Priority Area 01: Arthritis and Nontraumatic Joint Disease

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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.

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 close to diffusion into practice in the United States. 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 interventions that experts deemed, 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 6 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 horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Financial Disclosure Statement
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 interventions 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.

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 identifying 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 11,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas and one cross-cutting area.

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 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) 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 information on topics and issuing topic 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 designation of potentially high impact. 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 seven topics for which (1) preliminary phase III or later phase data were available for drug and biologic topics; (2) information was compiled and sent for expert comment before April 15, 2012; and (3) we received six to eight sets of comments from experts between February 2011 and April 26, 2012. (Thirty-one topics were being tracked in this priority area in the system as of May 2012.) Three topics emerged as having potential for high impact on the basis of experts’ comments and their assessment of potential impact. They are noted by an asterisk in the table below.

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Discussion

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

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 National Institute of Arthritis and Musculoskeletal and Skin Diseases estimates that almost 27 million people have some degree of OA. Current treatments for OA include over-the-counter analgesics and nonsteroidal anti-inflammatory drugs, 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 anticyclastic activity on chondrocytes, which are the cells responsible for maintaining cartilage. 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 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 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. Our searches of 11 representative third-party payers that publish their medical policy coverage determinations revealed that all of the payers that listed determinations for MSC consider the therapy investigational at this time. Reported charges for the procedure ranged from $7,000 to $10,000.

- **Key Expert Comments:** Experts were divided on the potential impact of MSC therapy on health outcomes of patients with OA because of the paucity of evidence at this point. Some experts stated that it would mark a major advancement if the therapy is proven effective in regenerating joint cartilage and restoring function. They stated that it would allow patients to avoid the cost and complications of joint replacement surgery. Other experts stated that the therapy might have a more limited role as adjunctive treatment or as another option among many from which patients can choose.

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

Platelet-Rich Plasma Therapy for Treatment of Osteoarthritis

- **Key Facts:** 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 injected directly into the intra-articular space, under ultrasound guidance. As with MSC therapy, preparation protocols and frequency of injection vary among treatment centers. The evidence base for PRP lacks large, blinded, prospective, randomized, controlled trials. A retrospective analysis reported that PRP improved OA symptoms better than intra-articular injection with hyaluronic acid, but such an
analysis is a weak study design that may not yield reliable results. Our searches of 11 representative private third-party payers that provide online medical coverage policies found 8 payers that have specific policies that deny coverage for the procedure because they consider PRP injections to be experimental/investigational. The cost of PRP therapy has been reported to range from $500 to $1,500 per injection, and a patient may receive more than one injection over time.

- **Key Expert Comments:** Overall, experts were divided on the impact that PRP might have on OA treatment. Similar to the experts’ comments on MSC therapy, 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 major 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

### 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 (TNF-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 as having high potential impact based on expert comments.

### Tofacitinib for Treatment of Rheumatoid Arthritis

- **Key facts:** Tofacitinib (Pfizer, Inc., New York, NY) is a selective and potent oral tyrosine kinase inhibitor that is being investigated as a targeted DMARD. Tofacitinib inhibits a Janus kinase-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 twice daily in 5 and 10 mg doses. In phase III trials, patients treated with tofacitinib demonstrated improvements in signs and symptoms of RA compared with placebo. These results also extended to patients taking methotrexate or whose disease was unresponsive to methotrexate or a TNF inhibitor. One open-label extension trial demonstrated durable responses to tofacitinib up to 36 months. In May 2012, the FDA’s Arthritis Advisory Committee recommended approval of tofacitinib for treating adult patients with moderate to severe RA, and a decision date was set by FDA for August 2012. No cost information is available at this time.

- **Key Expert Comments:** Overall, experts thought that the drug might address the unmet need for a new, more effective RA therapy with the enhanced convenience and lower cost of oral
administration. Experts thought that tofacitinib might also promote health through earlier diagnosis and treatment in the primary care setting. These potential improvements in access to care might reduce costs and health disparities for these patients. They thought that tofacitinib might have more favorable pricing (which has yet to be determined) than injectable biologic therapies, but some experts expressed strong concerns regarding its safety and tolerability because of 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
Osteoarthritis Interventions
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.\(^1\) 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.\(^2,3\) 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 (OA). However, the mechanism by which these cells lead to cartilage generation is still unclear.\(^1\) MSCs may differentiate into chondrocytes and fill in a cartilage defect. Additionally, 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.\(^1\) 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.\(^2\) MSCs isolated from these different tissues are purported to exhibit differences in their ability to proliferate and/or their propensity to differentiate into chondrocytes.\(^2\) 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.\(^3,4\) The method chosen to acquire adequate cells may also influence the nature of the MSCs used for treatment. Additionally, patient characteristics such as age and the presence of OA have been shown to affect the ability of MSCs to differentiate into chondrocytes.\(^2,5\) Thus, many factors can introduce variability in this procedure.

In patients with knee OA and a Kellgren-Lawrence status of II, III, or IV (n=22) who were treated with a combination of autologous MSC (concentrated bone marrow isolate), PRP, and fat matrix injected into the intra-articular space, improvements in several disease measures were reported.\(^4\) 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 improved 50% and 71% from baseline at 6 and 12 months, respectively.\(^4\) Ultrasound measurement of patellofemoral cartilage thickness at seven 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.\(^4\)

While the efficacy of MSC treatment for OA 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.\(^6,7\) One center offering MSC treatment quotes a price of about $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.\(^8\) A second center offering the treatment reportedly charges from $7,000 to $9,000 for the procedure.\(^9\) Our searches of 11 representative private third-party payers that provide online medical coverage policies (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found that 5 list coverage determinations for MSC therapy for treating OA.\(^10-14\) All of the payers that listed determinations stated MSC therapy is investigational because of insufficient evidence or long-term safety or efficacy outcomes.\(^10-14\)
**Clinical Pathway at Point of This Intervention**

Patients with OA are frequently prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, nabumetone, and naproxen as well as the COX-2 inhibitor celecoxib. Physicians can recommend exercise, physical and/or occupational therapy, and weight loss. More severe cases of OA may warrant prescription painkillers, corticosteroid injections, or visco-supplementation. For patients with severe persistent symptoms despite optimal treatment, clinicians can recommend surgery, including joint replacement. MSC therapy is intended to be used as a cartilage-restoring technique in patients with uncontrolled OA pain whose disease is not responding to conservative therapy.

**Figure 1. 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. 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 can 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 followup. 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 because of concerns about 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 whose disease is 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, an expert representing a health systems perspective stated several treatments for OA are available and this would be viewed as an additional option.
Platelet-Rich Plasma Therapy for Knee Osteoarthritis

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 to have potential to address the underlying pathology of OA rather than only ameliorating symptoms of the disease. PRP has been used in a number of hemostatic applications as well as for treating soft tissue injuries such as tendonitis and chronic wounds. Patient blood is collected and centrifuged to concentrate platelets in a small volume of plasma (about 5 mL) for each injection, which is injected into the intra-articular space under ultrasound guidance. Typically, multiple injections are given over the course of several weeks.

In one study, patients with knee OA (n=144) received either three injections of platelet concentrate (n=72) prepared with a single-spinning procedure (PRGF) or three injections of PRP (n=72) obtained with a double-spinning approach. Both treatment groups were reported to show statistically significant improvements in all endpoints and at all time points evaluated. Younger patients with less cartilage degeneration achieved better results in both procedures. Similar improvements were observed with both procedures. International Knee Documentation Committee (IKDC) subjective evaluation increased from 45.0±10.1 at baseline to 59.0±6.2, 61.3±6.3, and 61.6±16.2 at 2, 6, and 12 months in the PRGF group, respectively. IKDC increased from 42.1±13.5 at baseline to 60.8±16.6, 62.5±19.9, and 59.9±20.0 at 2, 6, and 12 months in the PRP group, respectively. Increases in swelling (p=0.03) and pain reaction (p=0.0005) were observed in patients treated with PRP injections.

In a retrospective analysis, consecutive patients with primary OA (n=86) treated with intra-articular PRP injection were compared with similar patients concurrently treated with hyaluronic acid injection (n=21) three times, 1 week between injections. The mean visual analog scale (VAS) to measure pain severity at baseline was 8.2 (range 7–10); it was 3.2 (range 1–4) and 2.9 (range 0–4) at 12 and 24 weeks after treatment, respectively. Mean IKDC knee score was 57.5 points (range 32–77) at baseline; it was 77.3 points (range 60–95) and 88.9 points (range 69–98) at 12 and 24 weeks after treatment, respectively. Patients receiving PRP demonstrated significant improvements in VAS and IKDC score measures compared with patients receiving hyaluronic acid injection. Both groups had similar safety profiles.

In a study of patients with knee OA (Outerbridge grades I–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 Western Ontario and McMaster Universities Osteoarthritis Index; pain and total score, distance, and daily life activities in the Lequesne index; the VAS score; and the Short Form 36 physical health domain (p <0.0001). No adverse events were reported.

In another trial, patients with 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 (IKDC form, EQ VAS quality of life score) were obtained from the baseline evaluation to the end of the therapy and at 6–12 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 baseline values (p<0.0005). By 24-months’ 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.\textsuperscript{27}

Autologous PRP is not currently considered a drug or a therapeutic substance by regulatory agencies; 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.\textsuperscript{23} Many devices have FDA marketing approval for use in preparing PRP.\textsuperscript{25} The cost of PRP therapy has been reported to range from $500 to $1,500 per injection.\textsuperscript{31} Our searches of 11 representative private third-party payers that provide online medical coverage policies found 8 payers that have specific policies that deny coverage for the procedure because they consider PRP injections to be experimental or investigational.\textsuperscript{32-39}

**Clinical Pathway at Point of This Intervention**

Patients with OA are frequently prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, nabumetone, and naproxen as well as the COX-2 inhibitor celecoxib. Physicians can recommend exercise, physical and/or occupational therapy, and weight loss. More severe cases of OA may warrant prescription painkillers, corticosteroid injections, or visco-supplementation. For patients with severe persistent symptoms despite optimal treatment, clinicians can recommend surgery, including joint replacement.\textsuperscript{15} 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 whose disease is not responding to conservative therapy.

**Figure 2. 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 major 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.\textsuperscript{40-46} 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 with 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.

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
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 treating rheumatoid arthritis (RA). Tofacitinib inhibits a Janus kinase-3 (JAK3) signaling pathway believed to mediate several processes involved in chronic inflammatory diseases, such as antibody production by B cells, and activation of T cells. By inhibiting the JAK3 pathway, tofacitinib may suppress the inflammatory reactions that are the basis of RA. In recent clinical trials, tofacitinib was administered in twice-daily (5 and 10 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 anti-inflammatory drugs (NSAID)-activated anti-inflammatory 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 patients given placebo. They also reported that patients given tofacitinib showed improved physical function and remission rate. Data comparing tofacitinib to placebo were expected to be reported in October or November 2011.

In a 6-month, 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 RA signs and symptoms and improved physical function and remission rate, investigators reported.

In a 12-month study of patients with moderate to severe, active RA who had an inadequate response to methotrexate (n=797), tofacitinib 10 mg twice daily met all primary efficacy endpoints. Statistically significant reductions in the signs and symptoms of RA, (measured by ACR20 response rate at 6 months), progression of structural damage (measured by mean change from baseline in modified Total Sharp Score at 6 months), disease activity (measured by rates of DAS28-4(ESR) <2.6 at 6 months), as well as improved physical function (measured by mean change in HAQ-DI at 3 months) were reported compared with patients treated with placebo.
Finally, an open-label, extension trial 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).\textsuperscript{52}

Overall, infection has been the most common serious adverse event reported with the use of tofacitinib.\textsuperscript{52} In May 2012, the Arthritis Advisory Committee to FDA recommended approval of tofacitinib for treating adult patients with moderate to severe RA, and a decision date was set by FDA for August 2012.\textsuperscript{53} Cost information is not available yet, although experts commenting opined on potential costs (see Results and Discussion section below).

**Clinical Pathway at Point of This Intervention**

Newly diagnosed RA is generally treated with a combination of DMARDs and anti-inflammatory 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.\textsuperscript{34,55} There is no cure for RA, and tofacitinib is a targeted DMARD intended to be a potential long-term solution because it appears to play several roles in interfering with progression of RA.

**Figure 3. Overall High Impact Potential: Tofacitinib**

Overall, experts thought that tofacitinib might address the unmet need for a new, effective RA therapy with the enhanced convenience and potentially lower cost of oral administration. The experts thought that tofacitinib could improve health outcomes in patients with RA and might 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 and regulatory decisions 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.\textsuperscript{56-61} Overall, the experts generally concurred that many of the current therapies for RA are expensive and are 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 reduce signs and symptoms of RA, although they had concerns regarding the adverse events associated with tofacitinib use. However, one expert representing a clinical perspective stated that there are some patients who could benefit from biologic therapy, but they perceive injectables as having more adverse events; all things being equal these patients could be responsive to tofacitinib therapy.

Some experts stated that tofacitinib might reduce health disparities by reducing the need for access or travel to infusion centers. Tofacitinib could also increase access to care if primary care physicians were comfortable prescribing tofacitinib; however, one clinical expert stated that this is unlikely because primary care physicians are typically already uncomfortable prescribing methotrexate. Disparities could also be reduced if the drug were lower in cost than biologic therapy, which the experts were also unsure would occur.

In general, the experts thought that tofacitinib would not make a large shift in how RA is treated or managed. Experts thought that as an oral agent, tofacitinib might become the preferred treatment after the failure of conventional DMARDs or used in combination with DMARDs, and before the use of injectable biologics, thus shifting the treatment model. Additionally, one clinical expert stated that tofacitinib could shift the care setting for RA from the specialist office to primary care offices, which might allow for earlier treatment, but could lead to inappropriate treatment by reducing access to a specialist.

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, other experts commented that the drug could supplant biologics, which are expensive and require injection, and would therefore be cost saving. An expert offering a clinical perspective stated that it was rumored the cost of tofacitinib would be set at about two-thirds the cost of biologics. 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 potentially significant barriers to acceptance and potential sources of controversy. One clinical expert stated that the frequency of adverse events would lower acceptance of tofacitinib by primary care physicians, but not rheumatologists who are very excited about having an additional treatment option.


60. Expert Commenter 408. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS495 - Tasocitinib (CP-690,550) for treatment of rheumatoid arthritis. 2012 Apr 10 [review date].