Priority Area 01: Arthritis and Nontraumatic Joint Disease
Potential High Impact Interventions

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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. HHSA29020100006C). 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.

This report’s content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual Topic Profiles are developed for technologies and programs that appear to be closer to diffusion into practice in the United States. Drafts of those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify those interventions that experts deem, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually, and topics included may change depending on expert comments received on interventions issued for comment during the preceding six months.

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

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

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor technologies and innovations in health care and to create an inventory of 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 the identification and monitoring of 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 the analysis of 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 utilization and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High Impact report. Send comments 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 e-mail to effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ’s interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as “interventions.” The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 7,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0 to 4 years of potential diffusion (e.g., in phase III trials for pharmaceuticals or biotechnologies or in phase II or a trial with some preliminary efficacy data on the target population for devices and programs) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling a profile on topics and issuing topic profile drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 350 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COI). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more
than two experts with a possible COI are considered out of a total of the seven or eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores and/or supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the high impact potential designation. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the potential high impact range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as potential high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

**Results**

The table below lists the six topics for which (1) preliminary phase III or later phase data were available; (2) information was compiled and sent for expert comment before November 1, 2011; and (3) we received six to eight sets of comments from experts between February 2011 and November 1, 2011. (A total of 27 topics were being tracked in this priority area in the system as of November 2011.) For purposes of the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). Each of these six topics emerged as having potential high impact on the basis of experts’ comments and their assessment of potential impact. They are listed in the table below.

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**Discussion**

The material on interventions in this Executive Summary and report is organized according alphabetically by disease state. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary. The topics that emerged as higher impact were in disease categories of gout, osteoarthritis (OA), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE), where experts perceived considerable unmet need because of the lack of effective treatments and the debilitating nature of these conditions.

**Gout**

Gout is a rheumatic disease resulting from an uncontrolled metabolic disorder, hyperuricemia, in which uric acid crystals are deposited in body tissues and fluids and can cause swelling, inflammation, and severe pain. Recurring flares can cause joint damage. Overproduction or underexcretion of uric
acid is the underlying cause of the condition, which affects about 6 million adults in the U.S. Patients may have chronic disease as well as acute flares, each requiring different treatment approaches. An estimated 750,000 gout patients initiate uric acid-lowering drug therapy in the U.S. annually. About 3% of those affected by gout do not respond adequately to conventional therapies, so there is interest in new options with new mechanisms of action to help these patients. Experts commenting on these interventions identified two agents in development as potentially high impact for this disorder.

**Pegloticase (Krystexxa) for Treatment of Gout**

- **Key facts:** Pegloticase (Krystexxa®, Savient Pharmaceuticals, East Brunswick, NJ) is the first drug approved (September 2010) by the U.S. Food and Drug Administration (FDA) for treatment of gout in adult patients who continue to experience chronic gout with abnormal serum uric acid despite conventional therapy and whose symptoms are not well managed with maximum medically suitable dose of xanthine oxidase inhibitors. The labeling includes a black box warning about possible anaphylaxis and infusion reactions during and after administration of any pegloticase infusion, including first and subsequent infusions. The drug is a genetically engineered form of recombinant porcine urate oxidase, an enzyme not found in humans that is responsible for breaking down uric acid. It is given intravenously in a clinical setting by health care providers prepared to manage anaphylaxis. The company announced that the drug’s wholesale acquisition cost would be $2,300 per 8mg vial, which totals $59,800 per patient per year based on 8mg dosed every 2 wks. As of January 1, 2012, Medicare assigned a product-specific billing code, or permanent J-code, for the drug.

- **Key Expert Comments:** Overall, experts were split on the potential impact of pegloticase in addressing the unmet need for patients with gout that is not responsive to current therapies. The experts providing comments thought that the therapy’s anticipated high cost and possible adverse events might temper clinical and patient acceptance despite its ability to reduce the presence of uric acid crystals in some treatment-refractory patients. Some experts thought that adoption might also discourage positive diet and lifestyle changes by patients and generate a mixed impact on health promotion.

- **Potential for High Impact:** Moderately high impact

**Rilonacept (Arcalyst) for Treatment of Gout**

- **Key Facts:** The targeted biologic therapy, rilonacept (Arcalyst®, Regeneron Pharmaceuticals, Inc., Tarrytown, NY) is in phase III development and is intended to block the inflammatory action of the cytokine interleukin 1 beta (IL-1-beta) to prevent acute gout flares in patients initiating allopurinol therapy. It is not under study for long-term use. When patients initiate allopurinol therapy, the breakup of uric acid crystals, previously deposited in joints, can result in release of IL-1, causing acute flares of joint pain and inflammation. IL-1 may be a problematic target with respect to safety in the gout patient population, however, and one IL-1 inhibitor in development stalled earlier this year because of an FDA advisory panel recommendation against approval. Canakinumab (Ilaris®, Novartis AG, Basel, Switzerland), an IL-1 antagonist, intended for treatment of acute gout flares in patients who do not respond to nonsteroidal antiinflammatory drugs (NSAIDs) or colchicine, was not recommended because of concerns about the risk-benefit profile. While panel members noted that efficacy was demonstrated, they cited safety concerns about infection, cardiovascular, and renal function risks. Thus, while IL-1 inhibition has shown
some success in late-phase trials in preventing acute gout flares in patients, biologics targeting this cytokine might be controversial because of concerns about their safety and their potentially high cost. Thus, rilonacept could have an uphill battle for approval, although use of rilonacept when initiating allopurinol therapy (rather than using it indefinitely, as in the canakinumab trials) to prevent gout flares, might make some difference in the risk-benefit ratio and favor rilonacept.

- **Key Expert Comments:** Rilonacept is not expected to shift the treatment paradigm for most gout patients because it is expected to be prescribed more by specialists, yet primary care physicians treat many cases of gout. However, experts thought that as a new therapy, rilonacept could diffuse more widely than intended due to patient-oriented marketing activities. Biologic costs, reimbursement, and injection administration route might pose barriers to acceptance, in addition to the natural tendency to use caution for new therapies with a small evidence base. Current preliminary data show that the use of rilonacept in the right population could potentially improve health outcomes.

- **Potential for High Impact:** Lower range of high impact

### Osteoarthritis

OA affects millions of Americans, and is expected to affect a greater proportion of the population in the coming decades as more people reach age 65 years and older. OA, the most common form of arthritis, is a chronic condition characterized by the progressive loss of cartilage in one or more joints. As the cartilage that cushions a joint gradually wears away from use, bones rub against each other causing pain, stiffness, and loss of joint flexibility. Increasing age, obesity, injury to or overuse of a joint, and genetics can all contribute to the disease. The U.S. National Institute of Arthritis and Musculoskeletal and Skin Disorders estimates that almost 27 million people have some degree of osteoarthritis. Current treatments for osteoarthritis include over-the-counter analgesics and NSAIDs, exercise and/or physical therapy, and weight loss if indicated. More severe cases may warrant corticosteroid or visco-supplementation injections. However these agents have no anabolic, or anticatabolic activity on chondrocytes. Two interventions are presented that might disrupt the current OA treatment paradigm because of their potential to regenerate articular cartilage or inhibit the degenerative process of OA. These interventions are not proprietary products, but rather biologic products prepared at the medical institutions delivering them to the patients.

### Mesenchymal Stem Cell Therapy for Treatment of Osteoarthritis

- **Key facts:** Mesenchymal stem cell (MSC) therapy for OA consists of adult stem cells derived from the patient’s own bone marrow, synovium, periosteum, skeletal muscle, or adipose tissue and combined with platelet-rich plasma (PRP), and fat matrix. The preparation is then injected into the intra-articular space. The methods used to prepare MSCs have not yet been standardized, and can differ among health care facilities making and administering the preparations. This may lead to different outcomes among treatment centers. MSCs are purported to lead to the regeneration of cartilage due to either the secretion of growth factors by the cells or differentiation of MSC into chondrocytes; the exact mechanism remains unknown. MSCs are purported to have immunomodulatory, antiapoptotic, proliferative, and angiogenic effects on cells in the intra-articular space. While the efficacy of MSC treatment for OA has not yet been conclusively established, the treatment can conceivably be performed by any suitably equipped health care center, and some physicians have begun to offer it as a treatment.
**Key Expert Comments:** Experts were divided on the impact of MSC therapy on health outcomes of patients with OA because of the paucity of evidence at this point. Some experts stated that if the therapy is proven effective in regenerating joint cartilage and restoring function, it would mark a huge advancement, allowing patients to avoid the cost and complications of joint replacement surgery. Other experts stated that the therapy might have a more limited role as an adjunctive treatment or as another option among many from which patients can choose.

**Potential for High Impact:** Moderately high impact

### Platelet-Rich Plasma Therapy

**Key facts:** Platelet-rich plasma (PRP) is a preparation of the plasma portion of a patient’s blood that has been processed to achieve a higher-than-normal concentration of platelets, which are purported to secrete a wide variety of growth factors and cytokines, and may promote tissue regeneration and repair. As such, PRP is thought by some researchers to have potential regenerative effects on cartilage in patients with OA. PRP therapy has been used by high-profile athletes to speed their recovery process after soft tissue injuries. PRP therapy is also injected directly into the intra-articular space, under ultrasound guidance. As with MSC therapy, preparation protocols and frequency of injection vary depending on each treatment center’s protocol for preparing PRP.

**Key Expert Comments:** Overall experts were divided on the impact that PRP might have on OA treatment. Several experts stated that if PRP were to become standard first-line therapy and actually regenerate joint cartilage and restore function, it would have a large impact on patient outcomes and be a huge cost-saving advance in OA treatment. However, more data and clinical experience are needed to demonstrate whether the procedure regenerates cartilage, has a durable effect, and reduces the need for additional OA treatment for the affected joint.

**Potential for High Impact:** Moderately high impact

### Rheumatoid Arthritis

RA is a chronic inflammatory disease that affects an individual’s joints throughout the body and often progresses to permanent joint damage, deformity, and functional disability, so the disease burden is high. In recent years, biologic therapies such as monoclonal antibodies (infliximab, adalimumab, tocilizumab) and tumor necrosis factor alpha inhibitors (etanercept) have become standard care for RA that no longer responds to first-line therapy of disease-modifying antirheumatic drugs (DMARDs). Biologics are intended to reduce disease activity, slow joint damage, and improve physical function. However, they require administration by intramuscular, subcutaneous, or intravenous injection and are associated with increased incidence of immunosuppression, resulting in serious infections, including tuberculosis. New RA therapies with improved efficacy, tolerability, and convenience that can effectively control RA symptoms without severe immunosuppression represent a challenging, but significant, unmet need. Expert comments led to designation of one RA therapy in phase III development based on expert comments.

### Tofacitinib for Treatment of Rheumatoid Arthritis

**Key facts:** Tofacitinib (Pfizer, Inc., New York, NY) is selective and potent oral tyrosine kinase inhibitor that is being investigated as a targeted DMARD. Tofacitinib inhibits a 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 this pathway, tofacitinib may suppress the inflammatory reactions that are the basis of RA. In the most recent phase III trials, tofacitinib was administered in once-daily (20 mg) or twice-daily (1, 3, 5, 10, and 15 mg) doses. Phase III trial results are expected in late 2011 and 2012. No information regarding submission of an new drug application to FDA was available at the time this report was prepared in November 2011.

- **Key Expert Comments**: Overall, experts thought that the drug might address the unmet need for a new more effective RA therapy with less severe immunosuppression than other DMARDs and enhanced convenience and lower cost because of oral administration. Experts thought that tofacitinib might also lead to health promotion via earlier diagnosis and treatment in the primary care setting. These improvements in access to care might reduce costs and health disparities. Tofacitinib might have more favorable pricing than injectable biologic therapies (which has yet to be determined), but some experts expressed strong concerns regarding its safety and tolerability due to safety concerns over infections reported in trials thus far. These safety concerns may present barriers to approval or barriers to diffusion if approved.

- **Potential for High Impact**: Moderately high impact

**Systemic Lupus Erythematosus**

SLE is a chronic and complex multisystem autoimmune disease characterized by chronic inflammatory damage to multiple organ systems; it has a substantial mortality rate. The etiology of SLE is poorly understood. Approximately half of patients with SLE experience a relapsing-remitting pattern of periodic flares followed by sustained periods of full or partial recovery; a very small minority of patients experience prolonged periods of disease-free remission between flares. The remaining proportion of SLE patients experiences the disease as a continuous condition. Of the estimated 1.5 million Americans with some form of lupus, about 70% have SLE, and about half of SLE patients experience organ damage within 5 years of diagnosis. SLE patients have a mortality rate 4 times greater than the general population, and the substantial mortality is due primarily to comorbid renal failure, pulmonary fibrosis, or heart failure, rather than the underlying autoimmune process itself. SLE is 6 to 8 times as prevalent among Afro-Caribbean and Asian populations as Caucasians and is about 8 to 10 times as prevalent in women than in men, especially in females from 15 to 40 years of age.

**Belimumab**

- **Key facts**: No new treatments had been developed or approved for SLE in the past 40 years until approval of belimumab (Benlysta®, (Human Genome Sciences, Rockville, MD, and GlaxoSmithKline, Middlesex, UK) in March 2011. Thus, this biologic, administered by intravenous infusion, was deemed to address an important unmet need. Belimumab is a monoclonal antibody targeting the B-lymphocyte stimulator (BLYS). BLYS plays an important role in stimulating B-lymphocyte production when the human body is battling an infection, but the overproduction has been shown to cause production of autoantibodies and autoimmune-like disease symptoms in mice. By inhibiting the biologic activity of BLYS, belimumab inhibits the stimulation, proliferation, and differentiation of B cells. Although many patients and clinicians are eager to have a new treatment option for this disease, belimumab may result in controversy because of the high anticipated cost of treatment.
combined with modest improvements in disease status. Early reports from financial analysts indicated that belimumab had not diffused as rapidly as expected, possibly because of controversy over its cost-benefit ratio. The annual per patient cost for belimumab is about $35,000. The company started phase III trials of a subcutaneous formulation in December 2011. A competitive product, LY2127399 (Eli Lilly and Co., Indianapolis, IN), is being developed as an IV infusion and subcutaneous injectable drug for treatment of SLE. LY2127399 is a fully human immunoglobulin G4 monoclonal antibody targeting the B-lymphocyte stimulator (BLyS, BAFF).

- **Key Expert Comments:** Overall, the experts commenting on this topic stated that belimumab could have a significant impact on SLE patients with clinically active disease that is not responding to other therapies. However, as a new agent, belimumab has a far less developed record of safety and efficacy than first-line agents used to treat SLE, which could prevent some patients and physicians from rapidly accepting the therapy. Additionally, clinical studies have shown that patients taking belimumab have an increased risk of infection. Considering the drug’s high cost and the fact that the new antibody may not completely replace the use of rituximab, the impact of this much-publicized therapy was considered by experts as moderate in improving treatment outcomes and advancing paradigms for SLE treatment and management. The cost-benefit ratio of belimumab is expected to be a hotly debated issue that will affect the diffusion of this therapy.

- **Potential for High Impact:** Moderately high impact
Gout Interventions
**Intervention**

**Pegloticase (Krystexxa) for treatment of chronic gout**

Pegloticase (Krystexxa®, Savient Pharmaceuticals, East Brunswick, NJ) is the first drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of gout in patients whose disease is unresponsive to conventional therapy or for whom conventional therapy with xanthine oxidase inhibitors is not indicated.\(^1\)\(^2\) It was approved in September 2010\(^3\) and on January 1, 2012, a billing code (J code) from the Centers for Medicare and Medicaid Services was slated to go into effect. The drug is a genetically engineered form of recombinant porcine urate oxidase, an enzyme not found in humans that is responsible for breaking down uric acid.\(^4\) Similar to this enzyme, pegloticase lowers uric acid levels by converting uric acid into a highly soluble waste product called allantoin, which can be more easily eliminated from the body.\(^2\) Pegloticase is administered intravenously in a clinical setting and by health care providers prepared to manage anaphylaxis.\(^3\) The recommended dose is 8 mg via intravenous (IV) infusion every 2 weeks in adult patients.\(^5\)

In two similar 2-year extensions of clinical trials, patients (n = 212) with chronic gout were given pegloticase (8 mg) administered as a 2-hour IV infusion every 2 or 4 weeks over 6 months. Normalization of patient plasma uric acid levels was measured at 3 and 6 months. Investigators reported a significant reduction in the number of tender and swollen joints and an improvement in patient-reported outcomes in pegloticase-treated patients who had received pegloticase every 2 weeks, compared with placebo-treated patients. Investigators reported that a large proportion of these treated patients had complete elimination of gout compared with placebo-treated patients, although this was not a statistically significant result. For both treatment groups, investigators reported that symptom improvement was greater in plasma uric acid responders than nonresponders, although nonresponders appeared to show improvement versus placebo.\(^2\) In another open-label extension, patients (n = 82) who elected to continue pegloticase therapy after completing phase III trials were administered 8 mg pegloticase every 2 or 4 weeks. Investigators reported that “continued normalization of plasma uric acid (PUA) was seen in 100% and 70% of patients who had normalized PUA during the original phase II trials, in the 2- and 4-week dosing groups, respectively. A total of 25% of patients who didn’t have PUA responses during the original trials showed PUA normalization during the extension trial. Up to 31% of the patients who were non-responders for the resolution of gout in the previous studies showed a complete response. No incidence of gout flares was reported in the 2-week arm after 5-months. Infusion reactions were reported by 21% of patients, a similar level to that reported during the original trials.”\(^2\)

Pegloticase is contraindicated in patients with a glucose-6-phosphate dehydrogenase (G6PD) deficiency. Treatment with pegloticase may cause hemolysis and methemoglobinemia (a blood disorder in which an abnormal amount of hemoglobin builds up in the blood) in these patients. Individuals at high risk of G6PD deficiency, including patients of African or Mediterranean descent, should be evaluated for G6PD deficiency before treatment with pegloticase.\(^3\)\(^6\) Additionally, use of pegloticase is not recommended in patients with asymptomatic hyperuricemia.\(^3\)\(^6\) The company announced that the drug’s wholesale acquisition cost would be $2,300 per 8mg vial, which totals $59,800 per patient per year based on 8mg dosed every 2 wks. As of January 1, 2012, Medicare assigned a product-specific billing code, or permanent J-code, for the drug.
Clinical Pathway at Point of This Intervention

Clinical guidelines state that treatment is most effective when initiated within 24 hours of a flare. Therapy for acute flares consists of nonsteroidal antiinflammatory drugs (NSAIDs), intramuscular or intra-articular steroid injections (as indicated), and oral (not IV) colchicine. Diet and lifestyle modifications (e.g., losing weight, avoiding alcohol, reducing dietary purine intake) may help prevent attacks. Medication changes (e.g., cessation of diuretics, antileukemic agents, aspirin, cyclosporine, epinephrine, ergotamine, ethacrynic acid, ethanol, loop diuretics [e.g., furosemide], nicotinic acid, pyrazinamide, salicylates, thiazide diuretics) associated with hyperuricemia may also help. Preventive therapy to lower blood uric acid levels in people with recurrent acute flares or chronic gout usually involves allopurinol or a new drug, febuxostat.

Pegloticase can be used for patients who are unresponsive to conventional therapy or for whom conventional therapy is not indicated.

Figure 1. Overall High Impact Potential: Pegloticase

Overall, experts were split on the impact that pegloticase might have on addressing the unmet need for patients with gout that is not responsive to current therapies. They concurred that the therapy could have a high cost and pose a high risk to patients because of adverse events, even though it may effectively reduce the presence of uric acid crystals in treatment-refractory patients. The adverse event risks, they thought, might limit adoption, reimbursement, and diffusion. However, if pegloticase does gain acceptance by the intended target population, the drug could also discourage positive diet and lifestyle changes, which could have a mixed impact on health promotion. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on this intervention. Overall, the experts generally concurred that there is an unmet need for treatment options for patients whose chronic gout is not well controlled with current medications and lifestyle modifications. Experts agreed that the underlying theory of pegloticase is sound and that this therapy has the potential to improve health outcomes in this subset of gout patients. However, some experts thought that some significant safety concerns were associated with the therapy.

Overall, experts did not think that pegloticase use would lead to a major shift in the understanding and treatment models for chronic gout as a whole. However, in the subset of patients for whom it is intended, pegloticase could significantly alter their management by providing an additional effective option. Experts stated that routine IV administration of the enzyme could increase demands on staffing and shift the treatment paradigm away from diet and lifestyle modification and self-administered therapy. Some experts also added that infusion therapy might be new to physicians who routinely treat gout, shifting treatment to infusion centers for some patients. However, one expert offering a clinical perspective stated that pegloticase should only be prescribed by rheumatologists to ensure that this treatment is used in the appropriate patient populations, and many rheumatologists are currently administering IV infusions.

Experts stated pegloticase would increase the cost of care. The black box warning and need to monitor patients for adverse events were also seen as increasing the cost of care. The potential for
adverse events was seen as a potentially significant barrier to care for patients and physicians. The need for IV administration was also identified as a barrier for patients. One expert offering a health systems perspective stated that some physicians may view the expensive IV administration of pegloticase as significant source of revenue, increasing acceptance.
**Intervention**

**Rilonacept (Arcalyst) for prevention and treatment of acute gout**

During gout flares, monosodium urate crystals accumulate in the joints, stimulating an innate immune response by macrophages and monocytes.\(^{15}\) Innate immune receptors (i.e., toll-like receptors) on the surface of these cells recognize the crystals and facilitate their uptake (phagocytosis).\(^{15}\) Once inside the phagocyte, urate crystals are recognized by the NALP3 (cryopyrin) inflammasome, which initiates a proinflammatory signaling cascade resulting in the production of interleukin 1 beta (IL-1-beta), interleukin 18, and tumor necrosis factor alpha (TNF-alpha). The production of these cytokines further amplifies the inflammatory process by recruiting more leukocytes to the area, precipitating a gout flare.\(^{15}\) In particular, interleukin 1-beta (IL-1) has been identified as a key mediator of gout flares because IL-1 receptor signaling leads to the production of additional proinflammatory cytokines including interleukin 6, TNF-alpha, and neutrophil-attracting chemokines.\(^{15}\) Uric-acid-lowering medicines, such as allopurinol, may be prescribed to eliminate the uric acid crystals in patients with frequent gout flares. During the initial months of uric acid-lowering therapy, previously deposited urate crystals can dissolve and break up, triggering the release of IL-1, and causing acute flares.\(^{16}\) Currently, NSAIDS, intramuscular or intra-articular steroid injections, and oral colchicine may be used to treat gout flares. However, some patients cannot tolerate these therapies, which may be associated with significant side effects.\(^{15}\) New therapies are needed to treat acute gout flares in the approximately 750,000 patients who have gout and who initiate uric acid-lowering drug therapy annually in the United States.\(^{16}\)

Rilonacept (Arcalyst®, Regeneron Pharmaceuticals, Inc., Tarrytown, NY) is an agent in phase III development that blocks the activity of IL-1; in March 2008, the drug was launched for treatment of cryopyrin-associated periodic syndromes, including familial cold autoinflammatory syndrome and Muckle-Wells syndrome in adults and children aged 12 years or older.\(^{17}\)

Rilonacept is a recombinant protein IL-1 antagonist that acts as a high-affinity cytokine trap intended to prevent IL-1-associated inflammation in patients who experience gout flares.\(^{17}\) Its developer is pursuing an indication for prevention of acute gout flares in patients initiating urate-lowering therapy.\(^{16,18}\) A dimeric fusion protein, rilonacept consists of the ligand binding domains of the extracellular portions of the human IL-1 RI (IL-1 receptor component) and IL-1RacP (IL-1 receptor accessory protein) linked in line to the Fc portion of human immunoglobulin G1.\(^{19}\) Rilonacept is designed to be a high-affinity cytokine trap with the intention of binding and neutralizing circulating IL-1-beta before it can bind to cell-surface receptors and promote inflammation.\(^{20}\) In trials, it is administered subcutaneously by patients in a weekly dosing regimen, which may position the biologic favorably with clinicians and patients when compared with the daily administration of the IL-1 receptor antagonist anakinra, which is often used off-label for the treatment of gout.\(^{21}\)

In one phase III trial, patients experiencing acute gout attacks (n = 225; 1:1:1 randomization) were given either 320 mg rilonacept injection on day 1 followed by oral placebo for 12 days, 320 mg injection of rilonacept on day 1 plus oral indomethacin for 12 days, or placebo injection on day 1 followed by oral indomethacin for 12 days.\(^{22}\) Researchers reported that no significant benefit from the indomethacin plus rilonacept combination was observed. “Subjects treated with indomethacin alone had an average reduction of 1.55 points from baseline on the Likert scale, those on indomethacin plus rilonacept had an average reduction of 1.55 points, and those on rilonacept alone experienced an average reduction of just 0.69 points. Adverse events reported at an incidence of at least 5% in any group were headache (7.8% indomethacin alone, 5.5% with indomethacin plus rilonacept, and 10.8%
with rilonacept alone) and neurological signs and symptoms (dizziness; 5.2% with indomethacin alone, 4.1% with indomethacin plus rilonacept, and 2.7% with rilonacept alone).  

In a second double-blind, placebo-controlled, phase III study (PRE-SURGE 2), investigators reported that gout patients initiating allopurinol therapy, who also self-administered a weekly subcutaneous injection of rilonacept 160 or 80 mg had a 72% decrease in the mean number of gout flares compared with the placebo group (p <0.0001). The most frequently reported adverse events included injection-site reaction, infection, musculoskeletal pain/discomfort, and headache.  

The company filed a new drug application with FDA for gout indications in mid-2011.

Clinical Pathway at Point of This Intervention

Clinical guidelines state that treatment is most effective when initiated within 24 hours of a flare. Therapy for acute flares consists of NSAIDs, intramuscular or intra-articular steroid injections (as indicated), and oral (not intravenous) colchicine. Diet and lifestyle modifications (e.g., losing weight, avoiding alcohol, reducing dietary purine intake) may help prevent attacks. Medication changes (e.g., cessation of diuretics, antileukemic agents, aspirin, cyclosporine, epinephrine, ergotamine, ethacrynic acid, ethanol, loop diuretics [e.g., furosemide], nicotinic acid, pyrazinamide, salicylates, thiazide diuretics) associated with hyperuricemia may also help. Preventive therapy to lower blood uric acid levels in people with recurrent acute flares or chronic gout usually involves allopurinol or a new drug, febuxostat. Rilonacept is intended to prevent gout flares in patients with chronic gout initiating urate lowering therapy by binding IL-1-beta and preventing acute inflammation.

Figure 2. Overall High Impact Potential: Rilonacept

Experts commenting on this intervention thought rilonacept might be able to address a significant unmet need by improving health outcomes in a small population of patients with gout whose disease does not respond to currently available therapy or who are contraindicated for current therapies. Rilonacept is not expected to shift the treatment paradigm for most gout patients because it is expected to be prescribed more by specialists, yet primary care physicians treat many cases of gout. However, experts thought that as a new therapy, rilonacept could diffuse more widely than intended due to patient-oriented marketing activities. Biologic costs, reimbursement, and injection administration route might pose barriers to acceptance, in addition to the natural tendency to use caution for new therapies with a small evidence base. Current preliminary data show that the use of rilonacept in the right population could potentially improve health outcomes. Based on this input, our overall assessment is that this intervention is in the lower end of the high potential impact range.

Results and Discussion of Comments

Six experts, with clinical, research and health systems backgrounds, offered comments on rilonacept. Overall, experts were split regarding the unmet need for additional treatment options for prevention and treatment of acute gout. Current options appear to be generally effective. However, a small proportion of patients do not respond to therapy or are contraindicated for current therapies and need options.
Experts thought the underlying theory of inhibiting IL-1 activity was sound. Although clinical experts were optimistic about the ability of rilonacept to improve health outcomes in gout patients, they generally wanted to see more data to be certain.

In general, experts did not think that rilonacept would lead to a major shift in understanding and treatment of chronic gout as a whole. However, in the subset of patients whose disease is unresponsive or who are contraindicated to current therapies, more care could be shifted to specialists for treatment because of rilonacept. Additionally, patients would have to learn how to self-administer the biologic. One expert offering a health systems perspective also stated that direct-to-consumer marketing could shift the use of rilonacept earlier in the treatment/management model leading to a larger impact. This expert also stated that such marketing activities could influence more patients to go to emergency departments with gout flares requesting treatment with a biologic.

Rilonacept is expected to greatly increase the cost of gout care, which could be offset somewhat by decreasing the frequency and duration of hospitalizations from acute flares. Cost, reimbursement, and the cost-benefit ratio are expected to be a source of controversy and may pose barriers to patient and physician acceptance, especially if health insurers do not cover it or have conditional coverage. One expert offering a clinical perspective also stated that for rilonacept, self-administered injections can be met with resistance as evidenced by poor adherence to treatment in patients with diabetes, where the consequences can be severe. Additionally, gout patients are usually treated by a primary care physician, and having to follow up with a specialist might reduce acceptance of rilonacept. For clinicians, adverse events and the potential for liability from using new agents may pose barriers to acceptance of the IL-1 inhibitor if the benefits do not seem significant.
Osteoarthritis Interventions
Intervention

Mesenchymal stem cell therapy for treatment of osteoarthritis

Mesenchymal stem cells (MSCs) are adult stem cells that are involved in maintaining the relative stability of internal physiologic conditions of many tissue types in the body. As progenitor cells, MSCs are purported to retain the ability to differentiate into a number of cell types, including chondrocytes, which are the cells responsible for maintaining cartilage. MSCs derived from the patient (autologous) can be isolated and expanded in vitro, providing patient-matched stem cells to treat the large cartilage defects observed in osteoarthritis. However, the mechanism by which these cells lead to cartilage generation is still unclear. MSCs may differentiate into chondrocytes and fill in a cartilage defect. In addition, MSCs are also known to have effects on the intra-articular environment including immunomodulation, host cell survival, proliferation of endogenous tissue progenitor cells, local angiogenesis, and inhibition of fibrosis. The methods used to prepare MSCs have not yet been standardized; the cells can be isolated from bone marrow, synovium, periosteum, skeletal muscle, and adipose tissue. MSCs isolated from these different tissues are purported to exhibit differences in their ability to proliferate and/or their propensity to differentiate into chondrocytes. To have an adequate number of MSCs for treatment, the cells from a tissue sample must either be concentrated by centrifugation or expanded in vitro. The method chosen to acquire adequate cells may also influence the nature of the MSCs used for treatment. In addition patient characteristics such as age and the presence of osteoarthritis have been shown to affect the ability of MSCs to differentiate into chondrocytes. Thus, many factors can introduce variability in this procedure.

In patients with osteoarthritis of the knee with Kellgren-Lawrence status of II, III, or IV (n = 22) treated with a combination of autologous MSC (concentrated bone marrow isolate), platelet-rich plasma (PRP), and fat matrix, injected into the intra-articular space, improvements in several disease measures were reported. The investigators reported patients treated with MSC therapy had improvements in patient pain measured on a visual analog scale (VAS) improved 57% and 68% from baseline at 6 and 12 months, respectively. Patient Global Assessment of Disease improved 38% and 62% from baseline at 6 and 12 months, respectively. Physician Global Assessment improved 60% and 78% from baseline at 6 and 12 months, respectively. Fifty-Foot Walk Pain improved 47% and 70% from baseline at 6 and 12 months, respectively. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) improved 50% and 71% from baseline at 6 and 12 months, respectively. Ultrasound measurement of patellofemoral cartilage thickness at 7 standardized points also revealed that patients treated with MSC had a 0.4 mm and 0.8 mm mean improvement from baseline to 6 months and 12 months, respectively.

While the efficacy of MSC treatment for osteoarthritis has not yet been thoroughly established, the treatment could conceivably be performed by any suitably equipped health care center and some physicians have begun to offer it as a treatment. One center currently offering MSC treatment quotes a price of approximately $10,000 for a treatment regimen that involves a single injection of a bone marrow concentrate, PRP, and autologous fat scaffold plus the required pretreatment and posttreatment assessments. A second center offering the treatment has been reported to charge from $7,000 to $9,000 for the procedure.

Clinical Pathway at Point of This Intervention

Initial treatments for knee osteoarthritis include over-the-counter analgesics and nonsteroidal antiinflammatory drugs (NSAIDs), exercise and/or physical therapy, and weight loss if indicated. More severe cases can warrant prescription painkillers, corticosteroid injections, or visco-
supplementation.\textsuperscript{40} In patients with persistent symptoms despite optimal treatment, surgery, including joint replacement, might be recommended.\textsuperscript{40} If proven to be effective for treatment of knee osteoarthritis, MSC treatment would be employed as a cartilage-restoring technique in patients with uncontrolled osteoarthritis pain who are unwilling or unable to undergo knee replacement surgery.

**Figure 3. Overall High Impact Potential: Mesenchymal stem cell therapy**

Experts were divided on the impact that MSC therapy might have on patients with OA because of the paucity of evidence at this point. Experts representing varying perspectives stated that if the therapy is demonstrated to truly regenerate joint cartilage and restore function, it would mark a huge advance in treatment for many patients, allowing them to avoid the cost and complications of joint replacement surgery. Other experts stated that the therapy might have a more limited role as an adjunctive treatment for patients in whom microfracture surgery does not work or cannot be performed, or to bridge the gap in treatment between pain relief and joint replacement surgery, or as simply another option among many from which patients can choose. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

**Results and Discussion of Comments**

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.\textsuperscript{41-47} Overall, experts stated that current OA therapies treat only the symptoms and do not restore cartilage or joint function. Thus, a significant unmet need exists for treatments that could restore cartilage and obviate the need for joint replacement. Experts were cautiously optimistic about the potential of MSCs to improve patient health outcomes by relieving symptoms, regenerating cartilage, preventing joint replacement surgery, and delaying use of assisted living facilities. However, one clinical expert stated that double-blind studies are needed to compare MSC therapy to sham injection, visco-supplementation, and steroid injections. This expert also stated that both favorable pain outcomes and cartilage regeneration, evaluated by magnetic resonance imaging, would need to be shown by these studies for third-party payers to cover the procedure. Another expert representing a clinical perspective stated that based on the data presented, it is impossible to tell if the benefits observed were due to MSC or other components in the injection, which included PRP and fat matrix. Additionally, parallels cannot be drawn between cartilage thickness and joint functional activity. However this expert stated that if effective, MSC therapy could help reduce health disparities because the injections could replace the need for joint replacement surgery, which may save costs. If the procedure is adjunctive to current therapies it could increase health disparities by adding to costs. Other experts agreed that lack of third-party payment for MSC therapy and its implementation in specialty centers are more likely to create health disparities in the treatment of OA.

In general, the experts stated that MSC injection is similar to other injections used to treat OA, however changes in infrastructure such as equipment and facilities to handle, isolate, and expand MSC in a U.S. Food and Drug Administration (FDA)-compliant manner will be needed in many locations where there may already be demand for the procedure. Additionally, staff will require training in these methods. One expert representing a health systems perspective stated that clinicians would have to
become familiar with the procedure and learn a new paradigm for follow-up. The procedure may also change infrastructure and patient management by reducing demand on orthopedic facilities and staff. One expert representing a health systems perspective stated that joint replacement is a financial mainstay for many hospitals and MSC therapy is a less expensive, less involved treatment option; hospitals may need to adjust their dependence on revenue from orthopedic surgery.

The experts theorized that MSC therapy may be accepted by clinicians if safe and effective; however, the complexity of the procedure and the need for investment in capital equipment may limit diffusion of this technology at many centers. One expert also stated there may be some pushback or controversy from the orthopedic surgery community regarding the role of MSC therapy in the treatment of OA. Although some patients may be highly interested in new effective nonsurgical treatments for their OA, current lack of reimbursement and cost, availability of the procedure, and the use of “stem cells” may serve as barriers to acceptance for some patients, especially in cases where the cells used are “off-the-shelf” (heterologous) products. This may also serve as a barrier to clinician acceptance due to concerns over disease transmission.

Overall, experts were divided on the impact that MSC therapy may play in the treatment of OA. One clinical expert and three other experts representing each perspective surveyed stated that if it becomes the first therapy shown to regenerate joint cartilage and restore function it could be a huge advance in treatment for many patients, allowing them to avoid the cost and complications of joint replacement surgery. Another clinical expert stated that MSC therapy would be used only as an adjunct treatment for patients who are refractory to microfracture surgery. Another expert representing a research perspective stated that MSC could bridge the gap in treatment between pain relief and joint replacement surgery. Finally, another expert representing a health systems perspective stated there are several treatments for OA and this would be viewed as an additional option.
**Intervention**

**Platelet-rich plasma therapy for knee osteoarthritis**

PRP is a preparation of the plasma portion of a patient’s blood that has been processed to achieve a higher-than-normal concentration of platelets, which are purported to secrete a wide variety of growth factors and cytokines, and may promote tissue regeneration and repair.48 As such, PRP is thought by some to have potential to address the underlying pathology of osteoarthritis rather than only ameliorating symptoms of the disease.49 PRP has been used in a number of hemostatic applications as well as for treatment of soft tissue injuries such as tendonitis and chronic wounds.48 Patient blood is collected and centrifuged to concentrate platelets in a small volume of plasma (approximately 5 mL) for each injection, which is injected directly into the intra-articular space under ultrasound guidance.49-52 Typically, multiple injections are given over the course of several weeks.

In one study, patients with osteoarthritis (OA) of the knee (Outerbridge grades I through IV and symptoms of more than 3 months duration; n = 261) were treated with three intra-articular injections of PRP administered every 2 weeks. Assessments at 6 months posttreatment compared with baseline revealed statistically significant differences for pain, stiffness, and functional capacity in the WOMAC index; pain and total score, distance, and daily life activities in the Lequesne index; the VAS pain score; and the SF-36 physical health domain (p <0.0001).53 No adverse events were reported.

In another trial, patients diagnosed chronic degenerative condition of the knee (n = 100 patients, 115 knees) received three intra-articular injections of PRP. Statistically significant improvements in all clinical scores (International Knee Documentation Committee form, EQ VAS quality of life score) were obtained from the base-line evaluation to the end of the therapy and at 6 to 12 months followup (p <0.0005). The results remained stable from the end of the therapy to 6 months followup, before significantly declining at 12 months followup (p = 0.02). However improvements remained significantly higher with respect to the base-line values (p <0.0005).50 By 24-month followup, all of the evaluated parameters were significantly lower than the improvements at 12 months. Better results were obtained in younger patients (p = 0.0001) and lower degrees of cartilage degeneration (p <0.0005). The median duration of the clinical improvement provided by PRP for knee OA was 9 months.52

In a retrospective analysis, patients with knee OA were treated with intra-articular injection of an autologous PRP (n = 30) or hyaluronic acid injections (n = 30).54 By week 5, the observed success rates for the WOMAC pain subscale reached 33.4% for the PRP group and 10% for the hyaluronic acid group (p = 0.004). Percent reductions in the physical function subscale and overall WOMAC were also associated solely with treatment modality in favor of PRP (p = 0.043 and p = 0.010 respectively).54

Autologous PRP is not currently considered a drug or a therapeutic substance by regulatory agencies and, therefore, the preparation does not undergo regulatory marketing approval. The patient undergoes apheresis to collect blood to yield the PRP blood component at a facility (such as a hospital blood bank or blood processing laboratory) according to standard blood processing safety procedures. Thus, the treatment is readily available and may be employed by physicians.38 Many devices have FDA marketing approval for use in preparing PRP.50 The cost of PRP therapy has been reported to range from $500 to $1,500 per injection.55

**Clinical Pathway at Point of This Intervention**

Initial treatments for knee OA include over-the-counter analgesics and NSAIDs, exercise and/or physical therapy, and weight loss if indicated.40 More severe cases may warrant prescription painkillers, corticosteroid injections, or visco-supplementation.40 In patients with persistent symptoms
Despite optimal treatment, surgery including joint replacement may be recommended. If proven to be effective for treatment of knee OA, PRP therapy would be employed as a cartilage-restoring technique in patients with uncontrolled OA pain who are unwilling or unable to undergo knee replacement surgery.

**Figure 4. Overall High Impact Potential: Platelet-rich plasma therapy**

Overall experts were divided on the impact that PRP might have on OA treatment. Several experts stated that if PRP were to become standard first-line therapy and actually regenerate joint cartilage and restore function, it would have a large impact on patient outcomes and be a huge cost-saving advance in OA treatment. However, more data and clinical experience are needed to demonstrate whether the procedure regenerates cartilage, has a durable effect, and reduces the need for additional OA treatment for the affected joint. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

**Results and Discussion of Comments**

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention. Overall, experts stated that current therapies for OA treat only the symptoms and do not restore cartilage or joint function. Thus, a significant and growing unmet need exists for noninvasive treatments that could restore joint cartilage and function and delay or eliminate the need for joint replacement surgery. Experts were cautiously optimistic about the potential of PRP therapy to improve patient health outcomes by relieving symptoms, regenerating cartilage, and preventing joint replacement surgery. However, some of the experts stated that large, randomized, double-blind trials are needed to better understand PRP’s effects on knee and hip OA.

One clinical expert stated that in the case of knee OA, the placebo effect can be very pronounced. Another expert with a clinical perspective stated that PRP injections should be compared to visco-supplementation and steroid injections, because improved outcomes compared to these options will be needed for third-party payers to consider covering the procedure.

One expert with a clinical perspective stated that PRP therapy may help reduce health disparities because racial minorities and persons of low socioeconomic status have been well documented to opt out of knee replacement surgery and choose a less invasive nonsurgical option. Two other experts with research perspectives stated that the simple, minimally invasive nature of the procedure might enable easy adoption of the procedure in underserved areas. Other experts thought the experimental nature and lack of reimbursement currently associated with the procedure would increase health disparities if the procedure improves outcomes.

Because patients with OA already have the option of treatment delivered by injections in the knee or hip, experts thought, there would be minimal change in infrastructure and patient management by implementing PRP. However, changes in patient management and infrastructure might occur through reduction of joint replacement surgeries, which would cause many inpatient procedures to be handled as outpatient procedures, reducing costs. Additionally, some equipment may need to be purchased for preparing PRP, and staff would need training to handle blood collection and prepare PRP from the patient’s collected blood.

One expert with a research perspective stated that PRP injections are already performed by clinicians to treat many injuries, and many patients are aware of the procedure because of its use by
professional athletes. Other experts with clinical perspectives stated that PRP injections could gain larger acceptance if shown to be effective in randomized, double-blind trials and subsequently reimbursed by payers. If the procedure can eliminate the need for joint replacement surgery in some patients, PRP injections are expected to be cost saving. However if PRP injections become widely accepted, patients who are not candidates for knee replacement and who might not have had further treatment options might request the procedure, leading to increased costs. One expert with a health systems perspective stated the some of the available evidence suggests that PRP injections might not have a durable response and that a need for repeated injections could lead to significant long-term costs.
Rheumatoid Arthritis Intervention
**Intervention**

**Tofacitinib for treatment of rheumatoid arthritis**

Tofacitinib (Pfizer, Inc., New York, NY) is a selective and potent oral tyrosine kinase inhibitor that is being investigated as a targeted disease-modifying antirheumatic drug (DMARD) for treatment of rheumatoid arthritis (RA). Tofacitinib inhibits a 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 may suppress the inflammatory reactions that are the basis of RA. In the most recent clinical trials, tofacitinib was administered in once-daily (20 mg) or twice-daily (1, 3, 5, 10, and 15 mg) doses. A targeted therapy that can reduce RA-specific inflammatory processes in the way tofacitinib does may provide better symptom control with fewer adverse events than other DMARD or nonsteroidal antiinflammatory drugs (NSAID)-activated antiinflammatory pathways.

In November 2011, Strand and colleagues at Stanford University reported at the annual meeting of the American College of Rheumatology that patients (n = 792) with moderate to severe active RA who had an inadequate response to at least one DMARD were given tofacitinib (5 or 10 mg) or placebo twice a day for 3 months. They reported that on a “100-point scale of patient global assessment of disease activity, treatment with 5 mg or 10 mg tofacitinib twice daily for three months led to significant decreases of 24.82 and 28.19 points, respectively, compared with a decrease of only 12.54 points (p <0.0001) among those receiving placebo.” The study authors had defined the minimum clinically important change on this measure as a difference of 10 points.

In another clinical trial, patients in whom RA was diagnosed (n = 1,070) were given tofacitinib (5 or 10 mg) or placebo twice or tofacitinib (5 or 10 mg) or placebo twice plus methotrexate. Researchers reported, “ACR response rates showed a trend for improvement over time (month 1-24) with similar ACR20 [American College of Rheumatology 20% improvement in a number of different measures] response rates in tofacitinib monotherapy and tofacitinib on background methotrexate groups at month 24.”

In a year-long, phase III trial, patients with moderate to severe active RA (n = 717) with an inadequate response to methotrexate were given tofacitinib 5 or 10 mg twice daily, adalimumab (Humira®, Abbott Laboratories, Abbott Park, IL) 40 mg injected every other week, or placebo added to a stable methotrexate background. At 3 months, patients taking placebo who were not responding were given tofacitinib. At 6 months, all placebo-assigned patients were advanced to tofacitinib. At 6 months, investigators reported that tofacitinib showed statistically significant reductions in signs and symptoms of RA compared with placebo. They also reported that patients given tofacitinib showed improved physical function and remission rate. Data comparing tofacitinib were expected to be reported in October or November 2011.

In another 6-month-long, phase III trial, patients (n = 399) with moderate to severe active RA who had an inadequate response to at least one tumor necrosis factor (TNF) inhibitor were given tofacitinib 5 or 10 mg twice a day or placebo, added to a stable methotrexate therapy. Placebo patients were given tofacitinib at 3 months. After 3 months of treatment, patients receiving tofacitinib showed a statistically significant reduction in reducing RA signs and symptoms and improved physical function and remission rate, investigators reported.

Finally, an open label extension of patients with active RA (n = 3,227) enrolled in phase II/III trials who were treated with tofacitinib (5 or 10 mg, twice daily) revealed durable ACR 20, 50, and 70 responses at 36 months (72.7%, 52.3%, and 35.2%, respectively).

Overall, infection has been the most common serious adverse event reported to be associated with the use of tofacitinib.
2011 and 2012. No information regarding submission of a new drug application to the U.S. Food and Drug Administration (FDA) was available at the time this report was prepared; however, one financial analyst states that tofacitinib may gain FDA approval in 2012.

**Clinical Pathway at Point of This Intervention**

Newly diagnosed RA is generally treated with a combination of DMARDs and antiinflammatory drugs such as NSAIDs and COX-2 inhibitors. For patients in whom combination therapy is not indicated, monotherapy with DMARDs is used. When satisfactory disease control is reached, the DMARD dosage is gradually reduced to minimum levels needed to maintain control of disease. Flares are treated by increasing DMARD dosages and administering short-term glucocorticoid therapy. Repeated failure of DMARD therapy is typically followed by biologic therapy targeting TNF-alpha. After long-term treatment of RA, joint replacement surgery may be suggested for some patients whose RA has not responded to optimal medical management. There is no cure for RA, and tofacitinib is a targeted DMARD intended to be a long-term solution because it appears to play several roles in interfering with progression of RA.

**Figure 5. Overall High Impact Potential: Tofacitinib**

Overall, experts thought that tofacitinib might address the unmet need for a new effective RA therapy with less severe immunosuppression and the enhanced convenience and lower cost of oral administration. The experts thought that tofacitinib could improve health outcomes in patients with RA as well as lead to health promotion via earlier diagnosis and treatment in the primary care setting. These improvements in access to care could also reduce cost and reduce health disparities. Tofacitinib might have more favorable pricing than injectable biologic therapies (which has yet to be determined), but some of the experts expressed strong concerns regarding its safety and tolerability. These safety concerns may present significant barriers to approval and diffusion if approved. Pending data from larger trials will continue to define the potential role of tofacitinib in improving health outcomes in patients with RA. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

**Results and Discussion of Comments**

Six experts, with clinical, research, and health systems backgrounds, offered comments on this intervention. Overall, most experts generally concurred that many of the current therapies for RA are expensive injectables that only slow disease progression and can induce severe immunosuppression, thus presenting a significant unmet need for new effective oral therapies that can minimize RA symptoms with fewer side effects, better tolerability, and lower cost. The experts agreed that the underlying theory behind tofacitinib action is sound, providing a new targeted mechanism of action for immunoregulation. The experts were optimistic about the potential of tofacitinib to improve health outcomes. One clinical expert stated that even a 20% improvement in the condition would be a significant improvement for patient outcomes. However, one expert offering an independent research perspective stated that current results reported were not convincing, safety concerns were present, and tofacitinib might be the least impressive of three new treatments for RA in clinical development.

In general, the experts thought that tofacitinib would not make a large shift in how RA is understood, treated, or managed, with the exception of the targeting of JAK-3 (which is ultimately immunosuppressive). Experts thought that as an oral agent, tofacitinib may become the preferred...
treatment after the failure of conventional DMARDs and before the use of injectable biologics, thus shifting the treatment model. In addition, one clinical expert stated that tofacitinib could shift the care setting for RA treatment from the specialist office to primary care offices, which might allow for earlier diagnosis and treatment.

Experts all thought tofacitinib would have a large impact on costs, but diverged in how the impact would play out. Some experts stated that the cost for tofacitinib would be high because as a new agent it would be used adjunctively. However, it was also proposed that it could supplant biologics, which are expensive and require injection; therefore, tofacitinib could be cost saving. An expert offering a clinical perspective stated that earlier treatment, shifting at least some part of treatment out of a specialist’s office to primary care, would lower costs to patients and payers. Experts thought that many patients and physicians would be eager to try tofacitinib if it could eliminate expensive injections with biologics. However, adverse events observed in clinical trials completed to date, such as infections, increases in cholesterol levels, and liver damage in some patients, were also cited as significant barriers to acceptance and potential sources of controversy.
Systemic Lupus Erythematosus Intervention
## Intervention

**Belimumab (Benlysta) for treatment of systemic lupus erythematosus**

Belimumab (Human Genome Sciences, Rockville, MD, and GlaxoSmithKline, Middlesex, UK) is a monoclonal antibody targeting the B-lymphocyte stimulator (BLyS). 77-79 It is intended to complement, not replace, current standard therapy in patients with systemic lupus erythematosus (SLE) with poor response to standard therapy. 78,80 BLyS (or B-cell activating factor [BAFF]) can be secreted or membrane-bound and is a key regulator of B-cell survival, maturation, and lifespan. 81 BLyS binds to receptors on B cells, most notably a receptor (BR3) found on newly formed and transitional immature B cells; it also binds to other receptors (TACI and BCMA) present on many B cell stages. 77,78,80 While BLyS plays an important role in stimulating B-lymphocyte production when the human body is battling an infection, the overproduction has been shown to cause production of autoantibodies and autoimmune-like disease symptoms in mice. 78,82 By inhibiting the biologic activity of BLyS, belimumab inhibits the stimulation, proliferation, and differentiation of B cells. 77,80 Anti-BLyS antibodies are anticipated to reduce the B cells responsible for autoantibody production in SLE and potentially other autoimmune diseases, without eliminating the body’s ability to fight infections. 83 Treatment with belimumab consists of an intravenous (IV) infusion every 4 weeks, administered by a nurse or physician in an ambulatory infusion clinic or physician’s office in a way similar to other biologic therapies currently used off-label for SLE (notably rituximab).

Two phase III efficacy trials were recently completed that reported on patients with SLE after 52 weeks and 76 weeks of belimumab therapy. In Bliss-52 and Bliss-76, patients with SLE were given either 1 mg/kg of body weight or 10 mg/kg doses plus standard care in the active treatment groups. These trials enrolled only patients with SLE with a positive antinuclear antibody status. The SLE responder index, the primary endpoint measure and a novel evaluation survey created for use in these trials, incorporates aspects of the SLE Disease Activity Index, the British Isles Lupus Assessment Group Instrument, and the Physician’s Global Assessment. Patients with severe SLE (i.e., life-threatening organ involvement) were excluded from these studies. After 52 weeks, 57.6% and 43.2% of subjects receiving 10 mg/kg of belimumab achieved the studies’ primary endpoints, as compared with 43.6% and 33.8% of patients in the placebo groups. The rates of treatment-related death and infections were not significantly different between the placebo and treatment groups in either study. 77-79,84 Recent results from a phase II extension revealed that belimumab therapy in patients with active SLE was well-tolerated and resulted in sustained disease improvement over 6 years. 85

In March 2011, the U.S. Food and Drug Administration approved intravenous belimumab for the treatment of adult patients with active, autoantibody-positive SLE who are receiving standard therapy. 86 In December 2011, the company started a phase III trial of a subcutaneous formulation. Belimumab has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus. In July 2011, the European Commission granted marketing approval for belimumab 10 mg/kg as an add-on therapy in adult patients with active autoantibody-positive SLE, with a high degree of disease activity (e.g., positive anti-dsDNA and low complement), despite standard therapy. 87 The annual per patient cost for belimumab in the U.S. is about $35,000.

A competitive product, LY2127399 (Eli Lilly and Co., Indianapolis, IN), is being developed as an IV infusion and subcutaneous injectable drug for treatment of SLE. LY2127399 is a fully human immunoglobulin G4 monoclonal antibody targeting the B-lymphocyte stimulator (BLyS, BAFF). 88,89 A phase III safety and efficacy trial of LY2127399 for treatment of patients with SLE was expected to be completed by January 2014. 88,90
Clinical Pathway at Point of This Intervention

Treatment options following diagnosis will depend on whether the patient’s condition is considered stable or life- or organ-threatening (“flare”). Treatment of stable disease can include medical therapy with daily NSAIDs, antimalarials such as hydroxychloroquine, and low doses of oral glucocorticoids such as prednisone. Treatment of life- or organ-threatening disease entails nonsteroidal antinflammatory drugs (NSAIDs), high-dose oral glucocorticoids, and the addition of mycophenolate mofetil (CellCept) or azathioprine (Imuran). Continued unremitting flares may entail IV cyclophosphamide 7 to 25 mg/kg once a month for up to 6 months. Following discontinuation of cyclophosphamide therapy, the patient continues maintenance therapy with CellCept® or Imuran®. If appropriate maintenance is achieved, the physician may consider tapering off doses of mycophenolate/azathioprine. If the patient does not achieve desired response to IV cyclophosphamide after 6 months, experimental treatment is considered. Belimumab is a new monoclonal antibody therapy intended to be used in patients unresponsive to treatment with first-line agents such as NSAIDs, hydroxychloroquine, and low doses of oral glucocorticoids.

Overall, the experts commenting on this topic stated that belimumab could have a significant impact on SLE patients with clinically active disease that is not responding to other therapies. As the first new therapy for SLE approved in 4 decades, this new agent is highly anticipated. However, as a new agent, belimumab has a far less developed record of safety and efficacy than first-line agents used to treat SLE, which could prevent some patients and physicians from rapidly accepting the therapy. Additionally, clinical studies have shown that patients taking belimumab have an increased risk of infection. Considering the high cost of belimumab and the fact that the new antibody may not completely replace the use of rituximab, the impact of this much-publicized therapy was considered by experts as moderate in improving treatment outcomes and advancing paradigms for SLE treatment and management. The cost-benefit ratio of belimumab is expected to be a hotly debated issue that will affect the diffusion of this therapy. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered their perspectives on this intervention. Overall, experts generally concurred that there is a significant unmet need for new treatment options for patients with SLE, because there have been no new therapies approved for about 40 years. Experts agreed that the underlying theory of belimumab, targeting B cells to reduce the production of autoantibodies, is valid. However, some experts were uncertain regarding how much of an impact belimumab would have on improving the health outcomes of patients with SLE. Only modest reductions in disease scores have been observed in addition to an increase in infection events. One expert offering a health systems perspective also stated that belimumab should be used only in patients with serologically active SLE who also are positive for antinuclear antibodies. Identifying patients who will benefit most from belimumab prior to initiating treatment will be an important issue.

In general, the experts did not think that belimumab would lead to a major shift in the understanding and treatment models for SLE as a whole, as the biologic is indicated to be used with current first-line therapies. However, a clinical expert thought that belimumab might spur more
research on biologics for SLE treatment. Additionally, experts thought that as an add-on therapy, belimumab would significantly increase costs. Some experts even suggested that belimumab might not fully replace rituximab. Therefore, patients could be treated with two different monoclonal antibodies, resulting in significant treatment costs.
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