4A HCV protease inhibitor co-administered with ritonavir and is under study in many clinical trials in combination with other HCV treatments. It is administered as ABT-450 (tablets) dosed with ritonavir (capsules) Abbott Laboratories, Abbott Park, IL Enanta Pharmaceuticals, Inc., Watertown, MA Phase III trial ongoing	Boceprevir Pegylated interferon plus ribavirin Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
NS5A inhibitor (daclatasvir, BMS-790052) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C infection (HCV) has been diagnosed	HCV treatment options are not effective in all patients, are associated with frequent adverse events, a long duration of therapy, and low patient adherence. Effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. BMS-790052 is a 1st-in-class inhibitor of HCV NS5A which is a multifunctional, nonenzymatic endoplasmic reticulum (ER) membrane-associated phosphoprotein. This protein regulates multiple steps of the HCV life cycle, including viral RNA replication and virion maturation. Although the role of the protein is poorly understood, NS5A is known to be required for viral replication. Researchers propose that BMS-790052 destabilizes the association of NS5A with the ER membrane, thus inhibiting the formation of functional virions. It may be used in combination with standard of care and other investigational agents including pegylated interferon (IFN) lambda. Administered orally, 60 mg, once daily. Bristol-Myers Squibb, New York, NY Phase III trials ongoing	Boceprevir Sofosbuvir (investigational) Pegylated IFN plus ribavirin Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nucleotide analog reverse transcriptase inhibitor tenofovir disoproxil fumarate (Viread) for prevention of HIV infection	People at high risk of HIV infection	HIV remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments. HIV-drug resistance, high lifelong cost of therapy, and adverse events continue to suggest that prophylactic HIV measures be pursued for individuals at high risk of infection. Tenofovir disoproxil fumarate (Viread®) is a nucleotide analog reverse transcriptase inhibitor used in combination with other antiretroviral agents for treating HIV infection. Truvada® (emtricitabine with tenofovir disoproxil fumarate) has been approved as preexposure prophylaxis for people at high risk of HIV infection. Clinical studies have suggested that daily prophylactic use of tenofovir without emtricitabine can also reduce the risk of sexual acquisition of HIV. Administered orally, 300 mg, once daily. Gilead Sciences, Inc., Foster City, CA Phase III trial ongoing	Condoms Harm reduction campaigns Preexposure prophylaxis (tenofovir with or without emtricitabine) Prophylactic vaccines (in development) Vaginal microbicide gels (in development)	Reduced HIV transmission Reduced HIV incidence
OraQuick in-home rapid test for detection of HIV infection	Patients who may have been exposed to HIV	Despite advances in treatment, prevention, detection, and education, HIV continues to spread, and better, rapid, early detection methods might help limit this spread. The OraQuick® In-Home HIV Test was adapted from the FDA-approved OraQuick rapid HIV test available since 2009 for use in clinics. The new test is an over-the-counter version for home use. To perform the test, individuals swab their upper and lower gums and place the swab into a vial of test fluid. Results (colored lines on the test strip) can be read within 20 minutes. A positive result is intended to signal the need for the patient to have followup testing by a health care provider. The kit includes an information booklet with directions to call a manufacturer's support center 24 hours a day, 7 days a week for counseling on the test results and referral to medical services. OraSure Technologies, Inc., Bethlehem, PA FDA approved Jul 2012	Home-based blood tests (mail-in) Clinic-based rapid test (OraQuick)	Reduced HIV transmission Earlier intervention to control viral load Increased HIV screening rate

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ozonated water disinfectant to prevent health care–acquired infections	Patients in a hospital or other health care setting in which where health care–acquired infections (HAIs) are a concern	HAIs are a major cause of death in the U.S. About 1 in 20 hospitalized U.S. patients acquires an HAI, resulting in 100,000 deaths each year. Bacteria on surfaces in intensive care units are said to be responsible for 35% to 80% of HAIs. Cleaning surfaces with ozonated water purportedly cleans as effectively as using other chemicals for terminal cleaning, but ozonated water is said to be less harsh on hospital staff and patients. Additionally, ozonated water is thought to leave no harmful residue after cleaning. Ozone is a highly active form of oxygen that purportedly reacts with microorganisms leading to efficient killing. After reacting, elemental oxygen is thought to remain. Windsor Regional Hospital, Windsor, Ontario, Canada No regulatory clearance required; available for implementation	Antimicrobial copper touch surfaces Terminal cleaning procedures using bleach and cleaning of visibly soiled surfaces as necessary Ultraviolet light	Reduced costs associated with HAIs Reduced bacteria isolated from surfaces Reduced infection rates Reduced HAI morbidity and mortality
Patient-centered signage to improve hand washing among health care workers	Patients attending health care facilities	Hand-washing adherence by health care workers is only about 40% in many health care settings, leading to the transmission of deadly and costly infections. It is purported that many health care workers have expressed the opinion that because they are frequently exposed to infections, they are more immune to infection and, thus, do not wash their hands. Signage posted where hand washing should occur stating “Hand Hygiene Prevents Patients from Catching Diseases” may be more effective than “Hand Hygiene Prevents You from Catching Diseases” or a generic catchy message such as “Gel In, Wash Out.” A patient-centered message may appeal to the “do no harm” precept of the Hippocratic oath. University of North Carolina at Chapel Hill	Standard hand-washing practices Radiofrequency identification hand-washing systems	Reduced costs associated with health care–acquired infections (HAIs) Reduced HAI incidence Reduced HAI morbidity and mortality
Peramivir for treatment of influenza	Patients in whom H1N1 influenza has been diagnosed or is suspected	Because of resistance to existing antiviral agents used for flu, new antiviral therapies are needed. Additionally, therapies that provide broad coverage against different strains of influenza virus are needed. Peramivir is a cyclopentane neuraminidase inhibitor that is intended to bind the active site of the protein and inhibit viral budding. Peramivir has activity against influenza A and B viruses as well as in patients refractory to oseltamivir. Administered as an intravenous drug, 600 mg, once daily, for 5–10 days. BioCryst Pharmaceuticals, Inc., Research Triangle Park, NC Phase III trials terminated for administrative reasons; approved for emergency use in patients with confirmed or suspected H1N1 influenza	Oseltamivir (Tamiflu®; for influenza) Zanamivir (Relenza®; for influenza)	Decreased length of hospitalization Reduction in virus titers Relieved symptoms

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Pharmacist-provided medication therapy management for patients with HIV/AIDS	Patients in whom HIV infection/AIDS has been diagnosed	Antiretroviral therapy (ART) regimens comprise multiple classes of medications used to treat HIV infection. A significant correlation between improved ART adherence and reduced viral load and therapeutic outcomes has been demonstrated. Treatment options for patients with HIV-AIDS are limited once resistance occurs, and resistance can be associated with poor treatment adherence; programs to optimize treatment adherence are needed to optimize outcomes. Pharmacist-provided medication therapy management services are being provided to California residents with HIV-AIDS as part of a pilot program of Medi-Cal (the State's Medicaid program); participating pharmacies and pharmacists select various services offered above and beyond standard counseling, such as the following: evaluating patients' ability to adhere to medications, in consultation with doctors and case managers; identifying and managing adverse drug reactions; tailoring drug regimens to fit patient lifestyle or special needs; scheduling individual appointments with pharmacists to discuss medication therapy; adherence packaging beyond any provided by manufacturer (e.g., personalized blister packs for all ART medications); identifying peer advocates to assist in medication adherence; and making weekly telephone call or home visit after initiation of therapy. School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego	Medication therapy management in another care setting Nurse care coordinator	Decreased cost of care Decreased incidence of opportunistic infections Reduced need for inpatient services Reduced need to change treatment regimen Improved treatment adherence Reduced viral load
PneumoniaCheck device for detection of pneumonia	Patients in whom pneumonia is suspected	Only 40% of suspected pneumonia cases are thought to be accurately detected because organisms from the mouth and lungs contaminate the sample, leading to inappropriate treatment and increased morbidity and mortality. The PneumoniaCheck™ device purportedly uses fluid mechanics in a simple design that separates upper and lower airway aerosols, allowing contaminating organisms from the mouth to be eliminated from the lower respiratory isolates needed for appropriate diagnosis. The device consists of a plastic tube with a mouthpiece. A patient coughs into the device to fill up a balloon-like upper airway reservoir before the lung aerosols go into a filter that can be analyzed with standard polymerase chain reaction methods. MD Innovate, Inc., Decatur, GA Exempt from FDA regulatory clearance processes; classified as a class I device	Sputum and culture detection methods	Improved accuracy of diagnosis Improved treatment plan Reduced duration of symptoms through appropriate treatment

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Point-of-care testing systems for methicillin-resistant *Staphylococcus aureus* screening	Patients who may be infected by methicillin-resistant *Staphylococcus aureus* (MRSA)	Current MRSA screening tests are time-intensive and typically require highly trained laboratory workers to perform the test. Testing systems and assays are being developed that could be used by nonclinical laboratory staff in the point-of-care setting and provide results in 10–15 minutes. Multiple manufacturers: Blaze Venture Technologies, Ltd., Ware, UK Enigma Diagnostics, Ltd., Salisbury, UK InstantLabs Medical Diagnostics Corp., Reston, VA QuantaLife, Inc., Pleasantville, CA Smiths Group, plc, London, UK TwistDx, Ltd., Cambridge, UK Unphased trials ongoing; devices and test kits expected to be cleared through 510(k) pathway with no requirement for clinical evidence of efficacy	MRSA culture Conventional 1st-generation polymerase chain reaction (PCR) assay 2nd-generation quantitative PCR	Reduced transmission of MRSA Increased sensitivity and specificity of MRSA detection Faster MRSA detection
Polymerase inhibitor (sofosbuvir, GS-7977) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	HCV treatment options are not effective in all patients, are associated with frequent adverse events, a long duration of therapy, and low patient adherence. Effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. Sofosbuvir is a uridine nucleotide analog intended to inhibit HCV NS5B polymerase activity, which may limit viral replication by inhibiting viral genome replication. Sofosbuvir is being evaluated in conjunction with standard-of-care pegylated interferon plus ribavirin (IFN/RBV) and in interferon-free regimens that include ribavirin, daclatasvir, simeprevir, and other agents. Administered orally 400 mg, once daily. Gilead Sciences, Inc., Foster City, CA Phase III trial ongoing; received FDA fast track status	Boceprevir IFN/RBV Telaprevir	Cured infection (sustained virologic response with no detectable virus) Reduction of symptoms Delayed or halted progression to end-stage liver disease Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Protease inhibitor (simeprevir) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	HCV treatment options are not effective in all patients and are associated with frequent adverse events and a long duration of therapy. Effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. Simeprevir in an oral NS3/4a HCV protease inhibitor that may be used to limit viral replication in combination with pegylated interferon plus ribavirin (IFN/RBV). Administered 150 mg, once daily. Tibotec BVBA, Beerse, Belgium Phase III trials ongoing; FDA granted fast track status	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Protease inhibitor (vaniprevir, MK7009) for treatment of chronic hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) infection has been diagnosed	HCV treatment options are not effective in all patients, and are associated with frequent adverse events and a long duration of therapy. Effective treatments that improve clinical outcomes and safety in a shorter period of time are needed. Vaniprevir (MK7009) is a next-generation is a NS3/4 protease inhibitor intended to block the activity of HCV protease, preventing the cleavage and maturation of functional viral particles. Vaniprevir is used in combination with pegylated interferon plus ribavirin (IFN/RBV). Administered orally 300 mg, twice daily. Merck & Co., Inc., Whitehouse Station, NJ Phase III trials ongoing	Boceprevir IFN/RBV Telaprevir	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Rapid molecular detection test (Gene Xpert MTB/RIF) for Mycobacterium tuberculosis infection with rifampin resistance	Patients suspected of having Mycobacterium tuberculosis infection	Automated molecular test (Xpert® MTB/RIF) for M. tuberculosis infection that also simultaneously tests for resistance to rifampin. Cepheid, Sunnyvale, CA Currently, the test is available for research use only as a 10-test kit; Conformité Européene (CE) marked; World Health Organization endorsed MTB/RIF in late 2010 for use in the “High Burden Developing Countries” and Gates Foundation is supporting adoption of test in these 145 countries	Microscopy Tuberculin skin test (Mantoux test) Ziehl-Neelsen microscopy	Less lab staff training time Rapid detection Improved treatment Better control of antibacterial resistance

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
RTS,S for prevention of malaria caused by *Plasmodium falciparum*	Patients living in or traveling to areas endemic for malaria	Almost half of the world population is at risk of contracting malaria. Current treatments to the *Plasmodium falciparum* parasite can be ineffective, particularly in young children and immunosuppressed individuals. The lack of effectiveness results in high morbidity and mortality. RTS,S consists of a recombinant, circumsporozoite protein in which the 9 central tandem repeat and carboxyl-terminal regions are fused to the N-terminus of the hepatitis B virus S antigen in a particle expressed in yeast that also includes unfused S antigen. The vaccine is also administered with the AS02A adjuvant (proprietary oil-in-water emulsion with the immunostimulants monophosphoryl lipid A and QS21). The vaccine purportedly targets the pre-erythrocytic stage of *P. falciparum* by inducing protective immune responses against the parasite when it 1st enters the human host's bloodstream and/or when it infects liver cells, thus inhibiting the infection cycle. Administered in 3 intramuscular injections at 0, 1, and 2 months. GlaxoSmithKline, Middlesex, UK PATH Malaria Vaccine Initiative, Washington, DC Phase III trials completed; phase II/III trial ongoing	Chloroquine phosphate Mosquito nets	Reduced incidence of malaria infection Increased overall survival
Streaming weekly educational soap opera episodes to smartphones for people at high risk for HIV	Patients who are at high risk of contracting HIV infection	Despite HIV prevention and education efforts, the epidemic continues to spread. New methods to educate patients about how to better avoid activities associated with elevated risk of contracting HIV are needed. A 12-episode soap opera video series called "Love, Sex, and Choices" was designed to educate women about HIV risk reduction methods. Women were given a secure cell phone that streamed weekly episodes incorporating HIV risk-reduction messages. Delivering risk-reduction messages in this format could lead to better awareness. Rutgers College of Nursing, Newark, NJ Study completed	Standard risk-reduction programs Text messaging risk reduction programs	Reduced HIV incidence in at-risk women Increased knowledge and identification of high-risk behavior

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Telaprevir (Incivek) for treatment of hepatitis C virus infection	Patients in whom chronic hepatitis C virus (HCV) genotype 1 infection has been diagnosed	HCV treatment with pegylated interferon plus ribavirin (IFN/RBV) is generally ineffective in more than half of infected patients; effective treatments that improve clinical outcome in a shorter period of time are needed. Telaprevir (Incivek™) is a NS3/4 protease inhibitor intended to block the activity of HCV protease, preventing the cleavage and maturation of functional viral particles. Administered orally, 750 mg, 3 times daily, in combination with IFN/RBV. Vertex Pharmaceuticals, Inc., Cambridge, MA FDA approved May 2011	Boceprevir IFN/RBV	Rapid virologic response (HCV RNA undetectable at week 4) Slowed or halted disease progression (fibrosis and cirrhosis) Sustained virologic response (defined as undetectable virus at 24 weeks) Decreased need for liver transplant Improved quality of life
Tenofovir and emtricitabine (Truvada) for prevention of HIV infection	People at risk of HIV infection	Truvada® is a combination of 2 reverse transcriptase inhibitors Viread® (tenofovir disoproxil fumarate) and Emtriva® (emtricitabine) given as preexposure 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 both men who have sex with men and in heterosexual men. Data for prophylactic use in women have been confounding due to lack of efficacy. The 2 drugs are combined into 1 oral tablet taken daily. Gilead Sciences, Inc., Foster City, CA FDA approved the drug Jul 2012 to reduce the risk of HIV infection in high-risk, uninfected individuals who may engage in sexual activity with infected partners. As a condition of approval part of the approval, FDA also directed Gilead to develop a Risk Evaluation and Mitigation Strategy to help ensure safe use as part of a comprehensive prevention strategy for the disease. The company will also provide vouchers for free HIV testing and condoms, an opt-in service for reminders about HIV testing, and subsidized HIV resistance testing for any person who becomes HIV-positive while taking the drug as prescribed for prevention.	Condoms Harm reduction campaigns Prophylactic vaccines (investigational) Vaginal microbicide gels (investigational)	Reduced transmission and incidence of HIV

Table 10 AHRQ Priority Condition: 10 Obesity: 9 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Controlled-release phentermine-topiramate (Qsymia) for treatment of obesity	Overweight adults with body mass index (BMI) >27 kg/m^2 with a comorbidity or obese adults (BMI >30 kg/m^2)	The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Long-term weight loss drugs on the U.S. market (Belviq® and orlistat) in the U.S. result in relatively small amounts of weight loss in only a portion of patients taking them. The drugs also have side effects that often lead to cessation of therapy. Controlled-release phentermine-topiramate (Qsymia™) is a combination of the appetite suppressant phentermine (approved for short-term use in weight loss) and topiramate (an approved antiepileptic agent with known weight loss side effects). It is a controlled-release pill that is intended to be taken once daily and in trials resulted in more weight loss by more patients than other available antiobesity drugs. Vivus, Inc., Mountain View, CA FDA approved Jul 2012 for "for chronic weight management in adults who are obese, or overweight with at least 1 weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia" with diet and lifestyle modifications. Obese is defined as BMI 30 kg/m^2 or higher; overweight is BMI 27 kg/m^2 or higher. The approval included a Risk Evaluation and Mitigation Strategy requiring physician training, physician registration, pregnancy avoidance counseling for patients of reproductive age on the drug, and dose-escalation strategy.	5-HT_{2C} receptor agonist (Belviq) Behavioral and lifestyle modifications Combination norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (Contrave; under development) Pancreatic lipase inhibitor (orlistat, Xenical®) Surgical therapy (e.g. bariatric surgery)	Excess-weight loss Decreased rate of obesity-related comorbidities (e.g., prediabetes, high blood pressure) Improved quality of life

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) >30 kg/m^2	The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Pharmacologic options have expanded with new drug approvals in 2012; however, the approved drugs have significant potential side effects and work in only a proportion of patients taking them. Additional pharmacologic options are needed. Attiva™ is a polymer that may promote weight loss without any unwarranted central nervous system effects. Attiva is a highly absorbent hydrogel containing polymer particles solely comprised of food materials that expand when in contact with liquid in the stomach; the polymer expands into numerous hydrogel beads in the stomach, giving a "full" feeling to suppress hunger. The hydrogel keeps food in the stomach longer, giving stomach acid more time to break down both the food and the hydrogel, which begins to release its water; everything then moves to the small intestine where the gel can re-expand to some extent, slowing the absorption of fatty materials and sugars. Attiva capsules may be taken orally, after meals. Gelesis, Inc., Boston, MA Pilot study completed; company pursuing FDA 510(k) clearance	Behavioral and lifestyle modifications Belviq® Combination appetite suppressant/stimulant and anticonvulsant (Qsymia®) Combination norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (Contrave; under development) Pancreatic lipase inhibitor (orlistat, Xenical®) Surgical therapy (e.g. 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) ≥40 or ≥35 kg/m^2 with comorbidity	Current surgical options for treating obesity are often effective, but some of them alter the size, shape, and/or architecture of the gastrointestinal (GI) tract, potentially leading to side effects such as nausea, digestive issues, and nutritional deficits. The Abiliti® gastric pacemaker is proposed as an alternative that does not alter the structure of the GI tract, but senses the ingestion of food and stimulates the stomach with electrical pulses to try to induce satiety, which might lead to weight loss. IntraPace, Inc., Mountain View, CA 1 unphased trial completed and another ongoing; Conformité Européene (CE) marked Mar 2011; IntraPace was discussing with FDA requirements in 2012 for a U.S. investigational device exemption pivotal trial	Behavioral and lifestyle modifications Belviq® Combination appetite suppressant/stimulant and anticonvulsant (Qsymia®) Combination norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (Contrave; under development) Pancreatic lipase inhibitor (orlistat, Xenical®) Surgical therapy (e.g. bariatric surgery)	Excess-weight loss Total weight loss Decreased obesity-associated comorbidities (e.g., prediabetes, high blood pressure) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Liraglutide (Victoza®) for treatment of obesity	Patients at risk for diabetes with a body mass index (BMI) greater than 30 kg/m^2 or between 27 and 30 kg/m^2 with an associated comorbidity	The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Pharmacologic options have expanded with new drug approvals in 2012; however, the approved drugs have significant potential side effects and work in only a proportion of patients taking them. Liraglutide (Victoza) is approved for treatment of T2DM and acts as a glucagon-like peptide 1 analog; drug acts to reduce blood glucose levels by increasing insulin secretion, which delays gastric emptying, and suppresses glucagon secretion, potentially leading to weight loss. This once-daily treatment showed potential in preclinical studies and studies in overweight patients without diabetes to reduce food intake and induce weight loss. Novo Nordisk A/S, Bagsværd, Denmark Phase III trial ongoing	5-HT$_{2C}$ receptor agonist (Belviq®) Behavioral and lifestyle modifications Combination appetite suppressant/stimulant and anticonvulsant (Qsymia®) Combination norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (Contrave; under development) Pancreatic lipase inhibitor (orlistat, Xenical®) Surgical therapy (e.g. bariatric surgery)	Excess-weight loss Total weight loss Decline in obesity-associated comorbidities (e.g., prediabetes, high blood pressure) Improved quality of life
Lorcaserin (Belviq) for treatment of obesity	Overweight adults (BMI >27 kg/m^2) with a comorbidity or obese adults (BMI >30 kg/m^2)	The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Pharmacologic options have expanded with new drug approvals in 2012; however, competing approved drugs have significant potential side effects and work in only a proportion of patients taking them. Lorcaserin (Belviq®) is in a new class of selective serotonin 2C receptor agonists. It is taken twice daily in a 10-mg tablet. If 5% weight loss is not achieved by week 12 of therapy, labeling requires that the drug therapy be discontinued. Arena Pharmaceuticals, Inc., San Diego, CA (manufacturer) Eisai, Inc., U.S., a subsidiary of Eisai Co., Ltd., Tokyo, Japan (U.S. distributor) FDA approved Jun 2012 on basis of 3 completed phase III trials “as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m^2 or greater (obese), or 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes).” The drug is to be classified by U.S. Drug Enforcement Administration as a schedule IV drug, after which Eisai will announce when the drug will be available for prescribing. No Risk Evaluation and Mitigation Strategy required.	Behavioral and lifestyle modifications Combination appetite suppressant/stimulant and anticonvulsant (Qsymia®) Combination norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (Contrave; under development) Pancreatic lipase inhibitor (orlistat, Xenical®) Surgical therapy (e.g. bariatric surgery)	Excess-weight loss Total 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
Naltrexone and bupropion extended-release (Contrave SR) for treatment of obesity	Adults with body mass index (BMI) >30 kg/m^2 or >27 kg/m^2 with comorbidities	The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Pharmacologic options have expanded with new drug approvals in 2012; however, the approved drugs have significant potential side effects and work in only a proportion of patients taking them. Additional pharmacologic options are needed. Contrave is a fixed-dose combination of naltrexone sustained-release (SR) and bupropion SR. Bupropion purportedly acts on weight control by stimulating the POMC neuron. Naltrexone purportedly prevents inhibition of POMC neurons by blocking the action of beta-endorphin. Naltrexone and bupropion extended release (Contrave SR®) is taken orally, once a day. Orexigen Therapeutics, Inc., La Jolla, CA FDA rejected new drug application Feb 2011; requested additional trial on cardiovascular effects; the trial began enrolment in Jun 2012 and the company announced it had enrolled more quickly than anticipated and that it expects to complete data collection by end of 2013. The company anticipates a resubmission of data in early 2014.	5-HT_{2C} receptor agonist (Belviq®) Behavioral and lifestyle modifications Combination appetite suppressant/stimulant and anticonvulsant (Qsymia®) Pancreatic lipase inhibitor (orlistat, Xenical®) Surgical therapy (e.g. bariatric surgery)	Excess-weight loss Total weight loss Adverse events Improved quality of life
Off-label exenatide for treatment of pediatric obesity	Children and adolescents receiving a diagnosis of “extreme” obesity (body mass index [BMI] ≥1.2 times the 95th percentile or BMI ≥35 kg/m^2)	A single weight-loss pharmacotherapy is available for adolescents older than 12 years of age: orlistat (Xenical®). However, prescription medications are not recommended for child or adolescent use. Exenatide is a glucagon-like peptide-1 receptor agonist approved for type 2 diabetes mellitus treatment that reduces BMI, waist circumference, and body weight in addition to improving the glycemic index. Exenatide purportedly increases satiety sensation and appetite suppression. In this trial, exenatide was administered subcutaneously twice daily at 5 mcg/dose for the 1st month and increased to 10 mcg/dose for 2 months. University of Minnesota, Minneapolis Pilot trial completed; phase II trials ongoing	Behavioral and lifestyle modifications Pancreatic lipase inhibitor (orlistat, Xenical®) Surgical therapy (e.g. bariatric surgery)	Excess-weight loss Total 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
Restorative obesity surgery (endoluminal ROSE) for treatment of postgastric-bypass weight regain	Patients who have undergone gastric bypass, but regained weight and stretched the stomach pouch or stoma	The World Health Organization estimates that more than 1.5 billion adults are overweight, and 500 million are considered obese. Invasive surgical options have severe health outcomes, warranting the need for less invasive options. Restorative obesity surgery (endoluminal ROSE) is intended to restore the stomach or stoma to its original postsurgical (i.e., smaller) size in patients who have undergone gastric bypass surgery and regained weight. The procedure is minimally invasive and incisionless because it is performed through the mouth. Van Den Bossche and Elemental Healthcare, Ltd., Berkshire, UK Pilot study ongoing	Bariatric revision surgeries	Reduction in stoma Total weight loss Quicker recovery than open revision surgery No scarring
Vagus nerve blocking (Maestro system VBLOC) for treatment of obesity	Adults with body mass index (BMI) between 40 and 45 kg/m^2 or ≥35 kg/m^2 with comorbidities	The World Health Organization estimates that more than 1.5 billion adults are overweight and 500 million are considered obese. Available pharmacological and surgical options can have severe adverse events, warranting the need for more novel approaches for treating obesity. High frequency, low-energy electrical impulses are emitted to block the vagus nerve (VBLOC™) in an effort to inhibit gastric motility and increase feelings of fullness. Electrical impulses are delivered by an implanted neuroregulator which is powered either by an external controller (Maestro™ RF System) or an integrated rechargeable battery (Maestro RC System); implanted laparoscopically. EnteroMedics, Inc., St. Paul, MN Pivotal ReCharge trial ongoing; phase III EMPOWER™ trial ongoing, with expected completion in 2013	$5\text{-}HT_{2C}$ receptor agonist (Belviq®) Behavioral and lifestyle modifications Combination appetite suppressant/stimulant and anticonvulsant (Qsymia®) Combination norepinephrine/dopamine reuptake inhibitor and opioid receptor antagonist (Contrave; under development) Pancreatic lipase inhibitor (orlistat, Xenical®) Surgical therapy (e.g. bariatric surgery)	Amount of weight loss Duration of weight loss Resolution of comorbidity (cardiovascular, diabetes)

Table 11. AHRQ Priority Condition: 11 Peptic Ulcer Disease and Dyspepsia: 15 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Acetylcholinester-ase inhibitor (acotiamide) for treatment of functional dyspepsia	Patients in whom functional dyspepsia (FD) has been diagnosed	FD is a highly prevalent condition, but no efficacious treatments are available. Acotiamide represents a novel drug class for this indication; it is a muscarinic receptor antagonist and acetylcholinesterase inhibitor under development for treating FD. Acotiamide is 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). Drug is also known as Z-338 or YM443. Administered orally, 100 mg, 3 times daily. Zeria Pharmaceutical Co., Ltd., Tokyo, Japan, in collaboration with Astellas Pharma, Inc., Tokyo, Japan Phase III trial completed in Japan; phase II trial completed in U.S.; submitted application for marketing authorization in Japan Sept 2010	Antacids Antibiotics Antispasmodic agents Behavioral therapy Gas remedies H_2 receptor blockers Low-dose antidepressants Prokinetic agents Proton pump inhibitors	Postprandial fullness Early satiety Decreased upper abdominal bloating Improved rate of gastric emptying Improved gastric accommodation Improved quality of life
Allogeneic precultured adult bone marrow–derived mesenchymal stem cells remestemcel-L (Prochymal) for treatment of Crohn's disease	Patients in whom Crohn's disease has been diagnosed	Patients with Crohn's disease frequently experience damage to their bowels and require surgery; no regenerative therapies are approved. Remestemcel-L (Prochymal®) consists of allogeneic, bone marrow–derived human mesenchymal stem cells, which are purported to reduce inflammation and promote crypt regeneration in damaged intestine. The manufacturer has developed a specific "expansion" process for these cells, which are intended to be used off the shelf and delivered as an intravenous infusion. Administered in a clinical trial 3 times, 200 million cells per infusion, 42 days apart. Osiris Therapeutics, Inc., Columbia, MD Phase III trials ongoing; FDA granted fast track status	Autologous bone marrow–derived mesenchymal stromal cells (in development) Teduglutide (in development)	Increased disease remission Improved disease symptoms Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fecal microbiota transplantation for treatment of ulcerative colitis	Patients in whom ulcerative colitis (UC) has been diagnosed	Patients with UC have an abnormally and chronically activated immune system in the absence of any known invader, leading to periodic bouts of abdominal pain, diarrhea, and rectal bleeding. UC is typically treated with anti-inflammatory drugs with varied success, and Investigators have not found a long-term cure or strategy to prevent periodic disease flares besides surgery. Fecal microbiota transplantation is a procedure designed to restore balance to the microbiota of the bowel after it has been disturbed by antibiotics or other environmental changes in the colon, leading to the dominance of toxin-producing strains that can cause disease. Fecal matter from a healthy donor is collected and mixed with a solution and transplanted into the recipient via colonoscopy. Phase II trial ongoing; procedure may be adopted by gastroenterologists who are using the procedure for treating recurrent *Clostridium difficile* infection	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (e.g., prednisone) Immunomodulators (e.g., azathioprine) Monoclonal antibodies (e.g., natalizumab, infliximab)	Reduced relapse frequency Reduced use of medications Reduced symptoms Reduced or postponed need for surgery Improved quality of life
GSK1605786 (Traficet-EN) for treatment of Crohn's disease	Patients who have been given a diagnosis of moderate to severe Crohn's disease	GSK1605786 (Traficet-EN™) is an oral CCR9 antagonist. CCR9 is a chemokine receptor that plays a central role in the inappropriate inflammatory response thought to underlie Crohn's disease. By blocking CCR9, GSK'786 selectively impairs the movement of activated T cells that are involved in causing inflammation of the digestive tract. GlaxoSmithKline, Middlesex, UK Phase III trials ongoing	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (e.g., prednisone) Immunomodulators (e.g., azathioprine) Monoclonal antibodies (e.g., natalizumab, infliximab)	Delayed or avoided surgery Improved quality of life Reduced flares Reduced side effects Disease remission Symptom improvement
Helminthic therapy (pig whipworm) for treatment-resistant ulcerative colitis	Patients in whom treatment-resistant ulcerative colitis has been diagnosed	The rationale for pig whipworm therapy using *Trichuris suis* ova is that inflammatory bowel diseases are uncommon in developing countries where helminths are common and that people with helminth infection have an altered immunological response to antigens. In animal models, helminths prevent or improve colitis by the induction of regulatory T cells and modulatory cytokines. Parasites are obtained from U.S. Department of Agriculture. Patients ingest 2,500 pig whipworm eggs, every 2 weeks, for 3 months. University of California, San Francisco Trial ongoing at NYU School of Medicine; 2 trials completed; 1 for ulcerative colitis and 1 for Crohn's disease	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (e.g., prednisone) Immunomodulators (e.g., azathioprine) Monoclonal antibodies (e.g., natalizumab, infliximab)	Increased safety Reduced flare symptoms Maintained remission Reduced or postponed need for surgery Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
JAK 3 kinase inhibitor (tofacitinib) for treatment of ulcerative colitis	Patients in whom ulcerative colitis (UC) has been diagnosed	Current therapies for UC temporarily control symptoms and are poorly tolerated in some patients. Tofacitinib is an oral tyrosine kinase inhibitor specifically targeting the Janus kinase-3 (JAK 3) signaling pathway believed to mediate several processes involved in chronic inflammatory diseases, such as antibody production by B cells, production of rheumatic factor, and activation of T cells. By inhibiting the JAK 3 pathway, tofacitinib might suppress the inflammatory reactions that are the basis of UC. Tofacitinib has been administered twice daily (0.5, 1, 3, 5, 10, and 15 mg) doses. Pfizer, Inc., New York, NY Phase III trial ongoing	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (e.g., prednisone) Immunomodulators (e.g., azathioprine) Monoclonal antibodies (e.g., natalizumab, infliximab)	Improved clinical response Reduced flare symptoms Reduced or postponed need for surgery Improved quality of life
Linaclotide (Linzess) for treatment of irritable bowel syndrome with constipation	Patients in whom irritable bowel syndrome (IBS) with constipation has been diagnosed	Linaclotide (Linzess™) is a peptide agonist of guanylate cyclase 2C located on the luminal surface of the intestine. In preclinical models, linaclotide was purported to reduce visceral hypersensitivity, increased fluid secretion, and accelerate intestinal transit. Linaclotide is taken orally, once daily, 290 mcg. Ironwood Pharmaceuticals, Cambridge, MA FDA approved Aug 2012 to treat chronic idiopathic constipation and to treat irritable bowel syndrome with constipation (IBS-C) in adults; approval included a warning that it should not be given to patients aged 16 years or younger	Antispasmodic drugs Laxatives Serotonin agonists Tricyclic antidepressants	Reduced abdominal pain and constipation symptoms Long-term relief
Magnetically guided capsule endoscopy for diagnosis of gastrointestinal disorders	Patients appropriate for gastrointestinal (GI) endoscopic examinations	Current GI endoscopic procedures are invasive, require sedation, and have low rates of patient acceptance and satisfaction. Additionally, existing capsule endoscopy technology does not enable clinicians to guide the capsule as it travels through the GI tract to ensure images of desired areas are captured. Magnetically guided capsule endoscopy is intended to allow the clinician more control of where the capsule travels and captures images; the patient swallows a capsule, which wirelessly transmits images to processing system, as the clinician navigates the capsule via a joystick and a magnetic field. The procedure is noninvasive and requires no sedation. Siemens AG, Munich, Germany Olympus Corp., Tokyo, Japan Unphased trial ongoing	Endoscope procedure Pill Cam	Increased sensitivity and specificity Positive and negative predictive values Improved diagnostic accuracy Impact on clinical decisionmaking for managing symptoms

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
MuDelta (JNJ-27018966) for treatment of diarrhea-predominant irritable bowel syndrome	Patients in whom diarrhea-predominant irritable bowel syndrome (IBS-d) has been diagnosed	MuDelta is a mu-opioid receptor agonist and delta-opioid receptor antagonist that may provide relief for both pain and diarrheal symptoms of IBS-d without the constipating effects typically seen with mu receptor agonists. Pharmacology data suggest that MuDelta acts locally in the digestive tract, thus having a low potential for systemic side effects. Furiex Pharmaceuticals, Morrisville, NC Phase III trials ongoing; received fast track status from FDA Jan 2011	Antispasmodic drugs Opioids Serotonin agonists Tricyclic antidepressants	Reduced abdominal pain and bloating symptoms Long-term relief
PerOral endoscopic myotomy for treatment of esophageal achalasia	Patients in whom esophageal achalasia has been diagnosed	Current surgical treatment for esophageal achalasia generally requires at least 5 abdominal incisions to access the blocked esophageal pathway. PerOral endoscopic myotomy is a procedure proposed for treating esophageal achalasia by inserting an endoscope through the mouth and esophagus, allowing surgeons to directly cut abnormal muscle fibers of the lower esophageal sphincter at the base of the esophagus. It is intended to allow food to enter the stomach, and the procedure purportedly is less invasive, thereby potentially reducing complications, recovery time, and pain. Northwestern Memorial Hospital, Chicago, IL Phase IV trial ongoing	Heller myotomy	Improved Esophageal Function Tests (upper endoscopy, barium swallow, esophageal manometry, pH test) scores Improved quality of life
Plecanatide (SP-304) for treatment of chronic idiopathic constipation	Patients in whom chronic idiopathic constipation has been diagnosed	Current treatments for constipation are ineffective or poorly tolerated in some patients. Effective, well tolerated therapies are needed. Plecanatide is a synthetic peptide uroguanylin analog that targets guanylate cyclase C receptors in the gastrointestinal (GI) tract. Uroguanylin is a natural peptide hormone that regulates ion and fluid transport in the GI tract. Plecanatide is purported to be more potent than uroguanylin. It may be used to treat chronic constipation or constipation-predominant irritable bowel syndrome. In trials, it is being administered orally, 0.3–9.0 mg, once daily. Synergy Pharmaceuticals, Inc., New York, NY Phase II/III trial ongoing	Enemas Laxatives Lubiprostone	Decreased straining and abdominal discomfort Increased frequency of bowel movements Improved stool consistency Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Rifaximin (Xifaxan) for treatment of nonconstipating irritable bowel syndrome	Patients in whom nonconstipating irritable bowel syndrome has been diagnosed	Rifaximin (Xifaxan®) is a nonabsorbable oral antibiotic approved for treating traveler's diarrhea. Salix Pharmaceuticals, Inc., Morrisville, NC Phase III trial ongoing; company received complete response letter from FDA Mar 2011, received advice from FDA advisory committee	Antispasmodic drugs Opioids Serotonin agonists Tricyclic antidepressants	Reduced abdominal pain and bloating symptoms Long term relief
Spherical carbon adsorbent (AST-120, Zysa) for treatment of diarrhea-predominant irritable bowel syndrome	Patients in whom diarrhea-predominant irritable bowel syndrome (IBS-d) has been diagnosed	Current treatments for IBS-d are purported to be ineffective in many patients, and no new treatment options have been available for decades. The only approved treatment in the U.S. for IBS-d is alosetron, and this intervention is associated with safety issues. Other treatments include off-label antispasmodic agents and antidepressants and probiotics. AST-120 (Zysa™) is an oral spherical carbon adsorbent purported to bind to and neutralize the activity of several compounds associated with IBS-d pathogenesis as well as ammonia, indoles (serotonin), histamine, bile acids, advanced glycation endproducts, and certain bacterial toxins. By binding and neutralizing toxins in the gut, AST-120 could relieve IBS-d symptoms. Ocera Therapeutics, Inc., San Diego, CA Phase II trial completed; FDA granted fast track status	Antispasmodic drugs Opioid receptor agonist in development Opioids Serotonin agonists Tricyclic antidepressants	Reduced abdominal pain and bloating Long-term relief
Teduglutide (Gattex) for treatment of short bowel syndrome	Patients in whom short bowel syndrome (SBS) has been diagnosed	SBS typically arises after extensive resection of the bowel because of Crohn's disease and is a highly disabling condition that can lead to serious, life-threatening complications as well as malnutrition, severe diarrhea, dehydration, fatigue, osteopenia, and weight loss due to the reduced intestinal absorption. Current treatments supplement and stabilize nutritional needs; however, parenteral support does not improve absorption and is associated with infections, blood clots, liver damage, poor quality of life, and high costs. Teduglutide (Gattex™) is a recombinant analog of human glucagon-like peptide 2 that purportedly increases nutrient absorption and intestinal cell growth in patients with SBS. NPS Pharmaceuticals, Inc., Bedminster, NJ Phase III trials ongoing; FDA approved Dec 2012 for treating SBS	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
Vedolizumab for treatment of moderate to severe ulcerative colitis	Patients in whom moderate to severe ulcerative colitis (UC) has been diagnosed	Vedolizumab is an infused monoclonal antibody; current treatments for UC have limited effectiveness; the only cure is surgery. This may provide an alternative treatment. Millennium Pharmaceuticals unit of Takeda Pharmaceutical Co., Ltd., Osaka, Japan Phase III trial ongoing	Aminosalicylates (mesalazine) Antibiotics (for acute flares) Corticosteroids (e.g., prednisone) Immunomodulators (e.g., azathioprine) Monoclonal antibodies (e.g., natalizumab, infliximab)	Reduced flare symptoms Maintained remission Reduced or postponed need for surgery Improved quality of life

Table 12. AHRQ Priority Condition: 12 Pregnancy, Including Preterm Birth: 11 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Blood test (ProNid) to predict spontaneous preterm birth	Pregnant women	About 1 in 10 pregnant women have a spontaneous preterm birth in the U.S. each year; however, no diagnostic test is available to identify women at risk of preterm birth early in pregnancy to plan preterm birth prevention strategies. Sera Prognostics has developed ProNid™, a panel of proteomic markers that purportedly indicates the likelihood of spontaneous preterm birth. The proteomic assay is performed on a blood sample taken at 28 weeks of pregnancy. Sera Prognostics, Salt Lake City, UT Validation study ongoing on 3,000 patients to develop as a commercial assay	Home uterine activity monitoring Salivary estriol testing Fetal fibronectin Detection of bacterial vaginosis Assessment of cervical length	Earlier intervention for women at risk of preterm birth Reduced incidence of preterm birth Reduced neonatal complications Reduced use of neonatal intensive care services
Copolymer styrene maleic anhydride/dimethyl sulfoxide (Vasalgel) for male contraception	Male patients pursuing contraception	Vasalgel™ is a male contraceptive intended to inhibit sperm under guidance. It is a copolymer styrene maleic anhydride/dimethyl sulfoxide that becomes hydrated in seminal fluid and degrades sperm cell membrane as sperm attempts to pass through vas deferens. It purportedly provides a safer, less costly alternative to contraception and is intended to be reversible. One dose injected into vas deferens every 10 years. Indian Institute of Technology, Powai, Mumbai, India Phase III clinical trials ongoing (in India); has secured a U.S. patent with intent to bring to U.S. market	Condoms Vasectomy	Long-acting male contraception
Daily text messaging to encourage oral contraceptive continuation	Patients using an oral contraceptive pill (OCP)	63% of reproductive-age women who practice contraception use nonpermanent methods, with OCP as the leading method for women younger than 30 years of age. On average, 6-month OCP continuation rates in young women range from 12% to 58%. In the U.S., OCP discontinuation and misuse cause about 1 million unintended pregnancies a year. The OCP daily text messaging study evaluates the efficacy of a 2-way text-messaging program intended to deliver educational content on OCP continuation. This intervention is intended to reduce OCP discontinuation rates, especially for women in urban settings. Columbia University Medical Center Department of Obstetrics and Gynecology, New York, NY Pilot trials completed	Educational therapy Routine care	Increased OCP continuation Decreased risk of pregnancy

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Donor human milk program to feed very-low-birthweight infants	Very-low-birthweight infants (VLBW; less than 1,501 g weight at birth)	Women who give birth to infants of VLBW who must remain in the neonatal intensive care unit often are unable to supply any or sufficient breast milk. Donated breast milk for infants of VLBW whose mothers cannot supply sufficient breast milk purportedly leads to better health and neurodevelopmental outcomes for premature infants than preterm infants fed fortified formula. The milk is collected from lactating volunteers and should be screened for safety before administration to infants. Available through the Human Milk Banking Association of North America and commercially through Prolacta Bioscience, Inc., Monrovia, CA Phase III trials completed; others ongoing	Standard infant formula	Reduced health care costs Normal Bayley Scales of Infant Development, III (at 18–22 months of age)
Fetal programming to prevent metabolic disorders	Pregnant women	Many metabolic abnormalities may stem from the fetal environment and how the fetus' metabolism becomes established during pregnancy; measures taken to ensure healthy fetal development include adherence to prenatal vitamin intake and routine prenatal care. Fetal programming (FP) is a comprehensive concept that aims to enhance a child's metabolism into adulthood by using drug therapy, nutritional supplements, and enhanced nutrition during pregnancy. FP aims to decrease risk of many adult diseases, including coronary artery disease, breast cancer, and diabetes, by improving the uterine environment through programming of hormone-production levels with intention of maintaining healthy organ function throughout life. An example of FP is treating obese pregnant women with metformin even if they do not have a diagnosis of diabetes because blood glucose levels tend to be higher during pregnancy and glucose may pass through the placenta to the fetus. University of Edinburgh, Scotland, UK Pilot trial ongoing	Nutritional programs alone for pregnant women Prenatal vitamins alone Routine prenatal care	Improved health in newborns Decreased risk of development of metabolic disorders

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Gonadotropin-releasing hormone antagonist (Elagolix) for treatment of endometriosis	Patients in whom endometriosis has been diagnosed	Elagolix is the 1st oral nonpeptide gonadotropin-releasing hormone (GnRH) antagonist that, unlike available injectable GnRH agonists (which take up to several weeks to work), has a rapid onset in suppressing hormones (stops ovulation and endometriosis symptoms) without a hormonal flare or injection site reactions; titration might made it possible to maintain appropriate levels of estrogen, thus preventing menopausal-like hormonal levels and the need for management of bone loss while treating endometriosis. Neurocrine Biosciences, Inc., San Diego, CA Phase III trial ongoing	Pharmacotherapy (e.g., hormonal contraceptives, steroids) Surgical intervention (e.g., endometrial growth and scar tissue excision, hysterectomy)	Improved composite pelvic signs and symptoms score (measures dysmenorrhea, nonmenstrual pelvic pain, dyspareunia, pelvic tenderness and induration) Maintained bone mineral density Improved patient global impression of change Less pain (visual analog scale)
In utero fetal catheterization procedure for treatment of hypoplastic left heart syndrome	Pregnant women receiving a diagnosis of fetal hypoplastic left heart syndrome (HLHS)	HLHS is a congenital condition in which parts of the heart's left side do not completely develop (i.e., aorta, aortic valve, mitral valve). It occurs in about 1 in 6,000 live births. Once a baby with HLHS is born, treatment protocol involves admitting the patient to the neonatal intensive care unit, placing the neonate on a ventilator, and giving prostaglandin E1 to keep the ductus arteriosus patent. Texas Children's Fetal Center has created a fetal in utero catheterization program to better stabilize the baby at time of birth before undergoing phase I of HLHS surgery. Each fetal intervention procedure is specialized to the needs of the patient and depends on the specific cardiac malformation. For example, catheterization could occur in the aortic valve for a fetus with severe aortic stenosis that typically develops into HLHS, allowing blood to circulate throughout the entire body. Catheterization could also occur across the atrial valve (AV septum), connecting the 2 atrial chambers and allowing blood to pass through the heart's other side. In this case, a stent may also be placed to help sustain the patency of the hole created between the atrial chambers. These techniques can help blood pass to the left side of the heart, allowing the baby to become more oxygenated and increasing odds of postnatal survival. Texas Children's Fetal Center of Texas Children's Hospital, Houston, TX 4-patient surgical trial completed	Neonatal surgery	Increased oxygenation to fetus Increased survival to live birth Increased postnatal survival

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Nurse home visits to reduce second pregnancies in high-risk mothers	Low-income, high-risk mothers	Nurse home-visitation programs in which information on women's health, preconception health, and family planning is provided to low-income women who have delivered 1 child and are at high risk of a 2nd unplanned pregnancy. Children's Hospital of Philadelphia, Philadelphia, PA Pennsylvania Department of Public Welfare Pilot trial completed	Family planning clinics Healthy Start (Health Resources & Services Administration) Lay women home visitation programs (e.g., Resource Mothers, Promotoras)	Improved maternal and child health outcomes Improved planning of subsequent pregnancies
Off-label n-acetylcysteine for treatment of intra-amniotic infection and inflammation during pregnancy	Pregnant women with intra-amniotic infection and/or inflammation	Intra-amniotic inflammation in utero early in gestation is thought to possibly trigger a cascade of events that lead to preterm birth (i.e., premature rupture of membranes, cervical ripening, uterine contractions). N-acetylcysteine (NAC), an antioxidant, is a derivative of amino acid, L-cysteine, and mucolytic agent. It is proposed for treating pregnant women with intra-amniotic infection to prevent adverse neonatal outcomes by potentially reducing intracellular concentration of free radicals and cell damage. Administered intravenously. Yale University, New Haven, CT Phase II trial ongoing	Standard pharmacotherapy without NAC	Reduced early onset neonatal sepsis Prevention of neonatal death
Ulipristal acetate (CDB-2914) for treatment of uterine fibroids and excessive uterine bleeding	Premenopausal women in whom symptomatic uterine fibroids have been diagnosed	Uterine fibroids are the most common benign tumor in women, with some fibroids causing excessive pain and bleeding. Available therapies can work with limited efficacy, marking a need for more novel treatment. Ulipristal acetate (CDB-2914; EllaOne®) is a selective P receptor modulator with antiprogestin effects. Given orally, 10 or 20 mg, once daily. Laboratoire HRA Pharma, SA, Paris, France Phase IIb and phase III trials ongoing	Cryomyolysis ExAblate Gonadotropin-releasing hormone agonists Hysterectomy Uterine artery embolization	Avoided or delayed hysterectomy Reduced total fibroid volume Prevention of anemia due to heavy menstrual bleeding Reduced symptoms (e.g., pain) Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Vending machine dispensers for emergency oral contraceptives (Plan B One Step) to prevent pregnancy	Women at risk of pregnancy	According to the U.S. Centers for Disease Control and Prevention, about 50% of pregnancies in the U.S. are unintended. Women in underserved areas are at increased risk of unintended pregnancies. Access, fear of others' perception, and cost are several determinants in emergency contraceptive use. Shippensburg University in Pennsylvania has incorporated an emergency contraceptive, or "morning after pill," vending machine into the student health center, charging $25 for each dose for students 17 years of age or older. The vending machine also includes other reproductive health products, including condoms and pregnancy test kits. Shippensburg University, Shippensburg, PA Not yet subject to FDA approval	Over-the-counter access to emergency contraceptives	Decreased risk of pregnancy Increased emergency contraceptive use Increased risk of adverse events associated with emergency contraception

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Ataluren for treatment of nonsense mutation cystic fibrosis	Patients in whom cystic fibrosis (CF) due to a nonsense mutation (nmCF) has been diagnosed	No treatments are available that address the cause of CF rather than only the symptoms. Ataluren is a protein-restoration therapy designed to enable the formation of full-length, functional cystic fibrosis transmembrane regulator (CFTR) protein in patients with nmCF; nonsense mutations are the cause of CF in an estimated 10% of U.S. and EU cases and more than 50% of CF cases in Israel. Ataluren is intended to improve lung function, which could lead to improved survival. PTC Therapeutics, Inc., South Plainfield, NJ Phase III trials ongoing; FDA granted orphan drug status	Antibiotics Bi-level positive airway pressure ventilators Bronchodilators (albuterol or salmeterol) Chest physiotherapy DNase (such as Pulmozyme®) Gene therapies (viral vector or liposome delivery of normal *CFTR*; investigational) Hypertonic saline Mucolytics (acetylcysteine)	Improved lung function Increased survival Reduced need for additional therapies Improved quality of life
Endobronchial valve system (Zephyr) for treatment of heterogeneous emphysema	Patients in whom heterogeneous emphysema has been diagnosed	This implanted endobronchial valve system (Zephyr®) is intended as a minimally invasive method to treat hyperinflation in the lungs. The device is intended to reduce a patient's diseased lung volume without surgery. According to the company, the procedure involves placing "small, one-way valves in targeted airways to direct the flow of air out of diseased portions of the lung." Clinicians typically place 3–4 valves per lobe during a procedure, and the total procedural time purportedly takes 15–30 minutes, depending on the number of valves placed. The valves are coated with medical-grade silicone to prevent tissue growth through the nitinol retainer. Pulmonx, Inc. (formerly Emphasys), Redwood City, CA Phase III trial ongoing	Antibiotics Bronchodilators Corticosteroids Oxygen Pulmonary rehabilitation program Surgery: lung-reduction volume surgery, bullectomy, lung transplantation	Improved lung function Improved activities of daily living Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
GPS and Wi-Fi-enabled inhaler (Spiroscout) for treatment of asthma	Patients in whom asthma has been diagnosed	The few alternatives available for asthma patient data recording may introduce patient error, leading to less accurate and more subjective judgments about when inhaler doses are needed. The GPS and Wi-Fi-enabled inhaler (Spiroscout®) is a device that attaches to the top of a metered-dose inhaler, using GPS and Wi-Fi to accurately record time, geographic location, and frequency of inhaler use. The information is sent to a central server/database for analysis, and physicians and epidemiologists can use the information to make determinations about events and environments correlating to patients' inhaler use. If implemented, Spiroscout might provide an affordable and more accurate way for both physicians and patients to decrease triggers to asthma and consequent dependence on asthma inhalers. Spiroscout takes 1 reading per inhaler use. Asthmapolis, Madison, WI Received 510(k) clearance Jul 2012	Self-recorded logs (hand-written, mobile, Web)	Reduced need for recording logs for patients with asthma Enhanced detection of triggers for asthma Reduced health disparities Improved quality of life
Inhaled amikacin (Arikace) for treatment of nontuberculous *Mycobacteria* infection	Patients in whom pulmonary nontuberculous mycobacterial (NTM) lung infection has been diagnosed	Most NTM infections are resistant to many common antibiotics, and NTM infection requires treatment with lengthy multidrug regimens. Few effective treatments exist. Amikacin, an approved antibiotic against a variety of NTM, is a semisynthetic aminoglycoside derived from kanamycin. Arikace® is being developed as a sustained-release formulation of amikacin encapsulated inside small fat particles using an optimized, investigational eFlow® Nebulizer System. Arikace is intended to deliver higher levels of drug to the lungs than previously possible through current formulations of amikacin while also minimizing systemic exposure to the drug. Administration is via inhalation, once daily. Insmed, Inc., Richmond, VA Phase II recruiting with results expected in 2013; FDA granted orphan drug status. Arikace is approved for other indications and is sometimes used off-label for NTM indication, but existing formulation is not intended for that use and trials are ongoing for the NTM indication.	Amikacin (injectable) Other antibiotics such as: Amoxicillin/clavulanate Capreomycin Clarithromycin Clofazimine Ethambutol Ethionamide Fluoroquinolones Imipenem/cilastatin Isoniazid Kanamycin Linezolid p-Aminosalicylic acid Prothionamide Pyrazinamide Streptomycin Terizidone Thioacetazone	Resolved abnormalities as seen on computed tomographic scan Higher rate of culture conversion to negative Improved 6-minute walk distance and oxygen saturation Extended time before need for "rescue" antimycobacterial drugs

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Inhaled mannitol (Bronchitol) for treatment of mucus in noncystic-fibrosis bronchiectasis and cystic fibrosis	Patients in whom cystic fibrosis (CF) or non-CF bronchiectasis has been diagnosed	No curative treatments exist for CF or non-CF bronchiectasis mucus accumulation. Treatment is aimed at controlling infections, secretions, airway obstructions, and complications; no product is available to effectively clear excess mucus secretions. Bronchitol is a new approach, a proprietary formulation of mannitol administered as a dry powder through a handheld inhaler. It is being developed to reduce the amount of mucus buildup in the lungs. Restoration of airway surface liquid by hydration of the lungs could help restore normal lung clearance and clear excess mucus. Pharmaxis, Ltd., Frenchs Forest, Australia Phase III trial completed; FDA accepted new drug application in Aug 2012. FDA decision date is expected in the 2nd quarter of 2013	Cystic fibrosis: Antibiotics Bilevel positive airway pressure ventilators Bronchodilators (albuterol or salmeterol) Chest physiotherapy DNase (such as Pulmozyme®) Gene therapies (viral vector or liposome delivery of normal *CFTR*; investigational) Hypertonic saline Mucolytics (acetylcysteine) Noncystic-fibrosis bronchiectasis: Oxygen supplementation	Improved lung function Reduced pulmonary exacerbations Reduced antibiotic use Improved quality of life
Interleukin-5 antagonist (mepolizumab, Bosatria) for treatment of eosinophilic asthma	Patients in whom eosinophilic asthma has been diagnosed	Eosinophilic asthma occurs in about 30% of patients with severe uncontrolled asthma. Uncontrolled asthma can lead to hospitalization or death. Patients with severe asthma must take systemic corticosteroids that can lead to adverse events. Mepolizumab (Bosatria®) is a humanized monoclonal antibody designed to bind and inhibit the activity of interleukin-5 (IL-5). IL-5 purportedly plays a crucial role in the maturation, growth, and chemotaxis (movement) of eosinophils, inflammatory white blood cells implicated in asthma and not found in the lungs under normal circumstances. Administered intravenously, 75, 250, or 750 mg, every 4 weeks. GlaxoSmithKline, Middlesex, UK Phase III trial ongoing	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long-acting beta agonists Omalizumab (Xolair) Reslizumab (in development) Short-acting beta agonists Theophylline	Improved asthma control Improved asthma exacerbation rate Reduced emergency room visits Reduced hospitalization Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interleukin-5 antagonist (reslizumab, Cinquil) for treatment of eosinophilic asthma	Patients in whom eosinophilic asthma has been diagnosed	Eosinophilic asthma occurs in about 30% of patients with severe uncontrolled asthma. Uncontrolled asthma can lead to hospitalization or death. Patients with severe asthma must take systemic corticosteroids that can lead to adverse events. Reslizumab (Cinquil™) is a humanized monoclonal antibody designed to bind and inhibit the activity of interleukin-5 (IL-5). IL-5 purportedly plays a crucial role in the maturation, growth, and chemotaxis (movement) of eosinophils, inflammatory white blood cells implicated in asthma and not found in the lungs under normal circumstances. Cephalon, Inc., acquired by Teva Pharmaceutical Industries, Ltd., Petach Tikva, Israel, Oct 2011 Phase III trials ongoing	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long-acting beta agonists Mepolizumab (in development) Omalizumab (Xolair) Short-acting beta agonists Theophylline	Improved asthma control Improved asthma exacerbation rate Reduced emergency room visits Reduced hospitalization Improved quality of life
Ivacaftor (Kalydeco) for treatment of cystic fibrosis in patients with *G551D-CFTR* mutation	Patients 6 years of age or older with cystic fibrosis (CF) who have the *G551D-CFTR* gene mutation (10% to 15% of patients with CF)	Ivacaftor (Kalydeco™) is intended to improve lung function by improving function of mutant cystic fibrosis transmembrane conductance regulator (CFTR) protein; regulator protein is an epithelial ion channel involved in salt and fluid transport. Administered orally, 150 mg, twice daily, with fat-containing food. Vertex Pharmaceuticals, Inc., Cambridge, MA Phase III trial ongoing; FDA approved Jan 2012 for patients with CF who are aged 6 years or older with the G551D mutation	No treatment available for the cause of the gene mutation	Reduced lung damage 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	About 10% of patients with asthma do not respond to high doses of inhaled corticosteroids and long-acting beta$_2$ antagonists. Uncontrolled asthma can lead to hospitalization or death. Patients with severe asthma must take systemic corticosteroids that can lead to adverse events. Masitinib is an orally administered tyrosine kinase inhibitor that purportedly targets the activity of mast cells, which are involved in triggering asthma attacks. Masitinib purportedly targets mast cells through selectively inhibiting KIT, platelet-derived growth factor receptor, Lyn, and, to a lesser extent, fibroblast growth factor receptor 3. Masitinib is administered orally, 6 mg/kg of body weight daily, in clinical trials. AB Science S.A., Paris, France Phase III trial ongoing	Bronchial thermoplasty Inhaled corticosteroids Ipratropium (Atrovent) Leukotriene modifiers Long-acting beta agonists Omalizumab (Xolair) Short-acting beta agonists Theophylline	Improved asthma control Improved asthma exacerbation rate Reduced emergency room visits Reduced hospitalization Improved quality of life

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Lung volume reduction coil (RePneu) for treatment of emphysema	Patients with upper and/or lower lobe heterogeneous emphysema and/or multiple emphysematous lobes with focal tissue defects	Treatment for advanced emphysema involves lung volume reduction (LVR) surgery, and a less invasive approach to LVR is desirable. RePneu™ is a minimally invasive procedure intended to reduce lung volume by implanting devices that compress the volume of diseased hyperinflated lung tissue to make room the healthier lung tissue to function. RePneu is a wire-like device described as a lung volume nitinol preformed coil; intended to compress the volume of lung tissue where deployed and is delivered to the lung uncoiled (in a straight line) using a bronchoscope and fluoroscopic visualization (conscious sedation or general anesthesia). About 10 coils are delivered during a procedure; once deployed in the desired locations of the diseased alveolar tissue, the catheter is retracted and the coils regain their original curved shape, pulling and compressing diseased hyperinflated tissue to reduce the lung volume and enable healthy lung tissue to expand and contract to improve breathing. PneumRx, Inc., Mountain View, CA Pivotal phase III trial ongoing; Conformité Européene (CE) marked Oct 2010	Antibiotics Bronchodilators Corticosteroids Oxygen Pulmonary rehabilitation program Surgery: lung-reduction volume surgery, bullectomy, lung transplantation	Improved lung function, physical endurance and activities of daily living Improved scores in St. George's Respiratory Questionnaire (which measures impaired health and perceived well-being in airways disease)
Multikinase inhibitor (nintedanib, BIBF-1120) to preserve lung function in idiopathic pulmonary fibrosis	Patients in whom idiopathic pulmonary fibrosis (IPF) has been diagnosed	IPF is a progressive, debilitating disease characterized by inflammation and scarring (fibrosis) in the lungs, with a median survival time from diagnosis of 2–5 years; 5-year survival rate is about 20%. No approved treatments are available. BIBF-1120 (nintedanib) is a tyrosine kinase inhibitor that has activity against vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and fibroblast growth factor receptor tyrosine kinases, which regulate tumor growth and angiogenesis. Nintedanib is under study for treating IPF and slowing of disease progression and symptoms. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trials ongoing	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Methotrexate Penicillamine Pirfenidone (investigational) Pulmonary rehabilitation Supplemental oxygen	Improved lung function measured by forced vital capacity Improved ability to perform activities of daily living Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label azithromycin for prevention of chronic obstructive pulmonary disease exacerbations	Patients in whom chronic obstructive pulmonary disease (COPD) has been diagnosed	Patients experiencing severe acute exacerbations of COPD have a greater 30-day mortality rate than patients experiencing acute myocardial infarction. Acute exacerbations of COPD dramatically change the course of the disease and are associated with a rapid decline in lung function and worsening quality of life; better treatments are needed. Antibiotics have been used to prevent COPD exacerbations; however, they were shown to be ineffective. Recently macrolide antibiotics have been selected to prevent COPD exacerbations because of their purported antibacterial action combined with immunomodulatory and anti-inflammatory properties. Administered orally, 250 mg, once daily, for 1 year to prevent COPD exacerbations. University of Colorado Denver Health Sciences Center Phase III trials ongoing; FDA approved in 1992 for treating community-acquired respiratory infections and skin infections	Glucocorticoids Long-acting anticholinergic agents Long-acting beta2-agonists Roflumilast	Reduced cost due to exacerbations Reduced incidence of exacerbations Increased survival Improved quality of life
Pirfenidone (Esbriet) for treatment of idiopathic pulmonary fibrosis	Patients in whom idiopathic pulmonary fibrosis (IPF) has been diagnosed	IPF is a progressive, debilitating disease characterized by inflammation and scarring (fibrosis) in the lungs, with a median survival time from diagnosis of 2–5 years; 5-year survival rate is about 20%. No approved treatments are available. Pirfenidone (Esbriet®) is a small molecule that inhibits the synthesis of transforming growth factor-beta, which purportedly is involved in fibrosis, and tumor necrosis factor alpha, which is involved in mediating inflammation. The drug is administered orally. InterMune, Inc., Brisbane, CA Phase III trials ongoing; FDA granted fast track and orphan drug status	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Intedanib (investigational) Methotrexate Penicillamine Pulmonary rehabilitation Supplemental oxygen	Improved ability to perform activities of daily living Improved lung function measured by forced vital capacity Slowed disease progression Improved quality of life
Temperature controlled laminar air-flow device (Protexo) for treatment of atopic asthma	Patients in whom atopic asthma has been diagnosed	Despite pharmaceutical treatment and lifestyle modification, many patients continue to have difficulty controlling asthma symptoms. Protexo® is a temperature-controlled laminar air-flow device that is positioned over the patient while he or she sleeps. The device purportedly creates a downward flow of filtered air that surrounds the sleeping patient's breathing zone with the intention of providing air in convection currents that is free of allergens and irritants. Airsonett AB, Ängelholm, Sweden Phase III trials completed	Air purifiers Antiallergenic pillow/mattress encasements Home heating, ventilation, and air conditioning systems	Reduced asthma symptoms Improved peak nasal inspiratory flow Improved sleep quality Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
VX-809 for treatment of cystic fibrosis	Patients with cystic fibrosis (CF) who have the delta F508-*CFTR* gene mutation	No curative treatments exist for CF or non-CF bronchiectasis mucus accumulation. Treatment is aimed at controlling infections, secretions, airway obstructions, and complications; no product is available to effectively clear excess mucus secretions. VX-809 is considered a corrector of the cystic fibrosis transmembrane regulator (*CFTR*) gene mutation; intended to increase regulator's function by increasing its movement to the cell surface. Given as oral monotherapy and in combination with ivacaftor (Vertex's other CF drug). Vertex Pharmaceuticals, Inc., Cambridge, MA Phase II trial ongoing; FDA granted orphan drug and fast-track status	Antibiotics Bilevel positive airway pressure ventilators Bronchodilators (albuterol or salmeterol) Chest physiotherapy DNase (such as Pulmozyme®) Gene therapies (viral vector or liposome delivery of normal *CFTR*; investigational) Hypertonic saline Mucolytics (acetylcysteine	Improved lung function Increased survival Improved quality of life Reduced need for additional therapies

Table 14. AHRQ Priority Condition: 14 Substance Abuse: 10 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Buprenorphine implants (Probuphine) for treatment of opioid dependence	Patients in whom opioid dependence has been diagnosed	Many patients with opioid dependence attempt abstinence, but relapse rates remain high. 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 (manufacturer) Braeburn Pharmaceuticals subsidiary of Apple Tree Partners, New York, NY (licensee) Phase III confirmatory trial completed; new drug application submitted Oct 2012	Opioid maintenance/replacement therapy (e.g., buprenorphine, methadone, naltrexone) Psychotherapy (e.g., cognitive behavioral therapy)	Resolution of problems with adherence, diversion Reduced illicit use of opioids Improved health outcomes associated with abstinence Improved quality of life
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. 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, no longer recruiting. Vigabatrin is approved for use in patients with epilepsy, but is being redeveloped for cocaine-addiction treatment by a different company.	Off-label pharmacotherapy (e.g., disulfiram) Psychotherapy (e.g., cognitive behavior therapy)	Reduced reward associated with cocaine use Reduced cocaine consumption Prevented relapse Improved health outcomes associated with abstinence Improved quality of life
Handheld, portable fingerprinting device (Intelligent Fingerprinting Technology) to detect substance abuse	Individuals suspected of illicit drug use	Detection of drugs and their metabolites in body fluids (e.g., blood, urine, saliva) is limited by invasiveness, biohazard risks, cross reactivity with other substances in the samples, a requirement for cold or frozen sample transport and storage, susceptibility to contamination leading to false positives, and the potential for a person to undermine the test. To address these limitations, a manufacturer has developed Intelligent Fingerprinting Technology, a handheld fingerprint drug testing device that analyzes the minute traces of sweat deposited in subjects' fingerprints. According to the manufacturer, the technology detects drug metabolites, not the drug itself. Additionally, the company purports that samples are quick and easy to collect, are impossible to cheat, are stable at room temperature, and do not require additional sample preparation. The company is positioning this product for use by law enforcement and in workplaces and institutions (e.g., prisons, the military). SmartStart, Inc., Irving, TX, with Intelligent Fingerprinting, Norwich, UK U.S. launch planned for 2013	Other body fluid testing (urine, saliva, blood) Field sobriety tests	Improved detection of illicit substances Reduced invasiveness of drug testing Reduced turnaround time for drug testing Reduced biohazard risk Reduced risk of cross reactivity Improved health outcomes

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Interactive cell phone text message program (Text2Quit) for smoking cessation	Patients attempting smoking cessation	Although 75% of smokers want to quit smoking, fewer than 5% who attempt to quit are successful. Text2Quit is an interactive cell phone text-messaging program intended to help smokers stop smoking. The messaging system is intended to deliver customized educational content based on the user's own quit date; the program enables users to complete surveys to receive advice, play games to fight off cravings, select the best possible prescription or over-the-counter therapies as cessation aids, and collect data to help user monitor their achievement towards their own goals. It is designed to be especially useful for reaching underserved communities. The company intends to make the program available publicly and also through employers, health plans, and public health departments. Voxiva, Inc., and the George Washington University School of Public Health, both of Washington, DC Initial trials completed; program launched Jun 2011	One-way text messaging smoking cessation plans (not diffused) Hardcopy patient education Internet-based patient education Patient support groups Psychotherapy (e.g., cognitive behavior therapy)	Increased number of successful smoking cessation attempts Improved health outcomes associated with abstinence Reduced health disparities and improved access to cessation program 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	No therapies are indicated specifically for alcoholism secondary to PTSD disorder. Aprepitant (Emend®, approved for use in chemotherapy-induced nausea and vomiting) is a substance P antagonist that blocks neurokinin 1 receptor. Substance P, released in amygdala in response to stress, acts at neurokinin 1 receptors to mediate stress responses. Blocking the receptors represents novel approach (new target) for antistress actions; in alcoholism, it is intended to decrease alcohol cravings, attenuate cortisol response to stress, and decrease insula activation in response to negative sensory input. Merck & Co., Inc., Whitehouse Station, NJ (manufacturer) National Institute on Alcohol Abuse and Alcoholism (investigator) Phase II trial ongoing	Off-label pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone) Psychotherapy (e.g., cognitive behavior therapy)	Reduced alcohol consumption Reduced relapse Improved health outcomes associated with abstinence Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label aripiprazole (Abilify) for treatment of alcohol dependence	Patients in whom alcohol dependence has been diagnosed	Only 36% of patients with alcohol dependence experience full remission when using available pharmacotherapy. Aripiprazole is a dopamine partial agonist. Because dopamine is involved in the reward pathway that follows alcohol consumption, off-label use of aripiprazole may reduce the positive effects a person associates with consuming alcohol, thereby potentially reducing alcohol consumption. Additionally, this agent is associated with fewer negative side effects than other atypical antipsychotics, which are full agonists. In clinical trials, this drug is administered orally, daily. Bristol-Myers Squibb, New York, NY, and Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan (manufacturers) Medical University of South Carolina, Charleston (investigator) Phase III trial ongoing; drug is approved for treating bipolar disorder, schizophrenia, and major depressive disorder and is marketed as Abilify®; its manufacturers do not appear to be seeking a labeling expansion for this indication, and it would be used off label.	Pharmacotherapy (e.g. acamprosate, disulfiram, naltrexone) Psychotherapy (e.g., cognitive behavior therapy)	Reduced alcohol craving Reduced alcohol consumption Reduced relapse Reduced morbidity Improved long-term health outcomes associated with abstinence Improved quality of life
Off-label deep brain stimulation for treatment of alcohol dependence	Patients in whom treatment-refractory alcohol dependence has been diagnosed	Only 36% of patients with alcohol dependence experience full remission when using available pharmacotherapy. Deep brain stimulation (DBS) uses permanently implanted electrodes to electrically interfere with activity in targeted parts of the brain. DBS is approved for use in conditions such as Parkinson's disease and obsessive-compulsive disorder. Researchers have suggested that DBS may have utility in treating alcohol dependence because the electrodes can be placed in the ventral striatum/nucleus accumbens, which is an area known to play a role in upholding addictive behaviors. Medtronic, Inc., Minneapolis, MN (manufacturer) University of Cologne, Cologne, Germany (investigator) Several small pilot studies completed internationally; it does not appear that the manufacturer of the equipment used in these studies is seeking a labeled indication change for this product	Pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone) Psychotherapy (e.g., cognitive behavior therapy)	Reduced alcohol craving Reduced alcohol consumption Reduced relapse Improved health outcomes associated with abstinence Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label mifepristone (Mifeprex) for treatment of cocaine dependence	Patients in whom cocaine dependence has been diagnosed	No agents are approved for treating cocaine dependence. Mifepristone is a glucocorticoid receptor antagonist. Because cocaine dependence has been associated with glucocorticoid hormone hyperactivity, and because the glucocorticoid receptor has been found to mediate adaptation to environmental challenges and stress, mifepristone may have utility in reducing cocaine dependence. New York State Psychiatric Institute, New York The Scripps Research Institute, La Jolla, CA Phase II/III trial ongoing. Mifepristone is FDA approved to end early pregnancy and is marketed under the brand name Mifeprex® (Danco Laboratories, New York, NY); the manufacturer does not appear to be seeking a labeled indication for cocaine dependence; thus, it would be used off label for this indication	Off-label pharmacotherapy (e.g., disulfiram) Psychotherapy (e.g., cognitive behavioral therapy)	Reduced reward associated with cocaine use Reduced cocaine consumption Reduced relapse Improved health outcomes associated with abstinence Improved quality of life
Off-label olanzapine (Zyprexa) for treatment of alcohol dependence	Patients in whom alcohol dependence has been diagnosed	Only 36% of patients with alcohol dependence experience full remission when using available pharmacotherapy. Research has suggested that efficacy of pharmacotherapy is linked to genetic variants, leading researchers to conclude that no single agent will be found effective in the majority of individuals with alcohol dependence. Olanzapine (Zyprexa®) is an atypical antipsychotic that is approved for treating schizophrenia and bipolar disorder. Olanzapine is a D2/D4 antagonist, and research suggests that given the potential importance of the dopamine pathways (particularly the D4 receptor) in alcohol dependence and craving, the agent may have the ability to reduce craving for and consumption of alcohol, particularly patients with a variant in the gene that expresses D4 receptors. Eli Lilly and Co., Indianapolis, IN (manufacturer) Various academic centers, including The Mind Research Network, Albuquerque, NM (acquired Jan 2012 by Lovelace Respiratory Research Institute, also of Albuquerque); and University of Colorado, Boulder (investigators) Phase III trial completed; it does not appear that the drug's manufacturer is seeking this labeled indication change	Pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone) Psychotherapy (e.g., cognitive behavior therapy)	Reduced alcohol craving Reduced alcohol consumption Reduced relapse Improved health outcomes associated with abstinence Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label ondansetron for treatment of alcohol dependence	Patients in whom alcohol dependence has been diagnosed	Only 36% of patients with alcohol dependence fully recover when using available pharmacotherapy; serotonin 5-HT3 receptors are a novel therapeutic target for this population. Ondansetron is a serotonin 5-HT3 receptor antagonist, approved for treating chemotherapy-induced nausea and vomiting and 1st marketed by GlaxoSmithKline (Middlesex, UK) as Zofran®. The drug is intended to exert its effects on alcohol dependency through cortico-mesolimbic dopamine system modulation. The 5-HT system has been found to be a major regulator of the severity of alcohol consumption, which underpins the hypothesis that medications that affect the function of the 5-HT transporter may be viable treatments for this population. 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.) One phase III trial completed; several phase II and III trials ongoing	Pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone) Psychotherapy (e.g., cognitive behavior therapy)	Reduced alcohol craving Reduced alcohol consumption Reduced relapse Improved health outcomes associated with abstinence Improved quality of life

Table 15. AHRQ Priority Condition: 15 Cross-Cutting: 10 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Intelligent pills (The Raisin System) for chronic conditions requiring long-term drug therapy	Patients in whom long-term drug therapy is needed for various chronic conditions	According to the World Health Organization, however, the average medication adherence rate among patients with chronic diseases in developed nations is only 50%. The Raisin System™ a form of smart-pill technology, is being investigated to treat chronic diseases requiring ongoing medication, such as tuberculosis, diabetes, heart failure, AIDS, hepatitis C virus infection, and mental health disorders. This is an edible microchip affixed to oral drugs (tablets) to monitor patient adherence; wearable data recorder captures actual drug consumption and vital statistics, reminds patients of missed doses, and transmits patient data to clinicians. Proteus Biomedical, Inc., Redwood City, CA In Mar 2010, the company received marketing clearance from FDA for the monitoring device; in Jul 2012, the company also received marketing clearance for the ingestible sensor	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	Because of obstacles such as long waits for appointment times, lack of or insufficient insurance coverage, geographical dispersion, and transportation issues, many patients are unable or unwilling to routinely visit physicians for ongoing monitoring of symptoms. Also, physicians are backlogged because of the high number of routine cases they see in their offices. The Ideal Life® interactive wireless kiosk is intended to address this unmet need. The kiosk, placed in public areas (e.g., gyms, libraries) is intended to measure blood pressure, weight, blood glucose levels and other biometric readings, then wirelessly send the data to the patient's electronic health record. According to the manufacturer, the kiosk can detect when a patient experiences a sudden change in biometric parameters and in that case, will send the information to a physician or hospital emergency department for a quick decision on care. Ideal Life, Inc., Toronto, Ontario, Canada, and Sprint Corp., Overland Park, KS FDA approved for over-the-counter sales and launched in 2011; Health Insurance Portability and Accountability Act (patient privacy) compliant	Physical-presence appointments Phone-in data monitoring	Improved access to medical care Reduced health care disparities Decreased hospitalizations Fewer visits to emergency departments Improved health outcomes

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Partnering urban academic medical centers and rural primary care clinicians for treatment of complex chronic diseases	Patients with chronic or complex diseases living in rural or otherwise medically underserved areas (e.g., prisons)	For patients with chronic or complex diseases living in rural or medically underserved areas (e.g., prisons), receiving high-quality specialty care can be challenging because of access barriers, specialist shortages, geographical isolation, and other factors. Project ECHO (Extension for Community Healthcare Outcomes) is a health care delivery model that is intended to help develop rural communities' capacity to treat chronic, common, and complex disease in rural and underserved areas. The program utilizes telehealth technology and clinical management tools to train and support rural primary care providers in developing knowledge on diseases that would normally fall within the realm of specialist care. Clinicians are organized into learning networks with specialists at academic medical centers, which are intended to aid the clinicians in developing knowledge of and capability to treat certain complex conditions. University of New Mexico Health Sciences Center, Albuquerque Trials ongoing	Current model of specialist care for rural or underserved patient populations Other telemedicine delivery systems (e.g., Indian Health Service and the Veterans Health Administration)	Expanded primary care physician knowledge of complex conditions Improved patient health outcomes Reduced health disparities
Postdischarge clinics to provide transition care after hospital stay	Patients who have been recently discharged from the hospital and require followup care, but who do not have access to timely primary care	1/3 of patients discharged from the hospital do not see an outpatient physician within 30 days of their hospital visit, resulting in exacerbation of conditions and a high number of hospital readmissions. Barriers to visiting an outpatient physician (e.g., primary care physician) for followup include lengthy wait times for appointments and lack of health insurance. To address this unmet need, some hospitals have created postdischarge clinics. Postdischarge clinics are located in proximity to the hospital, are staffed by hospitalists, and are available for patients who are unable to get a followup appointment with their primary care physician within a week or 10 days after discharge, especially those who have been identified as being at high risk of readmission. The clinics are not intended to offer a substitute for primary or other outpatient care and are only intended to be used for a short amount of time (although times vary from clinic to clinic) until the patient can get care from a primary care physician. Various hospitals across the country, including Beth Israel Deaconess Medical Center, Boston, MA; University of California, San Francisco; and University of New Mexico Health Sciences Center, Albuquerque Several clinics have been launched in the U.S.	Outpatient followup care (e.g., with primary care physician)	Improved patient outcomes Reduced hospital readmissions

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Senior-specific emergency departments for treatment of elderly patients	Senior or elderly patients who visit an emergency department ED	20% of all seniors use an ED at least once a year, and half of all ED patients are seniors. General EDs are not senior-specific and can be uncomfortable or unsafe for elderly patients. Additionally, risk of hospital readmission and drug interactions are high in this population. Finally, EDs do not always have access to geriatrician staff members. EDs for seniors are designed specifically for the elderly population. Structural, safety, and comfort changes include wider hallways (for wheelchairs), hand rails, different lighting systems, easier-to-read visuals, pressure-reducing beds, and alarms for wandering patients. Care teams and care delivery are redesigned to include clinicians and nurses with special training in geriatric medicine, including education on issues related to ageism and sensory appreciation in the elderly (so that these skills can be used to communicate more effectively with older adults and their caregivers). The different approach to care involves being more thorough with each patient and conducting on a routine basis assessments that typically are only made as needed (e.g., cognitive exams to detect issues that normally would go unchecked in other EDs). Senior-specific EDs have been opened in Colorado, Missouri, New Jersey, New York, and Texas First senior-specific ED launched in 2008	General EDs	Improved health outcomes for seniors Improved quality of life
Wireless monitoring program (Care Beyond Walls and Wires) for rural patients with chronic conditions	Patients with chronic conditions who have been recently discharged from the hospital	Up to half of patients with heart failure discharged from the hospital are rehospitalized within 3–6 months. Reasons for this include not taking medications as prescribed, improper diet, lack of awareness of heart failure signs, and lack of planned followup with a doctor. These issues are particularly salient for rural populations, such as Native Americans, who often don't have access to cars, other transportation, running water, or electricity. The Care Beyond Walls and Wires program is intended to overcome these barriers and improve hospital readmission outcomes. The program uses smart phones and in-home monitoring equipment to collect data on weight, blood pressure, activity, and other important health indicators and transfer the data to nurses at a medical center. The nurses monitor the data daily and work with physicians to detect declines in a patient's health status and intervene early, potentially reducing unnecessary travel, physician office visits, costs, and hospital readmissions. The cell phones and monitoring equipment are donated by manufacturers. For rural residents without electricity, solar-powered batteries are used. Flagstaff Medical Center, Flagstaff, AZ 50-patient trial ongoing; the program is a National Institutes of Health Public-Private Partnership	In-person patient-monitoring visits Kiosk monitoring programs Other rural health programs in development (e.g., Project ECHO)	Fewer office visits and hospital readmissions Improved patient monitoring Improved patient outcomes Reduced costs

Section 2. Interventions Added Since Last Update: 15 Interventions

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Oral phosphodiesterase type 4 inhibitor (apremilast) for treating psoriatic arthritis	Patients in whom psoriatic arthritis has been diagnosed	In a subset of patients, psoriatic arthritis can progress to severe and painful symptoms that, without effective treatment, can lead to deformity and disability of the hands and fingers of patients. Apremilast is purported to inhibit phosphodiesterase type 4 (PDE-4). By inhibiting the PDE-4 enzyme, apremilast purportedly increases intracellular cAMP, which modulates multiple inflammatory mediators. Administered orally. Celgene Corp., Summit, NJ Phase III trials met primary endpoints Sept 2012; company plans to file new drug application 1st quarter 2013	Corticosteroids Disease-modifying antirheumatic drugs: methotrexate, sulfasalazine Immunosuppressants: azathioprine, cyclosporine leflunomide Nonsteroidal anti-inflammatory drugs Tumor necrosis factor-alpha inhibitors	Improved symptom scores as measured by the American College of Rheumatology 20/50/70 instruments Improved scores on disability measures Improved scores on quality of life measures

Table 17. AHRQ Priority Condition: 02 Cancer: 3 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Fosbretabulin tromethamine (Zybrestat) for treatment of anaplastic thyroid cancer	Patients in whom anaplastic thyroid cancer has been diagnosed	Few treatment options exist for patients with anaplastic thyroid cancer, and these patients often die from the disease within a year of diagnosis. Fosbretabulin tromethamine (Zybrestat®) is a vascular disrupting agent under study for treating patients with this condition. Vascular-disrupting agents such as fosbretabulin tromethamine purportedly acts as tubulin depolymerizing agents that selectively disrupt the cytoskeleton of proliferating endothelial cells. Proliferating endothelial cells are often found in the disordered vasculature of tumors, and abnormal endothelial cell function caused by cytoskeletal manipulation is thought to disrupt tumor blood supply, potentially leading to cell death within the tumor. In trials, fosbretabulin tromethamine is administered by intravenous infusion in combination with cytotoxic chemotherapy of carboplatin plus paclitaxel. OXiGENE, Inc., South San Francisco, CA Phase II/III trial complete; FDA granted orphan drug designation; special protocol assessment for phase III trial negotiated with FDA	Carboplatin and paclitaxel regimen	Increased overall survival Increased progression-free survival Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label maraviroc (Selzentry) for prevention of graft-versus-host disease	Patients at high risk for graft-versus-host disease (GVHD) after undergoing allogeneic stem cell transplantation	About 50% of patients undergoing allogeneic stem cell transplantation develop GVHD, a condition in which engrafted donor immune cells target the tissues of the transplant recipient. Current prophylactic treatments for GVHD target donor immune cells in a way that may delay immune system reconstitution and/or limit graft-versus-tumor immune responses. A potential molecular target in GVHD is chemokine (C-C motif) receptor 5 (CCR5), which has been shown to play a role in the pathogenesis of GVHD by promoting lymphocyte recruitment to tissues involved in GVHD. Maraviroc is a CCR5 antagonist that may limit lymphocyte recruitment to target tissues, potentially limiting the extent of recipient tissue damage. In clinical trials, daily maraviroc is administered orally in combination with standard GVHD prophylaxis. University of Pennsylvania, Philadelphia Phase I/II trial complete; FDA approved the drug in 2007 for treating HIV, and it is marketed by Pfizer, Inc. (New York, NY), as Selzentry, but the manufacturer does not appear to be seeking a labeled indication for this use	Methotrexate Tacrolimus	Reduced rate of acute GVHD Increased overall survival Improved quality of life
Primary care physician-administered colonoscopy (Endoscopy Training in Primary Care) for prevention of colorectal cancer	Patients eligible to receive colonoscopy	Research suggests that disparities exist in colorectal cancer (CRC) incidence and mortality for individuals who live in rural areas or otherwise medically underserved areas. This disparity may be attributable to the limited access that rural residents have to CRC prevention tools. To address this unmet need, researchers have begun investigating the feasibility and efficacy of training primary care physicians to perform colonoscopies in rural areas. According to its developers, the Endoscopy Training in Primary Care (ETPC) program involves the following: (1) an online didactic seminar, (2) an endoscopy simulator to provide the opportunity for basic and advanced skill acquisition, and (3) proctored endoscopy with an endoscopist. Colorado Area Health Education Center, Department of Family Medicine, University of Colorado, Denver Trials completed	Colonoscopy performed by gastrointestinal specialists	Earlier diagnosis of CRC Increased screening rates

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: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Video game therapy for treatment of attention-deficit hyperactivity disorder	Patients in whom attention-deficit hyperactivity disorder (ADHD) has been diagnosed	ADHD is the most-diagnosed behavioral disorder in children, affecting about 3% to 5% of children. ADHD can cause depression, sleeping problems, anxiety, learning disabilities, and other behavioral abnormalities. Available ADHD treatments have variable outcomes, warranting the development of more innovative treatment. Research has suggested that action video games can improve a person's cognitive abilities. Video game therapy is intended to improve concentration skills, reduce anxiety, and enforce correct and quick decisionmaking, skills lacking in patients with neurological conditions such as ADHD. Akili Interactive Labs, Boston, MA Pilot trial ongoing	Behavioral therapies Combination therapies Drug therapies	Improved attentiveness and academic performance Reduced behavioral abnormalities Improved quality of life

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
G-protein coupled receptor 40 agonist (TAK-875) for treatment of type 2 diabetes mellitus	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	Many treatments for T2DM help control glucose levels but can be associated with significant side effects, including nausea, diarrhea, weight gain, hypoglycemia, and edema. Additionally, many patients have difficulty achieving blood-glucose control with current treatments. TAK-875 is a selective G-protein coupled receptor 40 (GPR40) agonist, a specific receptor located and expressed in pancreatic islet cells. GPR40 agonists purportedly mediates fatty acid potentiation, which could acutely increase insulin secretion and, therefore, improve glucose tolerance. The developer purports the selectivity of this G-protein-coupled receptor could potentially reduce hypoglycemia risk. In trials, the drug is administered orally at dosages of 6.25 or 200 mg, once daily. Takeda Pharmaceutical Co., Ltd., Osaka, Japan Phase III trials ongoing	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers: pioglitazone, rosiglitazone Metformin Sitagliptin Sodium glucose co-transporter 1 and/or 2 inhibitors (in development) Sulfonylurea drugs (glimepiride)	Halted or delayed acute and secondary diabetes complications Improved glycated hemoglobin (HbA_{1c}) levels

Table 23. AHRQ Priority Condition: 08 Functional Limitations and Disability: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mobile phone monitoring application (MyVision Track) for age-related macular degeneration	Patients in whom age-related macular degeneration (AMD) has been diagnosed	According to the National Eye Institute, an estimated 1.75 million people in the U.S. have received a diagnosis of AMD. The standard for monitoring AMD consists of a complete eye exam including the Amsler grid test. MyVisionTrack has the potential to fulfill an unmet need brought about by a lack of self-monitoring diagnostics for AMD. It is a mobile application provided via hand-held digital devices such as smartphones. The application purportedly enables patients with retinal eye diseases to self-monitor their vision status at home, helping them notice changes or a decline in vision that could indicate a need for medical attention. Test results are stored and automatically compared with earlier results. The results may be sent to a physician's office or a central monitoring service when a statistically significant change occurs. Vital Art and Science, Inc., Richardson, TX Pilot study completed	Complete eye exam with Amsler grid test Optical coherence tomography	Earlier intervention for vision decline Slowed vision decline Improved quality of life

Table 24. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 2 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label maraviroc (Selzentry) for prevention of HIV infection	People at high risk for HIV infection	HIV remains a chronic illness resulting in high morbidity and mortality in the absence of effective treatments. HIV-drug resistance, high lifelong cost of therapy, and adverse events continue to suggest that prophylactic HIV measures be pursued for individuals at high risk of contracting HIV infection. Maraviroc (Selzentry®) is a chemokine receptor-5 antagonist (CCR-5) that is approved for treating CCR-5-tropic HIV-1 in combination with other antiretroviral agents. CCR-5 is expressed on the surface of T cells and has been identified as 1 of the 2 co-receptors needed for HIV to enter host cells. By preventing HIV from entering T cells, maraviroc could prevent HIV infection; thus, the drug is considered an entry inhibitor. It is intended to be administered daily as preexposure prophylaxis for people at high risk of HIV infection. Administered orally, 300 mg, once daily. ViiV Healthcare, Middlesex, UK Phase II trial planned	Condoms Harm-reduction campaigns Preexposure prophylaxis (tenofovir/emtricitabine) Prophylactic vaccines (investigational) Vaginal microbicide gels (investigational)	Reduced transmission and incidence of HIV Reduced morbidity and mortality
Silicone-based condom to prevent HIV infection during receptive anal intercourse	Persons engaging in anal intercourse	HIV remains a chronic illness associated with high morbidity and mortality in the absence of effective treatments. HIV-drug resistance, high lifelong cost of therapy, and adverse events suggest that prophylactic HIV measures to prevent infection should be pursued for individuals at high risk of infection. The Origami R. A. I. Condom is purportedly the first silicone-based condom designed for receptive anal intercourse. The condom is made of medical grade silicone, which is intended to improve the safety of receptive anal sex with respect to the transmission of HIV. The manufacturer purports latex condoms are not designed for the vigor of anal intercourse. Silicone is also purported to have a novel and improved feel compared to latex condoms and might increase condom use. The condom is intended to be inserted into the anus similar to female condoms. Origami Condoms of California, Culver City, CA Trial completed	Latex condoms Harm reduction campaigns Preexposure prophylaxis (tenofovir/emtricitabine) Prophylactic vaccines (investigational)	Reduced transmission and incidence of HIV Patient satisfaction Increased use of condoms during receptive anal intercourse

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Intragastric dual balloon (ReShape Duo) for treatment of obesity	Patients with a body mass index (BMI) between 30 and 40 kg/m^2 who wish to lose weight	Current surgical options for treating obesity have varying degrees of invasiveness, some of which are associated with significant adverse effects, and other surgical options have suboptimal efficacy. ReShape Duo is a nonsurgical, intragastric, dual balloon that is endoscopically inserted into the stomach in an uninflated state using a guidewire. Once the guidewire positions the dual balloon appropriately, the dual balloon is inflated with 900 cc of saline, occupying stomach space with the intended purpose of increasing satiety while avoiding overdistention. The dual balloon design purportedly reduces device displacement. Endoscopic placement takes 15–30 minutes. The device can stay in the stomach for up to 6 months, and then it must be removed endoscopically using a snare to deflate and remove the balloon through the mouth. ReShape Medical, Inc., San Clemente, CA Pivotal trial ongoing	Endoluminal sleeve (EndoBarrier) Gastric banding surgery Gastric pacemaker (in development) Pharmacotherapy Sleeve gastrectomy surgery	Decreased obesity-associated comorbidities (e.g., prediabetes, high blood pressure) Enabled eligibility for gastric bypass surgery (for superobese) Percentage excess weight loss Percentage total weight loss Improved quality of life

Table 26. AHRQ Priority Condition: 11 Peptic Ulcer Disease and Dyspepsia: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Linx Reflux Management System for treatment-refractory gastroesophageal reflux disease	Patients in whom treatment-refractory gastroesophageal reflux disease (GERD) has been diagnosed	GERD is a progressive disease that is not always managed by pharmacologic treatments, and many patients undergoing surgical treatment remain on pharmacologic therapy. The Linx® Reflux Management System purportedly augments the activity of the weak lower esophageal sphincter of patients with GERD, which may restore the body's natural barrier to reflux. The system comprises a small flexible band of interlinked titanium beads with magnetic cores. The magnetic attraction between the beads is intended to help the lower esophageal sphincter remain closed in response to gastric pressures to prevent reflux from the stomach into the esophagus. Swallowing force temporarily breaks the magnetic bond of the beads, allowing food and liquid to pass normally into the stomach; after swallowing, the lower esophageal sphincter closes. The system is implanted via laparoscopic surgery. Torax Medical, Inc., Shoreview, MN FDA approved Mar 2012 for patients with treatment-refractory GERD despite use of optimal medical therapy	Antacid medications Fundoplication H_2 antagonists Proton pump inhibitors	Reduced GERD symptoms Reduced risk of GERD-related cancer Improved quality of life

Table 27. AHRQ Priority Condition: 12 Pregnancy, Including Preterm Birth: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Bi-directional communication for personalized body weight management (SmartMoms) for pregnant women	Pregnant women	Pregnant women in the U.S. are at increased risk of exceeding pregnancy weight goals at term as recommended by current Institute of Medicine guidelines, leaving both mother and child susceptible to poor postpartum health outcomes. SmartMoms is a pregnancy weight-management program consisting of screening visits, weight management advice, 2nd and trimester health testing, and postnatal followup. The most recent SmartMoms intervention involves weekly delivery of weight management strategies from a weight management counselor via a smartphone. The patient will also be asked to provide weight (using a provided scale) and nutritional information via smartphone. Pennington Biomedical Research Center, Baton Rouge, LA Phase III trial ongoing	Other perinatal weight-management strategies	Improved perinatal weight management Reduced morbidity Improved maternal and fetal health outcomes Improved quality of life

Table 28. AHRQ Priority Condition: 13 Pulmonary Disease, Asthma: 2 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label thalidomide for treating cough associated with idiopathic pulmonary fibrosis	Patients in whom idiopathic pulmonary fibrosis (IPF) with persistent cough has been diagnosed	IPF is a progressive, debilitating disease characterized by inflammation and scarring (fibrosis) in the lungs with a median survival time from diagnosis of 2–5 years; 80% of patients have a dry nagging cough, for which no approved treatments are available. Thalidomide is considered to be a potent anti-inflammatory drug and is thought to suppress excessive tumor necrosis factor alpha production and down-modulate adhesion molecules involved in leukocyte migration. Thalidomide is also purported to suppress prostaglandin synthesis by macrophages, and modulate interleukin-10 and interleukin-12 production by peripheral blood mononuclear cells. These immunomodulatory effects could improve cough symptoms. Administered orally, 50–100 mg, daily. Celgene Corp., Summit, NJ Phase III trial completed; can be used off label	Azathioprine Bosentan Corticosteroids Cyclophosphamide Cyclosporine Intedanib (investigational) Methotrexate Penicillamine Pirfenidone (investigational)	Improved ability to perform activities of daily living Improved lung function measured by forced vital capacity Slowed disease progression Improved quality of life

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
School-based preventive asthma care technology (SB-PACT) program for management of asthma in school children	School children in whom asthma has been diagnosed	Children in inner city areas are more likely to not have their asthma well controlled. The School-Based Preventive Asthma Care Technology (SB-PACT) program is comprised of directly observed administration of preventive asthma treatments in school, combined with the use of a Web-based technology that helps coordinate systematic symptom screening, electronic report generation, and medication authorization from providers. University of Rochester School of Medicine and Dentistry, Rochester, NY Pilot study completed	Standard care	Fewer days missed from school Increased symptom-free days Reduced symptoms at night Reduced rescue medication use Reduced exhaled nitric oxide (inflammation)

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: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Mobile phone ultrasound imaging system (MobiUS SP1) for management of various conditions	Patients with various health conditions in need ultrasound imaging	Ultrasound imaging is a critical diagnostic tool used in various health care settings; however, access to ultrasound imaging can be difficult because of device cost and mobility. MobiUS™ SP1A is a wireless, smartphone-enabled diagnostic system that captures ultrasound images using a Toshiba TG01 smartphone and an ultrasound probe that connects to the phone's USB 2.0 port. This device platform purportedly allows health care professionals to capture images in any health care setting and store or share images using cellular, Wi-Fi, or other, personal-computer networks. Manufacturer purports this device can be used in primary care, obstetrics and gynecology, and emergency care settings. This device can only be used with the aforementioned phone. Device list price is $7,495. Mobisante, Inc., Redmond, WA FDA granted 510(k) clearance Feb 2011	Conventional ultrasound systems within health care settings GE VScan mobile ultrasound system	Convenience of portable ultrasound imaging Quicker diagnosis and monitoring of conditions outside of conventional medical facilities

Section 3. Interventions Tracked but Archived Since Last Update: 67 Interventions

Table 31. AHRQ Priority Condition: 01 Arthritis and Nontraumatic Joint: 3 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Interleukin-1-beta antagonist canakinumab (Ilaris) for treatment of systemic juvenile idiopathic arthritis	Patients in whom systemic juvenile idiopathic arthritis (SJIA) has been diagnosed	Available treatments for SJIA only partially mitigate symptoms and do not prevent the 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 purportedly plays a role in SJIA pathology. Canakinumab is intended to block the inflammatory activity of IL-1-beta. In a clinical trial, canakinumab was administered as a single subcutaneous dose, 4 mg/kg of body weight, to patients aged 2–19 years. Novartis International AG, Basel, Switzerland Phase III trials ongoing; approved for cryopyrin-associated periodic syndromes	Anakinra Corticosteroids Hydroxychloroquine Methotrexate Nonsteroidal anti-inflammatory drugs Tocilizumab	Improved adapted American College of Rheumatology pediatric 30/50/70/90/100 disability criteria Improved Child Health Assessment Questionnaire clinical response Improved quality of life	Expert comments indicated the unmet need was limited because many biologics are available, and they saw its potential as very incremental.
Interleukin-6 receptor antagonist tocilizumab (Actemra) for treatment of systemic juvenile idiopathic arthritis	Patients 2 years of age and older in whom active systemic juvenile idiopathic arthritis (SJIA) has been diagnosed	Available treatments for SJIA only partially mitigate symptoms and do not prevent long-term damage associated with the condition. Additionally, prolonged use of steroids can cause slowed growth and delayed puberty. Tocilizumab (Actemra®) is a humanized monoclonal antibody interleukin-6 (IL-6) receptor antagonist. IL-6 is a proinflammatory cytokine produced by a variety of cell types including lymphocytes, monocytes, and fibroblasts, as well as synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes. IL-6 is purported to upregulate lymphocyte activity, initiate acute phase protein synthesis, and stimulate hematopoietic precursor cell proliferation and differentiation. IL-6 can also stimulate osteoclast activity leading to inflammation and erosion of joint structures. Inhibiting IL-6 activity may relieve symptoms associated with SJIA. Tocilizumab can be used as monotherapy or in combination with methotrexate and is administered as an intravenous infusion, 12 or 8 mg/kg of body weight in patients weighing less than or more than 30 kg, respectively, every 2 weeks. F. Hoffmann-La Roche, Ltd., Basel, Switzerland FDA approved for treating SJIA Apr 2011; phase III trials ongoing	Anakinra Corticosteroids Hydroxychloroquine Interleukin-1-beta antagonist in development Methotrexate Nonsteroidal anti-inflammatory drugs	Improved adapted American College of Rheumatology pediatric 30/50/70/90/100 disability criteria Improved Child Health Assessment Questionnaire clinical response Decreased Child Health Questionnaire pain intensity as assessed on a 100 mm visual analog scale Improved quality of life	Diffused post FDA approval; no longer meets horizon scanning system criteria

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Monoclonal antibody (tabalumab, LY2127399) for treatment of rheumatoid arthritis	Patients in whom rheumatoid arthritis (RA) has been diagnosed	RA is a chronic inflammatory disease causing polyarthritis with frequent progression to permanent joint damage, deformity, and functional disability. Tabalumab is a fully human immunoglobulin G4 monoclonal antibody targeting B-lymphocyte stimulator (BLyS). BLyS plays an important role in stimulating B-lymphocyte production when the human body is battling infection, but overproduction can cause production of autoantibodies and initiate autoimmune-like disease symptoms in mice. By inhibiting the biologic activity of BLyS, tabalumab inhibits the stimulation, proliferation, and differentiation of B cells. Intravenous and injectable formulations are under development for RA. Eli Lilly and Co., Indianapolis, IN Phase III trials ongoing	Corticosteroids Disease-modifying antirheumatic drugs: hydroxychloroquine, methotrexate, sulfasalazine Nonsteroidal anti-inflammatory drugs Tocilizumab Tofacitinib (investigational) Tumor necrosis factor-alpha inhibitors	Reduced symptoms Delayed progression of disease Improved quality of life	Company halted development and ongoing trial because primary efficacy endpoints not met

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Biophotonic cervical screening system (LuViva Advanced Cervical Scan) for detection of cervical disease in adolescent females	Females aged 16–21 years who are sexually active	Luviva™ consists of a base unit and a single-patient-use calibration disposable scanner; uses biophotonic technology (hyperspectral imaging spectroscopy) to identify biochemical and morphologic changes at the cellular level associated with cervical cancer and precancer painless and minimally invasive. Device gives screening results immediately. Guided Therapeutics, Inc., Norcross, GA Premarket approval (PMA) application under FDA review; in Nov 2011, FDA stated that no FDA panel review was necessary prior to making a decision; in Jan 2012, company received a non-approvable letter from FDA regarding the PMA; company continues to pursue approval and submitted formal response to FDA May 2012	Biopsy Colposcopy Human papillomavirus DNA test Pap test	Earlier detection of cervical disease Improved screening and followup adherence Reduced unnecessary referrals to biopsy and colposcopy	Expert comments indicated low potential for high impact
BLP25 liposome therapeutic vaccine (Stimuvax) for advanced nonsmall cell lung cancer	Patients in whom stage III unresectable nonsmall cell lung cancer (NSCLC) has been diagnosed and who have undergone primary chemoradiotherapy treatment	Patients with advanced NSCLC have a poor prognosis and the disease often responds poorly to current chemotherapeutic regimens; new treatment strategies with novel mechanisms of action are needed. Stimuvax® is a therapeutic vaccine composed of a 25-amino acid sequence of the mucin-1 (MUC-1) protein, which is frequently expressed in NSCLC cells, encapsulated in a liposomal formulation; the vaccine is thought to work by stimulating anti-MUC-1 T cell responses. It is administered after a single intravenous infusion of 300 mg/m^2 of cyclophosphamide 3 days prior to the 1st immunization; then the vaccine is administered in 8 consecutive weekly subcutaneous injections (1,000 mcg Stimuvax); the vaccine is then administered at 6-week intervals beginning at week 14 until documented disease progression. Merck KGaA, Darmstadt, Germany Oncothyreon, Inc., Seattle, WA In Dec 2012, phase III trial was reported to have failed to meet primary endpoint of improving overall survival	No established maintenance therapy in the post-chemoradiotherapy setting	Increased overall survival Increased progression-free survival Improved quality of life	Trial did not meet primary endpoints

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Computer-aided multispectral digital analysis (MelaFind) for assessing atypical skin lesions	Patients in whom pigmented skin lesions are present requiring diagnosis	Computer-aided multispectral digital analysis (MelaFind®) uses a device that uses light to image skin through a thin layer of liquid (alcohol or oil) to try to make lesion structures visible under the skin surface; a digital camera inside the probe captures images and differentiates pigmented skin lesions to try to determine melanoma risk using algorithms. MELA Sciences, Inc., Irvington, NY FDA approved Nov 2011 “for use on clinically atypical cutaneous pigmented lesions with 1 or more clinical or historical characteristics of melanoma, excluding those with a clinical diagnosis of melanoma or likely melanoma. MelaFind is designed to be used when a dermatologist chooses to obtain additional information for a decision to biopsy. MelaFind should NOT be used to confirm a clinical diagnosis of melanoma.” Conformité Européene (CE) marked Sept 2011.	Biopsy Physician observation of skin lesions (dermoscope)	Increased sensitivity and specificity Reduced number of biopsies performed on suspect lesions Earlier detection of suspect lesions Increased overall survival Improved quality of life	Expert comments indicated the technology did not have high impact potential
CP-4126 (CO-101) for treatment of advanced pancreatic cancer	Patients in whom advanced pancreatic cancer has been diagnosed	CP-4126 is a lipid-conjugated version of the anticancer agent gemcitabine (nucleoside analog); gemcitabine is a standard chemotherapeutic treatment for pancreatic cancer; however, many pancreatic cancers do not readily take up gemcitabine (possibly because they express low levels of the main gemcitabine transporter). The lipid conjugation purports to overcome this problem by allowing the nucleoside to cross the lipid bilayer without having to use the transporter. Clavis Pharma ASA, Oslo, Norway Clovis Oncology, Boulder, CO Phase II trial complete; other phase II trials ongoing	Gemcitabine	Increased overall survival Increased progression-free survival Improved quality of life	Pivotal phase II trial failed to meet primary endpoint of improving overall survival.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Human papillomavirus vaccination (Gardasil) for prevention of anal cancer	Males and females 9–26 years of age	The incidence of anal cancer in the U.S. is rising and human papillomavirus (HPV) infection is associated with 90% of cases. Gardasil® is a quadrivalent HPV vaccine against HPV types 6, 11, 16, and 18 that has been approved for prevention of cervical, vulvar, and vaginal cancer. Merck & Co., Inc., Whitehouse Station, NJ FDA granted supplemental approval Dec 2010 for preventing anal cancer	Abstinence from anal intercourse Abstinence from sexual activity Safer sex practices	Decreased rate of anal intraepithelial neoplasia Decreased rate of anal cancer	Two years post-approval; no longer meets horizon scanning criteria for tracking
Levonorgestrel-release intrauterine device (Mirena) for uterus-sparing treatment of endometrial hyperplasia and early endometrial carcinoma	Females with endometrial hyperplasia or stage 1A endometrial cancer who wish to preserve fertility	Intrauterine device (Mirena®) is a levonorgestrel (a progestogen)-release intrauterine device, plus gonadotropin-releasing hormone. It has shown some efficacy against endometrial cancer and precancers in preliminary studies. Bayer AG, Leverkusen, Germany Multiple trials ongoing	Radical hysterectomy	Preserved fertility with similar clinical outcome to surgery	Expert comments indicated the technology did not have high impact potential
Therapeutic vaccine (tertomotide, GV-1001) for pancreatic cancer	Patients in whom pancreatic cancer has been diagnosed	Advanced pancreatic cancer has a 5-year survival rate of about 5% with few therapeutic options. Tertomotide (GV-1001) is a therapeutic peptide vaccine against telomerase, a protein responsible for adding telomeres, noncoding DNA at the ends of chromosomes, which help to determine the life span of cells; overexpression of telomerase can lead to immortalization of cells and oncogenesis; tertomotide purportedly induces cellular immune responses against telomerase. Tertomotide is administered intradermally in combination with granulocyte macrophage colony-stimulating factor on days 1, 3, and 5 in week 1; once weekly in weeks 2, 3, 4, and 6; and then once a month in the absence of disease progression or unacceptable toxicity. Patients may also be concurrently treated with gemcitabine. KAEL-GemVax Co., Ltd., Seoul, South Korea Phase III trial ongoing (data expected 2nd half of 2012)	5-fluorouracil/ leucovorin Gemcitabine	Increased overall survival Increased progression-free survival Improved quality of life	Phase III trial terminated after preliminary data showed no survival benefit in the GV-1001 group.

Table 33. AHRQ Priority Condition: 03 Cardiovascular Disease: 14 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Apixaban (Eliquis) for prevention of stroke and systemic embolism	Patients with nonvalvular atrial fibrillation (AF) at risk of deep vein thrombosis (DVT), pulmonary embolism (PE), or stroke	Apixaban (Eliquis™, BMS-562247-01) is an oral, highly selective coagulation factor Xa inhibitor intended to reduce the risk of stroke in patients with AF and to prevent or treat venous thromboembolism (VTE). Bristol-Meyers Squibb, New York, NY, in joint development with Pfizer, Inc., New York, NY FDA approved Dec 28, 2012 for reducing the risk of stroke and preventing systemic embolism in patients with atrial fibrillation that is not caused by a heart valve problem	Available pharmacotherapy (e.g., warfarin, dabigatran, rivaroxaban)	Reduced DVT events Reduced stroke incidence Reduced PE events	Expert comments indicated factor Xa inhibitors had low potential for high impact because dabigitran reached the market first.
Apo-B synthesis inhibitor (mipomersen, Kynamro) for treatment of familial hypercholes-terolemia	Patients in whom heterozygous or homozygous familial hypercholes-terolemia (FH) has been diagnosed	Outcomes with current medication for FH are suboptimal; mipomersen represents a new mechanism of action/drug class for this disease state. Mipomersen (Kynamro™) is a 1st-in-class apolipoprotein (Apo)-B synthesis inhibitor, intended to decrease production of apo-B (structural protein for atherogenic lipids, such as low-density lipoprotein C [LDL-C]), and reduce LDL-C (bad cholesterol) by preventing its formation. Drug is delivered via weekly self-administered injection. Genzyme Corp., a subsidiary of Sanofi, Paris, France ISIS Pharmaceuticals, Inc., a unit of Johnson & Johnson, New Brunswick, NJ Oct 2012, FDA advisory panel voted 9-6 to recommend approval; final decision date is Jan 29, 2013	Extracorporeal apheresis Pharmacotherapy (e.g., statins)	Reduced LDL levels Improved cardiovascular outcomes Improved long-term health outcomes Improved quality of life	Expert comments indicated low potential for highimpact because of safety concerns raised by FDA and weak endorsement by an FDA advisory committee.
Factor Xa inhibitor (betrixaban) for prevention of deep vein thrombosis or pulmonary embolism	Patients at high risk of thrombosis	Betrixaban is a direct coagulation factor Xa inhibitor and has the potential to be used in patients with severe renal impairment (excluding dialysis patients). Betrixaban keeps prothrombin from converting to thrombin to decrease clot formation. It is primarily eliminated unchanged in the bile, so it is metabolized through cytochrome 450 enzyme system. Portola Pharmaceuticals, Inc., South San Francisco, CA Phase III trial planned for 2012	Available pharmacotherapy (e.g., warfarin dabigatran, rivaroxaban)	Prevention of thrombosis Prevention of pulmonary embolism Decreased stroke events	Expert comments indicated factor Xa inhibitors had low potential for high impact because dabigitran reached the market first.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Factor Xa inhibitor (edoxaban) for prevention of thrombosis	Patients at risk of venous thrombo-embolism (VTE) or with atrial fibrillation (AF)-related stroke	Edoxaban is an agent in a new class of anticoagulants designed to inhibit coagulation factor Xa (FXa), which is known to be an important component of the coagulation cascade. It is intended to be administered orally, once daily. Daiichi Sankyo Co., Ltd., Tokyo, Japan Phase III trial ongoing for VTE indication; phase II trial complete for AF indication; received approval in Japan in Apr 2011 for preventing VTE after major orthopedic surgery; in the U.S., manufacturer is seeking indications only for VTE and preventing stroke in patients with AF	Available pharmacotherapy (e.g., other FXa inhibitors, dabigatran, warfarin)	Reduced thrombosis rate Reduced stroke incidence Reduced pulmonary embolism incidence	Expert comments indicated factor Xa inhibitors had low potential for high impact because dabigitran reached the market first.
Factor Xa inhibitor (otamixaban) for treatment of acute coronary syndrome	Patients in whom acute coronary syndrome (ACS) has been diagnosed	Otamixaban is a reversible, direct selective coagulation factor Xa (FXa) inhibitor that the manufacturer purports has a fast onset of action and a short half-life and may not require anticoagulation monitoring or dose adjustments for certain populations. Sanofi, Paris, France Phase III trial ongoing	Available pharmacotherapy (e.g., other FXa inhibitors, dabigatran, warfarin)	Reduced morbidity and mortality Reduced need for monitoring or adjusting anticoagulant dose	Expert comments indicated factor Xa inhibitors had low potential for high impact because dabigitran reached the market first.
Ivabradine for treatment of heart failure	Patients with symptomatic chronic heart failure (HF) and systolic dysfunction who are on stable background therapy and in a normal sinus rhythm	Ivabradine is an oral selective inhibitor of hyper-polarization-activated cyclic-nucleotide-gated funny current involved in pacemaking and responsiveness of the sinoatrial node; intended to slow heart rate and allow more time for blood to flow to the heart. Servier, Neuilly sur Seine, France Phase III trial (sponsored by IRCCS San Raffaele) ongoing; approved in EU in 2005 as Procoralan for treating stable angina; approved in EU in 2012 for treating heart failure.	Beta blockers Calcium channel blockers	Reduced HF hospitalizations Reduced coronary events Reduced incidence of myocardial infarction Improved quality of life	Status of phase III trial not verifiable since 2010. One phase IV trial ongoing but looking at ivabradine and digoxin. No US clinical trials.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Left ventricular assist device (HVAD) as bridge to transplantation for end-stage heart failure	Patients with end-stage heart failure (HF) who are eligible for heart transplantation	HeartWare is developing a left ventricular assist device (LVAD) for treating advanced HF. The device (HVAD™) propels blood centrifugally from the center of a spinning disc, which is suspended by magnetics and blood; smaller than marketed devices, it can be implanted directly in left ventricle and surrounding space (does not require abdominal surgery to create pocket). The device is implanted with less invasive surgery which could enable more patients to be candidates for the devices and at earlier stages of disease progression. HeartWare International, Inc., Framingham, MA U.S. multicenter late-phase clinical trial under FDA investigational device exemption status ongoing; Conformité Européene (CE) marked in 2009	Optimal medical management Other LVADs Total artificial heart	Improved survival Improved quality of life prior to transplant Reduced incidence of internal bleeding compared with continuous-flow devices	Experts considered this a next-generation incremental improvement with little potential for high impact.
Membrane active chelator (DP-b99) for neuroprotection during acute stroke	Patients experiencing an acute ischemic stroke	Only 1 drug, tissue plasminogen activator (tPA), is FDA approved for this indication, but tPA is effective only when administered within the 1st 3 hours of symptom onset, and only a very small percentage of patients experiencing an acute stroke receive tPA. When a cell is deprived of oxygen, the ability of membranes to control ion flux is disrupted, resulting in the loss of metal ion homeostasis, which can significantly impair cell or organ function and eventually lead to cell death. DP-b99 is a lipophilic chelator of calcium, zinc, and copper ions; it is intended to sequester metal ions only within and near cell membranes. The manufacturer claims it can bind to pathological levels of metal ions, making it useful for the suppression of cell damage in stroke patients. The technology is based on lipid modification of metal ion chelators, which sequester metal ions in all aqueous environments, causing potential toxic effects. The modified version binds metal ions selectively, which makes it potentially safer and is intended to increase treatment window to 9 hours. DP-b99 is delivered via intravenous infusion. D-Pharm, Ltd., Rehovot, Israel Phase III trial suspended by trial steering committee in Jan 2012; company later decided to halt development	tPA	Improved poststroke neuron survival Faster recovery Reduced need for rehabilitation services	Company halted development.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Off-label sildenafil (Revatio) to improve pediatric exercise tolerance after Fontan surgery for heart defect	Pediatric patients with exercise intolerance after undergoing Fontan operation to correct heart defect	No medical therapies have demonstrated a benefit in improving exercise tolerance in patients who have undergone a Fontan operation. The Fontan procedure is a palliative surgery for patients who have a single pumping ventricle; a staged reconstruction of the heart and the major blood vessels whereby the veins that usually bring blood back to the heart are connected directly to the pulmonary arteries; this creates a "new" circulatory system, in which blood from the body bypasses the heart and flows directly to the lungs; importantly, blood flow through the lungs is passive (not pumped) and the efficiency of flow through the cardiovascular system is related to the resistance to blood flow in the vessels of the lungs, or pulmonary vascular resistance (PVR). Sildenafil (®) is a phosphodiesterase type 5 inhibitor that has potent selective vasodilatory effects on pulmonary vasculature; may decrease PVR, resulting in increased pulmonary blood flow. Pfizer, Inc., New York, NY (manufacturer) Pennsylvania State University, Pennsylvania State Hershey Medical Center, Hershey (investigator) Aug 2012, FDA recommended against off-label sildenafil for the pediatric population due to high risk of death with high doses and no improved exercise tolerance with low doses; it does not appear that the manufacturer is seeking a labeled indication change	Exercise training	Improved PVR Improved pulmonary blood flow Improved cardiac filling Increased stroke volume Improved cardiac output response to exercise Increased exercise tolerance Increased time to transplant Improved quality of life	FDA issued a warning against use in pediatric patients.
Rivaroxaban (Xarelto) for prevention of deep vein thrombosis	Patients who have undergone hip or knee replacement	Rivaroxaban (Xarelto®) is a member of a new class of anticoagulants that are designed to inhibit factor Xa (FXa), which is known to be an important component of the coagulation cascade. It is administered orally, once daily at 10 mg dose for 35 days after hip replacement and 12 days after knee replacement for preventing deep vein thrombosis. Janssen Pharmaceuticals unit of Johnson & Johnson, New Brunswick, NJ FDA approved Jul 2011	Available pharmacotherapy (e.g., other FXa inhibitors, dabigatran, warfarin)	Reduced morbidity and mortality Reduced thrombotic events	Expert comments indicated factor Xa inhibitors had low potential for high impact because dabigitran reached the market first.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Rivaroxaban (Xarelto) for prevention of stroke in patients with nonvalvular atrial fibrillation	Patients in whom with non-valvular atrial fibrillation (AF) has been diagnosed	Rivaroxaban (Xarelto®) is a member of a new class of anticoagulants that are designed to inhibit factor Xa (FXa), which is known to be an important component of the coagulation cascade. It is administered orally, once daily, and is approved to reduce the risk of stroke in people who have abnormal heart rhythm (nonvalvular atrial fibrillation). Janssen Pharmaceuticals unit of Johnson & Johnson, New Brunswick, NJ FDA approved Nov 2011	Available pharmacotherapy (e.g., other FXa inhibitors, dabigatran, warfarin)	Reduced stroke incidence Reduced morbidity and mortality	Expert comments indicated factor Xa inhibitors had low potential for high impact because dabigitran reached the market first.
Rivaroxaban (Xarelto) for treatment of acute coronary syndrome	Patients in whom acute coronary syndrome has been diagnosed	Rivaroxaban (Xarelto®) is a coagulation factor Xa (FXa) inhibitor; keeps prothrombin from converting to thrombin, decreasing clot formation. Compared with previously available pharmaceuticals, it might offer fewer drug interactions, and might not require frequent blood checks. It is an oral medication taken daily. Janssen Pharmaceuticals Inc., a unit of Johnson & Johnson, New Brunswick, NJ In Jun 2012, FDA denied approval and issued a complete response letter requesting more data; Janssen is considering its next steps	Available pharmacotherapy (e.g., other FXa inhibitors, dabigatran, warfarin)	Reduced morbidity and mortality Reduced thrombotic events	Expert comments indicated factor Xa inhibitors had low potential for high impact because dabigitran reached the market first.
Robotic system (CorPath 200) for remotely controlled percutaneous coronary intervention	Patients undergoing percutaneous coronary intervention (PCI)	PCI, as it is performed, is associated with procedural challenges, radiation exposure, and spinal strain for interventional cardiologists. CorPath™ 200 is a console or cockpit with radiation shielding placed several feet from patient that allows the physician to use robotic-assisted tools to place coronary guidewire and stent/balloon catheters. The physician does not have to wear a lead shield apron during PCI; system is intended to fixate and hold devices to enable the cardiologist (while seated) to control contrast injection and manipulate the guidewire; intended to enhance visualization, minimize fatigue, and protect against exposure to radiation and back strain. According to manufacturer, improved control of contrast injection and visualization of angiography may also reduce the volume of contrast media and radiation dose administered to the patient. Corindus Vascular Robotics, Inc., Natick, MA Phase II completed; company received FDA 510(k) marketing clearance Jul 2012	Manually performed PCI	Improved procedural visualization Reduced radiation exposure Reduced physician spinal strain Reduced physician fatigue Increased number of PCI procedures performed Improved patient safety	Expert comments indicated low potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
School-wide electrocardiogram screening (Young Hearts for Life) for cardiac abnormalities in students	Students in high school or college, who may or may not participate in organized sports	More than 1,000 young adults die from sudden cardiac death annually in the U.S. The Young Hearts for Life Cardiac Screening Program is intended to provide free electrocardiograms (ECGs) to all high school students (who choose to participate) to identify students at risk of sudden cardiac death; screenings are conducted during the school day, usually during physical education classes, and echocardiograms are available on site at no cost for selected students who have an inconclusive screening ECG (intended to give additional information regarding whether further evaluation is necessary); ECGs are interpreted by volunteer cardiologists; parents receive test results about 3 weeks after the screening and are instructed to follow up with primary care physician if necessary. Midwest Heart Foundation, Lombard, IL As of Dec 2012, screenings had been provided to more than 74,000 students	American Heart Association-recommended screening that includes physical examination and family and personal medical history	Increased detection of potential cardiac abnormalities Earlier diagnosis of abnormalities Reduced incidence of sudden cardiac death Increased costs from screening general student population who would otherwise not be screened by ECG	Expert comments indicated little potential for high impact because it is impractical to administer and abnormalities are not readily evident with this screening.

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

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Nicotine patch for treatment of mild cognitive impairment	Patients in whom mild cognitive impairment (MCI) has been diagnosed	MCI may be a precursor to Alzheimer's disease (AD). No disease-modifying agents are approved for treating AD; available therapy options are limited to symptom management. Nicotine replacement therapy has been shown to improve outcomes in patients with AD, and now researchers are looking at it to improve outcomes in patients with MCI. The rationale for using this treatment in this population is that patients with AD have a reduced number of nicotinic receptors. University of Vermont, Burlington Trial completed and published Jan 2012; no indication of further development	Off-label AD pharmacotherapy	Improved cognitive performance Improved clinical status Delayed progression to AD Reduced morbidity Reduced mortality	Trial completed and published Jan 2012; no indication of further development.
Off-label bexarotene (Targretin) for treatment of Alzheimer's disease	Patients in whom Alzheimer's disease (AD) has been diagnosed	No disease-modifying agents are approved for treating AD; available therapy options are limited to symptom management. 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 clearance from the brain (beta amyloid is a substance associated with AD). For this off-label use, researchers have administered the drug orally in a murine model of AD. Eisai Co., Ltd., Tokyo, Japan (manufacturer) Case Western Reserve University School of Medicine, Cleveland, OH (investigator) Preclinical trial completed; drug can be prescribed off label in the U.S	Cholinergic agents (e.g., donepezil, galantamine, tacrine) NMDA inhibitor (e.g., memantine)	Reduced beta-amyloid load in brain Regression or slowing of disease progression Reduced morbidity and mortality Improved quality of life	Off-label use disrecommended by authors at the National Institutes of Health authors and University of California, Irvine, in editorials published in New England Journal of Medicine in Aug 2012.

Table 35. AHRQ Priority Condition: 05 Depression and Other Mental Health Disorders: 2 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Acupuncture for treatment of posttraumatic stress disorder	Patients in whom posttraumatic stress disorder (PTSD) has been diagnosed	Many patients with PTSD do not adequately respond to available treatments, which include pharmacotherapy (e.g., antidepressants) and psychotherapy; additional efficacious treatments are needed. Acupuncture is a type of Traditional Chinese Medicine in which needles are inserted into specific points along meridians of the body. From a Western medicine perspective, acupuncture's efficacy may be related to its regulatory effects on the nervous system, which increases the activity of biochemicals (such as endorphins and immune system cells) at specific sites in the body, or related to its effect on brain chemistry and the release of neurotransmitters and neurohormones, which affect immune reactions and processes that regulate a person's blood pressure, blood flow, and body temperature. It is being investigated for use in patients with PTSD to reduce anxiety, sleep disruption, and other signs and symptoms. Department of Veterans Affairs Trials completed	Pharmacotherapy (e.g., antidepressants and/or anxiolytics)	Reduced symptom burden Improved quality of life	Experts commented this intervention would not be widely accepted and has little potential for impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Off-label sodium oxybate for treatment of binge-eating disorder	Patients in whom binge-eating disorder has been diagnosed	No pharmacotherapies are approved for binge-eating disorder, and used off-label pharmacotherapies are associated with limited efficacy, undesirable side effects, and low adherence. 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 as Xyrem® for treating daytime sleepiness and cataplexy in patients with narcolepsy. Some investigators have suggested that binge-eating disorder may mediate the relationship between narcolepsy and obesity. This agent is administered orally, in liquid form, twice every night. Jazz Pharmaceuticals, Inc., Palo Alto, CA (manufacturer listed as a collaborator on clinical trials, but does not list active development for this indication on its Web site) Lindner Center of Hope, Mason, OH (primary investigator) Phase II/III trial completed; regulated as a Class III controlled substance by FDA and U.S. Drug Enforcement Agency	Off-label pharmacotherapies (e.g., antiepileptics, norepinephrine reuptake inhibitors)	Improved symptoms of binge eating Improved morbidity and mortality	Expert comments indicated low potential for high impact.

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

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

Table 37. AHRQ Priority Condition: 07 Diabetes Mellitus: 10 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
GFT 505 for treatment of prediabetes and diabetes	Patients in whom diabetes, abdominal obesity, or atherogenic dyslipidemia (low levels of high-density lipoprotein cholesterol, high triglycerides) has been diagnosed	Mixed peroxisome proliferator-activated receptor alpha/delta agonist (GFT 505) is based on Genfit's Selective Nuclear Receptor Modulator (SNuRM) platform; GFT 505 simultaneously targets several micro- and macro-vascular risk factors such as hyperglycemia and insulin resistance, dyslipidemia, inflammation, and hepatic steatosis. Genfit Corp., Lille, France Phase II trial completed; Sept 2012, FDA approved phase IIb trial.	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Improved blood glucose levels Improved lipid profiles Halted progression to diabetes Resolution of diabetes	Expert comments indicated low potential for high impact.
Glutamic acid decarboxylase-based vaccine (Diamyd) for treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus has been recently diagnosed	Subcutaneous injection with Diamyd® vaccine is intended to preserve insulin-producing islet cells in pancreas of patients with latent autoimmune diabetes of adults. Diamyd is thought to induce tolerance to GAD65, thereby preventing or reducing autoimmune attack on islet-beta cells and preserving the pancreas' capacity to produce insulin in patients with autoimmune diabetes. Given as 2 injections, administered 1 month apart. Diamyd Medical AB, Stockholm, Sweden Phase III trial ongoing; 1 phase III trial (EU) terminated because primary endpoint at 15 months was not met	Insulin modifications Islet cell transplantation Pancreas transplantation	Improved islet cell function Reduced need for insulin therapy Decreased diabetes complications	Multiple phase III trials terminated for failure to meet primary efficacy endpoints.
InsuPatch for improving insulin absorption in type 1 diabetes	Patients with type 1 diabetes mellitus who use an insulin pump	InsuPatch™ device is intended to improve insulin delivery into the blood by heating the area of the body around the point of insulin infusion; system includes a catheter that connects to the insulin pump, electrical contacts, and embedded wires. InsuLine Medical, Ltd., Petach-Tikvah, Israel Phase III trial completed; InsuLine intends to file a submission to the FDA for approval late in 2012	Insulin modifications	Improved insulin absorption Decreased frequency and severity of adverse events Avoided glycemic excursions	Expert comments indicated low potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Otelixizumab (TRX4) for early treatment of type 1 diabetes	Patients in whom type 1 diabetes mellitus has been diagnosed within the past 90 days	Otelixizumab is an anti-CD3 monoclonal antibody that preserves beta cell function if used early in the disease course; CD3-monoclonal antibodies bind to and inactivate cytotoxic T-lymphocytes, the cells that destroy beta cells. Additionally, CD3-monoclonal antibodies activate T cells, which helps control cytotoxic T-lymphocyte action. Tolerx, Inc., Cambridge, MA GlaxoSmithKline, Middlesex, UK Phase III trial completed; GlaxoSmithKline announced Mar 2011 that drug did not meet primary endpoint	Insulin modifications Islet cell transplantation Pancreas transplantation	Improved C-peptide levels, which indicate beta cell function Improved glycemic control Daily insulin required Reduced side effects	Company halted development; drug did not meet primary efficacy endpoints.
Sodium-glucose cotransporter-2 inhibitor (ASP1941) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	Many current treatments for T2DM 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. 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. Astellas Pharma, Inc., Tokyo, Japan Phase III trials completed; phase III trials ongoing in Japan	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Reduced blood glucose levels Weight loss	Expert comments indicated little potential for high impact

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
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	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. 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. Boehringer Ingelheim GmbH, Ingelheim, Germany Phase III trial completed; phase III trials ongoing	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Improved glycosylated hemoglobin (HbA_{1c}) levels Delayed progression of complications	Expert comments indicated little potential for high impact.
Sodium-glucose cotransporter-2 inhibitor (canagliflozin, [Invokan]) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	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. Canagliflozin (Invokana™) 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. Johnson & Johnson, New Brunswick, NJ Jan 10, 2013, FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 10-5 to recommend approval.	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Near-normal glycosylated hemoglobin (HbA_{1c}) levels Weight loss Fewer hypoglycemic events Halted or delayed acute and secondary complications	Expert comments indicated low potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
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	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. 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. Drug is taken orally, once a day. Bristol-Myers Squibb, New York, NY AstraZeneca, London, UK In Jan 2012 FDA rejected dapagliflozin for this indication and issued a complete response letter to the company. Approved by the European Commission in Nov 2012.	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Achieved target glycosylated hemoglobin (HbA_{1c}) levels Weight loss Decreased hypoglycemic events Halted or delayed secondary complications of diabetes	Expert comments indicated low potential for high impact.
Sodium-glucose cotransporter-2 inhibitor (tofogliflozin) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	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. 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. They also are believed to have potential to promote weight loss. Chugai Pharmaceuticals Co., Ltd., Tokyo, Japan Phase III trial ongoing	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Near-normal glycosylated hemoglobin (HbA_{1c}) levels Weight loss Decreased hypoglycemic events Halted or delayed acute and secondary complications	Expert comments indicated low potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Sodium-glucose cotransporter-2 inhibitor (TS-071) for treatment of type 2 diabetes	Patients in whom type 2 diabetes mellitus (T2DM) has been diagnosed	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. 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 purportedly reduces glucose reabsorption and increases 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. Taisho Pharmaceutical Co., Ltd., Tokyo, Japan Phase III trial ongoing, although trial is not registered in National Clinical Trials database	Dietary and lifestyle modifications Exenatide Insulin Insulin sensitizers (pioglitazone, rosiglitazone) Metformin Sitagliptin Sulfonylurea drugs (glimepiride)	Near-normal glycosylated hemoglobin (HbA_{1c}) levels Weight loss Fewer hypoglycemic events Halted or delayed acute and secondary complications	Expert comments indicated low potential for high impact.

Table 38. AHRQ Priority Condition: 08 Functional Limitations and Disability: 17 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Aflibercept (Eylea) for treatment of wet age-related macular degeneration	Patients in whom the neovascular form of age-related macular degeneration (ARMD; "wet") has been diagnosed	Vascular endothelial growth factor (VEGF) Trap-Eye (Eylea™, aflibercept) is a recombinant fusion protein consisting of human VEGF receptors 1 and 2 extracellular domains that are fused to the Fc portion of human immunoglobulin G1. The drug is formulated as a solution for intravitreal injection. It is intended to inhibit the binding and activation of VEGF receptors. Aflibercept is "indicated for the treatment of patients with neovascular ARMD (wet AMD)." It is "contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients" in the drug. The recommended dose is 2 mg by injection once a month for the 1st 3 months, followed by 2 mg every 2 months. Regeneron Pharmaceuticals, Inc., Tarrytown, NY Phase III trials completed; FDA approved Nov 2011	Pharmacotherapy(e.g Lucentis®) Laser therapy Photodynamic therapy	Improved visual acuity Improved treatment adherence because of reduced number of eye injections	Expert comments indicated low potential for high impact because of incremental benefit compared to other available pharmacotherapy.
Amino-benzothiazole (dexpramipexole) for treatment of amyotrophic lateral sclerosis	Patients in whom amyotrophic lateral sclerosis (ALS) has been diagnosed	Only 1 agent (riluzole) is FDA approved for treating ALS, and it is associated with limited efficacy in improving survival time and little to no efficacy in improving motor function; novel therapies for ALS are urgently needed. Dexpramipexole likely represents a new mechanism of action for this disease state. Dexpramipexole is a synthetic amino-benzothiazole; (R)-(+) enantiomer of pramipexole (high-affinity dopamine agonist, already approved for Parkinson's disease and restless leg syndrome, but would be dosed at very high levels for ALS); its mechanism of action is unknown, but may be related to its ability to increase the efficiency of mitochondria, which undergo significant stress in patients with ALS. Dosed orally, daily. Biogen Idec International GmbH, Zug, Switzerland Knopp Bioscience, Pittsburgh, PA Phase III trial; FDA granted fast track and orphan drug status	Riluzole Supportive care	Increased survival Delayed disease progression Improved symptoms Improved quality of life	Company halted development Dec 2012 for failure to meet primary endpoint

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Beta-3 adrenoceptor agonist (Mirabegron) for treatment of overactive bladder	Patients in whom overactive bladder leading to urinary incontinence has been diagnosed	Current therapeutic approaches for overactive bladder have a poor side-effect profile and are generally not very effective. Mirabegron is a selective beta-3 adrenoceptor agonist that purportedly relaxes bladder smooth muscles, potentially allowing bladder filling and urine storage. Drug is administered orally. Astellas Pharma, Inc., Tokyo, Japan FDA approved Jun 2012 extended-release tablets for treating overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency and urinary frequency	Pharmacotherapy (e.g., darifenacin, oxybutynin, oxybutynin skin patches, solifenacin, tolterodine, trospium) Onabotulinum toxin A Sacral nerve stimulation Surgical therapy Behavioral and lifestyle modifications	Decreased urge to urinate Decreased urination episodes per week Improved International Consultation on Incontinence Questionnaire-Overactive Bladder score Improved quality of life	Expert comments indicated low potential for high impact
Bupivacaine extended-release liposome injection (Exparel) for treatment of postsurgical pain	Patients who have undergone soft-tissue or orthopedic procedures and require local anesthesia postsurgery	Local analgesics such as bupivacaine have been successfully used for many years in managing postsurgical pain; however, their activity is of limited duration (about 7 hours). A need exists for a long-acting nonopioid postsurgical analgesic. Exparel® is a formulation of bupivacaine that is an extended-release liposome injection that uses the manufacturer's DepoFoam® technology; it is intended to provide up to 72 hours of post-surgical analgesia. Pacira Pharmaceuticals, Inc., Parsippany, NJ FDA approved Oct 2011 for treating postsurgical pain	Pharmacotherapy (e.g., opioids, nonsteroidal anti-inflammatory drugs)	Reduced pain on visual analog pain scale Reduced need for other pain medication	Does not meet revised horizon scanning (Jan 2013) criterion to use Department of Health and Human Services definition of disability for this priority area

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Ear implant for treatment of Meniere's disease	Patients with persistent, severe vertigo in whom Meniere's disease has been diagnosed	No cure exists for Meniere's disease. Current treatment options include anti-vertigo and anti-nausea medications, but provide suboptimal treatment for many patients and also can impair performance of daily activities. This intervention is an inner ear implant modeled after cochlear implant and designed to quell vertigo attacks experienced by people with Meniere's disease. An electrode is inserted into each of 3 semicircular canals; external processor is worn behind the ear and communicates wirelessly with internal components; patient activates when vertigo episode begins; less invasive, permanent alternative to surgery, alternative to medications that address only symptoms and have many side effects. University of Washington, Seattle Trial status could not be confirmed	Pharmacotherapy (e.g., motion sickness medications, anti-nausea medications) Surgical therapy	Cessation of vertigo Improved quality of life	No further development activity reported for 2 years; no ongoing trial registered with ClinicalTrials.gov.
Fentanyl iontophoretic transdermal system (Ionsys™) for patient-controlled delivery of pain medication	Patients who would receive opioid treatment for pain (e.g., postsurgery patients)	The iontophoretic transdermal system delivers fentanyl (Ionsys™) for pain relief through a device about the size of a credit card that is affixed to the patient's upper arm or upper chest. The patient pushes a button on the patch, activating a battery and allowing iontophoretic (electrotransport) delivery of fentanyl HCl (40 mcg) over 10 minutes through intact skin. The device can be activated up to 6 times an hour and automatically shuts off after 24 hours. Incline Therapeutics, Inc., Redwood City, CA Received FDA new drug application approval May 2006, but product was not launched; Incline Therapeutics was acquired by The Medicines Company in Dec 2012, which must reapply for FDA approval for new safety features built into the device	Non-patient–controlled fentanyl patches Patient-controlled analgesic pumps	Adequate postsurgery pain management Fewer side effects because of delivery mode	Incline was sold to The Medicines Company in late Dec 2012. The Medicines Company expressed intent to pursue Ionsys approval, but the timeframe is unclear at this time.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Glucocerebrosidase (taliglucerase alfa) for treatment of Gaucher's disease	Patients with Gaucher's disease who have not yet begun treatment or who are being treated with enzyme replacement therapy via imiglucerase (Cerezyme)	Gaucher's disease is caused by a hereditary deficiency of glucocerebrosidase, which leads to enlarged and malfunctioning organs, skeletal disorders, and painful neurologic complications. Taliglucerase alfa is a plant-cell expressed form of glucocerebrosidase; intended as a lower-cost enzyme replacement therapy; compound also known as recombinant active form of lysosomal enzyme, glucocerebrosidase. Administered via an infusion. Pfizer, Inc., New York NY Protalix BioTherapeutics, Inc., Carmiel, Israel Phase III trial completed; new drug application submitted to FDA; complete response letter from FDA issued in Feb 2011; timeline for resubmission unclear pending meeting with FDA; granted orphan drug status; available under "expanded access" protocol; marketing authorization application submitted to European Medicines Agency Nov 2010; granted orphan designation in Europe	Blood transfusions Bone marrow transplant Enzyme replacement therapy (e.g., imiglucerase) Joint replacement surgery Splenectomy	Decreased spleen volume as confirmed by MRI Secondary endpoints including the following: Reduced liver volume Improved hemoglobin measurements Increased platelet counts Improved quality of life	Expert comments indicated low potential for high impact; incremental benefit only.
Laquinimod for treatment of relapsing-remitting multiple sclerosis	Patients in whom relapsing-remitting multiple sclerosis (RRMS) has been diagnosed	Results seen with current RRMS therapies are unsatisfactory. Laquinimod represents a new mechanism of action for this disease state. Laquinimod is a synthetic immunomodulator with anti-inflammatory properties; exact mechanism of action has not yet been elucidated, but may exert its effect by modulating the immune system from a proinflammatory to an anti-inflammatory response and by preventing damaging immune system cells from entering the central nervous system. Dosed once daily, orally. Teva Pharmaceutical Industries Ltd., Petach Tikva, Israel Active Biotech, Lund, Sweden Two phase III trials completed; others ongoing; Teva decided to not file a new drug application and after discussions with FDA in Aug 2012 agreed on a 3rd clinical trial (CONCERTO) to evaluate 2 doses (0.6mg and 1.2mg) in about 1,800 patients for up to 24 months	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Reduced brain tissue loss/atrophy Reduced frequency of relapse Slowed disease progression Improved quality of life	Expert comments indicated low potential for high impact because it addresses same unmet need as the recently approved drug, Gilenya.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Nitroglycerin for prevention of osteoporosis	Postmenopausal women who have normal bone density or osteopenia	Available treatments for osteoporosis either prevent bone resorption or promote bone formation, but no compound performs both functions, which nitroglycerin purported does. Nitroglycerin leads to the production of nitric oxide, which has been demonstrated in vitro to cause decreased bone resorption, increased osteoblast cell proliferation, increased osteocalcin synthesis, and increased osteoblastic cell mineralization; these processes could all prevent bone loss. National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD Phase III trial completed	Anti-bone–resorptive drugs (bisphosphonates, selective estrogen receptor modulators, estrogen, calcitonin, denosumab) Bone formation stimulators (teriparatide)	Increased lumbar vertebrae and hip bone mineral density Improved serum osteocalcin levels Improved bone-specific alkaline phosphatase levels Reduced hip and spine fractures	Incremental benefit only.
Obeticholic acid (INT-747) for treatment of nonalcoholic steatohepatitis	Patients in whom nonalcoholic steatohepatitis (NASH) has been diagnosed	Obeticholic acid (INT-747) is a farnesoid X receptor agonist derived from human bile intended for administration to decrease liver tissue scarring and fibrosis. Intercept Pharmaceuticals, Inc., New York, NY Phase II trial completed in type II diabetes patients with nonalcoholic fatty liver disease; study of 280 patients with NASH to be initiated in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD	Disease-specific treatments not available; comparator would be to standard of care	Reduced tissue scarring Slowed progression of fibrosis Improved liver function Improved quality of life Reduced need for liver transplantation	Expert comments indicated low 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 beta blockers for treatment of serious infantile hemangiomas	Infants in whom a hemangioma has been diagnosed	Superficial hemangiomas often are not treated and resolve on their own to leave normal-appearing skin. Sometimes, laser ablation is used to remove small vessels. Significant hemangiomas, however, can impair vital or sensory functions or cause disfigurement. They are treated with lasers and/or steroid injections. Oral pharmacologic options are desired. Propranolol is a nonselective beta blocker that works via vasoconstriction and could decrease expression of vascular endothelial growth factor 1 and basic fibroblast growth factor by downregulating the RAF-mitogen-activated-protein kinase pathway; this is believed to trigger apoptosis in endothelial capillary cells, thereby reducing size of hemangiomas. Hackensack University Medical Center, Hackensack, NJ, and various centers conducting trials Unphased trials completed; phase II and III trials ongoing	Pharmacotherapy (e.g., corticosteroids) Laser treatment	Reduced hemangiomas Improved functional ability Prevention of future complications Improved quality of life	Expert comments indicated this has diffused widely.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Oral growth hormone secretagogue (AEZS-130) for diagnosis of adult growth hormone deficiency	Patients in whom adult growth hormone deficiency (AGHD) has been diagnosed	AGHD affects about 35,000 adults in the U.S., leading to complications such as reduced muscle mass and bone mass, reduced energy levels, increased body fat, cardiac dysfunction, and increased insulin resistance. Current diagnostic measures for growth hormone (GH) deficiency are blood screenings without provocation by an agent, intravenous application of pharmacologic agents to stimulate GH production, or MRI detection of pituitary dysfunction. These diagnostic tests have been deemed invasive, inconclusive, or have unwanted adverse effects. AEZS-130 is an orally active molecule, ghrelin agonist that purportedly stimulates the secretion of GH. Stimulation of GH secretion, which normally occurs in the body during sleep, is believed to allow a clinician to observe the body's response to AEZS-130. If GH levels remain low after administration of AEZS-130, this might confirm a diagnosis of AGHD. Growth hormone secretagogues are potent regulators of lipid, sugar, and protein metabolism that directly stimulate GH secretion from the pituitary gland without the involvement of growth-hormone-releasing hormone or somatostatin. AEZS-130 is administered once, orally, for the stimulation of GH secretion. Æterna Zentaris, Inc., Quebec, Quebec, Canada Phase III trial completed; FDA granted orphan drug status; company filed for fast track designation in Jul 2012	Blood GH testing Insulin-like growth factor level testing Insulin tolerance testing MRI of pituitary to detect dysfunction	Increased sensitivity and specificity Improved diagnostic accuracy Increased patient adherence with recommended diagnostic strategy Reduced risk of adverse events from invasive tests	Expert comments indicated low potential for high impact.
Phrenic nerve stimulation (Remedē system) for central sleep apnea associated with heart failure	Patients in whom central sleep apnea associated with heart failure (HF) has been diagnosed	Remedē™ system is a device that is implanted in chest (similar to pacemaker). It is attached to 2 insulated wires inserted into veins; stimulation wire placed in vein near 1 of patient's phrenic nerves sends communication between diaphragm and the brain, which stimulates phrenic nerve and returns patient to normal breathing. Respicardia, Inc., Minneapolis, MN Phase II trial ongoing	Adaptive servoventilator Oxygen therapy	Slowed progression of HF Improved quality of life	Expert comments indicated low potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Recombinant human parathyroid hormone (PTH 1-84; Natpara) for treatment of hypo-parathyroidism	Patients in whom hypoparathyroidism has been diagnosed	Hypoparathyroidism is a rare disorder in which parathyroid hormone is markedly decreased or absent from the circulation: the hormone regulates and maintains a balance of calcium and phosphorus; low levels of parathyroid hormone may lead to low calcium levels in blood and bones and an increased amount of phosphorus. Therapy to replace missing hormone has been unavailable up to this point; treatment has consisted of daily supplementation of calcium; recombinant human (rh)PTH 1-84 (Natpara™) is hormone replacement therapy intended to provide long-term control of serum calcium and urinary calcium excretion. Administered by injection. Columbia University, New York, NY Phase III trial completed; Biologics License Application to FDA expected to be filed mid-2013	High-dose calcium High- dose vitamin D	Controlled serum and urinary calcium Improved safety Improved quality of life	Expert comments indicated low potential for high impact.
Sclerostin neutralizing monoclonal antibody (AMG 785) for treatment of postmenopausal osteoporosis	Patients in whom postmenopausal osteoporosis (PMO) has been diagnosed	Sclerostin antibodies represent a new class of anabolic therapy for PMO. AMG 785/CDP7851 is a humanized monoclonal antibody that binds to and inhibits sclerostin, a protein secreted by osteocytes that inhibits bone formation by reducing osteoblastogenesis; AMG 785 is intended to allow the body to add more bone to the skeleton through osteoblastogenesis. Delivered via subcutaneous injection in 4 doses. Amgen, Inc., Thousand Oaks, CA Phase II and phase III trials ongoing	Bisphosphonates Calcitonin Denosumab Estrogen therapy Glucagon-like peptide 2 Osteoprotegerin Parathyroid hormone Selective estrogen receptor modulators Strontium ranelate	Higher bone density Reduced fracture rate Improved quality of life Increased survival	Incremental benefit only; no significant unmet need.
Sumatriptan iontophoretic patch (Zelrix) for treatment of acute migraine	Patients who are having an acute migraine episode	The Zelrix patch is new formulation of sumatriptan; a single-use transdermal patch that delivers low, controlled levels of migraine drug sumatriptan; patch is based on SmartRelief patch technology. NuPathe, Inc., Conshohocken, PA Phase III trials completed; new drug application (NDA) submitted to and accepted by FDA Jan 2011; company received complete response letter from FDA in Aug 2011; resubmitted the NDA in Jul 2012	Pharmacotherapy (e.g., pain relievers, triptans, ergot, anti-nauseates, opiates, dexamethasone)	Fast pain relief Reduced side effects compared with high level oral dose	Expert comments indicated low potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
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®) purportedly is an immunomodulator with anti-inflammatory properties, but its exact mechanism of action is not fully known. Researchers believe it may involve reducing the number of activated lymphocytes in the central nervous system, and it is intended to block new synthesis of pyrimidines and reduce T- and B-cell proliferation. The medication is administered as a once daily oral pill in a 7 mg or 14 mg dose. Genzyme Corp., A Sanofi Company, Cambridge, MA FDA approved Sept 2012, for treating RRMS with boxed warning citing risk of hepatotoxicity and teratogenicity	Dimethyl fumarate (investigational) Fingolimod Glatiramer acetate Interferon beta-1a Interferon beta-1b Mitoxantrone Natalizumab	Longer remission time Reduced relapse rate Improved quality of life	Expert comments indicated low potential for high impact because of recently approved drug, Gilenya.

Table 39. AHRQ Priority Condition: 09 Infectious Disease, Including HIV-AIDS: 5 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Disinfection of high-touch surfaces with peracetic acid disinfectant to prevent transmission of hospital-acquired infections	Patients in a hospital or other health care setting in which where health care–acquired infections (HAIs) are a concern	HAIs are a major cause of death in the U.S. About 1 in 20 hospitalized U.S. patients acquires an HAI, resulting in 100,000 deaths each year. Bacteria on surfaces in intensive care units are said to be responsible for 35% to 80% of HAIs. Cleaning the most frequently touched surfaces (i.e., bed rails, bedside tables, call buttons, telephones) in patient rooms daily with a surface sporicidal and disinfectant containing peracetic acid purportedly reduces the transmission of the bacteria *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* more than standard terminal-cleaning procedures using bleach. Cleveland VA Medical Center, Cleveland, OH	Antimicrobial copper touch surfaces Terminal cleaning procedures using bleach and cleaning of visibly soiled surfaces as necessary Ultraviolet light	Reduced infection rates Reduced bacteria isolated from surfaces Reduced morbidity and mortality	Low potential for impact because of incremental benefit.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Duct tape Red Box safe zone to prevent transmission of hospital infections and improve care	Patients with infections requiring isolation	Patients with infections requiring isolation sometimes have simple communication needs, yet, hospital infection control procedures require that personnel gown-up to enter the patient's room prior to communicating, thus introducing a barrier to communication. A duct tape Red Box safe zone can be applied to the floor extending 3 feet outside of the patient's room signifying the barrier to entry of an isolated room and providing a clear boundary where a health care provider can communicate with a patient regarding simple requests such as getting a glass of water; this intervention is intended to decrease the need for excessive gowning and to increase the frequency with which health care providers check on patients in isolation. Trinity Medical Center, Rock Island and Moline, IL, and Bettendorf and Muscatine, IA	Standard infection control procedures	Improved frequency of communication Improved patient experience/ satisfaction Reduced staff hours/costs spent gowning	Expert comments indicated low potential for high impact.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
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	Most HIV-infection diagnostics require 15–30 minutes for preliminary results, which must be confirmed by more costly and time-consuming Western blot and indirect fluorescent antibody tests. Using a multi-test rapid algorithm can 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 purportedly provides greater than 99% sensitivity and specificity and can add to the predictive power of any rapid testing algorithm in use. INSTI uses a novel flow-through technology that purportedly allows more rapid detection of HIV, within 60 seconds, compared with the lateral-flow technology used in rapid HIV detection kits. INSTI also includes a unique procedural control using a true human immunoglobulin G which would allow the test to react only when the correct quantity of human blood is added. The test is said to be highly stable, not requiring refrigeration. By combining pretest and posttest counseling into a single visit, INSTI may increase the capacity of a healthcare facility to provide HIV testing to more patients and promote prompt treatment. BioLytical™ Laboratories, Inc., Richmond, British Columbia, Canada FDA approved Dec 2010 for detection of antibodies to HIV-1 in whole blood, finger stick blood, or plasma specimens	OraQuick Advance® Uni-Gold Recombigen® Clearview® Complete HIV 1/2 and Clearview® HIV 1/2 Stat-Pak Reveal™ HIV	Improved HIV counseling Improved HIV detection Improved treatment outcomes Increased rates of HIV testing	Diffused 2 years post- approval, so it no longer meets horizon scanning system criteria.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Topical microbicide (VivaGel) for treatment of bacterial vaginosis	Patients in whom bacterial vaginosis (BV) has been diagnosed	BV is common and is associated with complications in the female reproductive tract such as premature labor and increased risk of sexually transmitted infections. Current treatments are purported to have low cure rates and be associated with high BV recurrence and complication rates, as well as antibacterial resistance. VivaGel® is a topical lubricant and microbicide gel containing a proprietary dendrimer (polymer), SPL7013. It purportedly inhibits the activity of many viruses and bacteria. Because it is not an antibiotic, the gel might limit development of antibiotic-resistant infections. VivaGel might then be used more frequently or prophylactically without concerns about developing antibiotic resistance. The gel is self-administered at bedtime for treating BV. Dendritic Nanotechnologies, Inc., unit of Starpharma Holdings, Ltd., Melbourne, Australia Phase III trials ongoing	Clindamycin cream (Cleocin®) Metronidazole (Flagyl®) Metronidazole gel (Metrogel®) Tinidazole (Tindamax®)	Increased clinical cure rates Reduced antibiotic-resistance rates Reduced recurrence rates	Trials did not meet primary endpoints required for approval.
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 purportedly 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	Incremental benefit deemed low potential for high impact.

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

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

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

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

Table 42. AHRQ Priority Condition: 12 Pregnancy, Including Preterm Birth: 3 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Cell-free fetal DNA test (MaterniT21 PLUS) for prenatal trisomy 13, 18, and 21 screening	Pregnant mothers at risk of trisomy 21 mutation	Trisomy 21 test (MaterniT21™) examines fetal DNA from the expectant mother's blood in 1st trimester. Massively parallel sequencing is performed to detect excess chromosome 21 DNA of fetal origin, which is indicative of trisomy 21 (Down syndrome). This test might replace invasive tests that pose a risk of miscarriage and allow earlier definitive screening to enable pregnant women to make decision earlier about continuing the pregnancy. Sequenom, Inc., San Diego, CA Late phase clinical trials completed; as of Oct 2011, lab-developed test has been made available to physicians in the U.S.; Sequenom planned to submit premarket approval application to FDA in late 2012 with hope for approval in 2013	Amniocentesis Blood serum markers for trisomy 21 Chorionic villus sampling Ultrasound detection of fetal abnormalities	Increased sensitivity and specificity Improved predictive values Avoided invasive procedures Earlier diagnosis for earlier decision making	Commercial kit development on hold because of ongoing litigation; no longer meets horizon scanning criteria.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Endoglin urine screening test to screen for preeclampsia in pregnancy	Pregnant women at risk of preeclampsia	Urine test intended to detect endoglin, a cell surface glycoprotein that has been shown to be elevated in pregnant women who develop preeclampsia. Miraculins, Inc., Winnipeg, Manitoba, Canada Inverness Medical Professional Diagnostics, Princeton, NJ Assay development and optimization ongoing	Screening pregnant women for elevated blood pressure and high levels of protein in the urine	More specific and earlier detection of preeclampsia Earlier management of secondary preeclampsia symptoms	Expert comments indicated low potential for high impact.
Vaginal progesterone gel (Prochieve) to prevent preterm birth in women with a short cervix	Pregnant women in whom a sonographic short cervix (10–20 mm) has been diagnosed	A sonographic short cervix has been demonstrated to be a good predictor of preterm birth (a major cause of perinatal morbidity and mortality). Current interventions for short cervix include hospital care, bed rest, surgery, and removable devices. According to investigators, progesterone appears to relax the myometrium by repressing the expression of genes that promote labor; micronized vaginal progesterone gel is being investigated to reduce the risk of preterm birth and associated neonatal complications in women with a sonographic short cervix; women self-administer the drug once daily in the morning using a vaginal progesterone capsules kit to prevent dispensing errors; Prochieve 8%, also known as Crinone 8%, is an off-white gel, in a single use, 1-piece, disposable polyethylene vaginal applicator. Watson Pharmaceuticals, Parsippany, NJ FDA advisory panel voted Jan 2012, to not recommend for approval citing trial had not met efficacy endpoint; Feb 2012, FDA issued complete response letter; Watson requested end-of-review meeting with FDA to determine if a viable path forward is possible	Bed rest (hospital admission or at-home) Cervical cerclage Tocolytic therapy Steroids Vaginal pessary	Sustained pregnancy to full-term Reduced preterm (delivery at <3 weeks before term) birth rate Fewer admissions to neonatal intensive care unit Reduced neonatal morbidity Reduced perinatal mortality Shorter length of neonatal stay	No clear path to approval had been identified as of Jan 2013.

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

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

Table 44. AHRQ Priority Condition: 14 Substance Abuse: 1 Intervention

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Off-label quetiapine (Seroquel) for treatment of alcohol dependence	Patients in whom alcohol dependence has been diagnosed	Only 36% of patients with alcohol dependence experience full remission when using available pharmacotherapy. Researchers have recently begun exploring a novel approach to improving medication efficacy, involving the identification of subtypes of patients with alcohol dependence that may respond preferentially to specific medications. One such subpopulation is type B alcohol-dependent patients, characterized by an early age of onset of alcohol problems, high severity of dependence, polydrug use, a high degree of concomitant psychopathology, and a poor prognosis after alcoholism treatment. Selective serotonin reuptake inhibitors have been tried in this population, but showed poor efficacy, leading researchers to suggest that adding dopamine blockade (dopamine is associated with the reward pathway for alcohol) may improve outcomes. Quetiapine is an atypical antipsychotic with activity at both the dopaminergic and serotonergic receptors and a favorable safety profile. This class of drugs has shown improvement in patients with alcohol dependence and concomitant psychiatric illness, suggesting that they could have utility in Type B patients, who are more likely to have associated psychopathology. AstraZeneca, London, UK (manufacturer) University of Pennsylvania, Philadelphia (investigator) Several phase III trials completed; 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 it has supplied medication for off-label trials	Pharmacotherapy (e.g., acamprosate, disulfiram, naltrexone) Psychotherapy (e.g., cognitive behavioral therapy	Reduced alcohol craving Reduced alcohol consumption Reduced relapse Improved health outcomes associated with abstinence Improved quality of life	Low potential for high impact on basis of weak data from completed trials; not likely to diffuse.

Table 45. AHRQ Priority Condition: 15 Cross-Cutting: 3 Interventions

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Barbershop-based medical screening and health education programs	Patrons of community barbershops	Health disparities in cardiovascular, diabetic, cancer, and mental health disease areas exist in minority areas. For example, African-American men have the highest death rate from hypertension of any race or ethnic group, or compared with women in the U.S. Furthermore, the U.S. Centers for Disease Control and Prevention has issued a new priority to develop novel hypertension-based outreach programs with community partners and deliver intervention messages that resonate with African-American men because of a paucity of programs to address this need. Barbershops are being used as an access point to conduct screenings for hypertension, diabetes, prostate cancer, and mental health. One program, the Black Barbershop Health Outreach Program (BBHOP), uses medical and nonmedical volunteers (including barbers) to screen for hypertension and diabetes because African-American-owned barbershops are considered a cultural institution within African-American communities. They provide an environment of trust and a means for disseminating health education. A 2nd program, the Barbershop Health Network, includes mental health screenings by physician and evening-hour clinics at UMass Memorial Medical Center, Worcester, MA, for patient followup. BBHOP: Diabetic Amputation Prevention Foundation, Inglewood, CA Barbershop Health Network, Worcester, MA Pilot program completed	Clinic-based health screenings	Improved health outcomes Improved access to care Reduced health disparities	Launched and implemented since 2008.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Medical homes network (South Side Healthcare Collaborative) to link emergency department patients to community care	Patients who do not have a primary care medical home (PCMH)	Patients without PCMHs often adopt less preventative care, experience exacerbations of ambulatory-care-sensitive conditions, contract illnesses and health conditions earlier, and seek care in the emergency department (ED), placing an avoidable burden on the health care system (e.g., ED overcrowding) and negatively affecting their personal health; EDs are not intended to treat or manage chronic illness or to offer preventive care. South Side Healthcare Collaborative is a program intended to link ED patients with (18 hospital-affiliated) community providers via an ED-based patient navigator (i.e., patient advocate); patient advocates approach eligible patients who are flagged by an ED electronic tracking system and offer patients services provided by primary-care referral and appropriate dental, mental health, and substance-abuse facilities. Appointments are scheduled for the patient, and pertinent ED medical data is faxed to the outlying sites. University of Chicago Medical Center, Chicago, IL Pilot trial completed	Current use of ED system for nonurgent conditions ED-MC Connect (Primary Care Coalition of Montgomery County, MD—PCMH model) ED Diversion Project (District of Columbia Primary Care Association—PCMH model)	Appropriate primary care use Increased mental health, dental, substance abuse care use Improved health prevention and promotion Improved patient health outcomes Reduced ED use for nonemergent conditions	Diffused; launched in 2009.

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts	Reason
Self-service automated kiosks to triage and treatment in the emergency department	Noncritical patients visiting an emergency department (ED)	Nearly half of ED patients experience long wait times because they are classified as low-risk; wait times and overcrowding contribute to poorer health outcomes and patient dissatisfaction. Kiosk-based patient self-service triage and treatment enables a patient to, without direct staff interaction, complete registration and assessment, measure vital signs, and dispense medication based on telemedicine control by a physician and pharmacist. The approach is intended to be implemented as follows: (1) patients register at the 1st kiosk by swiping/scanning their insurance cards; kiosk touch screen guides them through self-assessment where they register, describe symptoms, and outline the reasons for their visit; (2) patients' vital signs are taken at the 2nd kiosk; and (3) patients speak with a doctor via video conferencing for diagnosis and, if medication is prescribed, it is dispensed. NCR Corp., Duluth, GA; StayHealthy, Monrovia, CA Launched in Canada Sept 2010	Standard, non-automated ED triage and treatment	Reduced ED wait times Reduced ED overcrowding Improved health outcomes Improved patient satisfaction Reduced costs of ED visits for minor conditions	Anticipated launch in U.S. has not occurred in past two years of tracking in horizon scanning system.