

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

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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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 Interventions 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 email 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 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 18,000 leads about potential topics has resulted in identification and tracking of about 2,000 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 550 topics are being actively tracked in the system.

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 a year. Topics eligible for inclusion are those interventions expected to be within 0–3 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 150 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

(COIs). 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 five to 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 high-impact-potential 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 having potentially 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 four topics for which (1) at least preliminary phase III data were available; (2) information was compiled before May 15, 2014, in this priority area; and (3) we received five to eight sets of comments from experts between July 1, 2013, and May 23, 2014. (Fifteen topics in this priority area were being tracked in the system as of May 15, 2014.) Two topics emerged as having potential for high impact on the basis of experts’ comments and their assessment of potential impact. These topics are noted by an asterisk in the table below. The material in this Executive Summary and report is organized alphabetically by disease and then intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 01: Arthritis and Nontraumatic Joint Disease

Topic	High-Impact Potential
1. Apremilast (Otezla) for treatment of psoriatic arthritis	No high-impact potential; archived on basis of expert comments
2. Artificial cervical disc (Mobi-C) for treatment of 2-level degenerative disc disease	Prior high impact (December 2013) topic; new expert comments deemed little potential for high impact; archived
3. * Autologous mesenchymal stem cell therapy for osteoarthritis	Lower end of the high-impact-potential range
4. * Autologous platelet-rich plasma therapy for osteoarthritis	Lower end of the high-impact-potential range

Discussion

Prior High Impact Topic Archived Since December 2013 Report

- **Artificial cervical disc (Mobi-C) for treatment of two-level degenerative disc disease:** In the December 2013 report, this topic was deemed by expert commenters to have potential for high impact (moderate on the potential high-impact-potential scale). At that time, experts stated two-level disc replacement had potential to fulfill a significant unmet need by relieving symptoms, preserving range of motion, and preventing deterioration at adjacent discs after surgery. More recently, however, experts commenting on an updated profile of

this technology since its 2013 U.S. Food and Drug Administration (FDA) approval, questioned the need for cervical disc replacement in the absence of neurologic compromise, stating that patient symptoms can improve with conservative care. Additionally, limited diffusion, lack of reimbursement, and high out-of-pocket costs to patients were thought to limit patient and clinician acceptance. The limited use and reimbursement of single-level cervical disc replacement was a model experts used to project that two-level disc replacement would also have limited acceptance and utilization. Additionally, experts stated that lack of clinical data made assessing the potential health impact of Mobi-C difficult.

Eligible Topics not Deemed High Impact

- **Apremilast (Otezla) for treatment of psoriatic arthritis conditions:** The absence of effective oral treatment options for psoriatic arthritis, a disease with a significant clinical burden was considered by expert commenters to present a significant unmet medical need. Although apremilast appears to have a somewhat better tolerability profile than tumor necrosis factor (TNF) inhibitor therapy, experts had reservations about apremilast's efficacy. They noted the drug could offer a significant advantage over existing therapies if it was shown to halt joint destruction or provide clinical benefit over TNF inhibitors in a randomized controlled trial; however, no such trials are planned. Thus, experts did not see potential for impact because the drug was demonstrated to have clinical superiority only over placebo. This topic has been archived in the horizon scanning system.

The topics that emerged as higher impact were osteoarthritis (OA) interventions in which experts perceived considerable unmet need because of a lack of effective treatments and the negative impact of OA on quality of life.

Osteoarthritis

OA, the most common form of arthritis, affects an estimated 27 million Americans, according to the National Institute of Arthritis and Musculoskeletal and Skin Diseases; it is expected to affect a greater proportion of the population as more people reach the age of 65 years or older. OA 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. Current treatments for OA include over-the-counter pain medication, exercise and/or physical therapy, and weight loss if indicated. More severe cases may warrant injections with corticosteroids. However these agents have no anabolic or anticatabolic activity on chondrocytes, which are the cells responsible for maintaining cartilage. Two interventions were deemed by experts commenting on them to have potential to disrupt the current OA treatment paradigm because of their purported potential to regenerate articular cartilage or inhibit degenerative processes. Both interventions are available as autologous biologic products prepared onsite by health care facilities delivering the treatments to patients via intra-articular injection.

Autologous Mesenchymal Stem Cell Therapy for Osteoarthritis

- **Key Facts:** Autologous 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 manipulated in any number of ways, including both concentrating and culturing the cells to increase their numbers and combining with growth

factors and/or platelet-rich plasma (PRP) and fat matrix. Depending on the amount of processing performed, the preparation is reinjected into the patient's intra-articular space either the same day (for preparations that undergo only centrifugation with no additives) or up to a few weeks later (for highly processed, cultured preparations with additives). The methods used to prepare MSCs have not yet been standardized and differ among facilities making and administering the preparations. This may lead to different outcomes among treatment centers.

MSCs purportedly secrete growth factors and retain the ability to differentiate into chondrocytes, allowing them to regenerate worn areas of cartilage. The exact mechanism remains unknown. MSCs purportedly have immunomodulatory, anti-apoptotic, proliferative, and angiogenic effects on cells in the intra-articular space. Preliminary reports suggest that intra-articular injection with some MSC preparations may reduce pain and improve function in some patients. Study results are limited at this time because of lack of controls, high variability in MSC preparations, and small sample sizes. Larger randomized controlled trials that use standardized MSC preparation methods and report longer followup are needed to determine efficacy. The therapy can conceivably be made and delivered by any suitably equipped health care center, and dozens of orthopedic centers that treat OA have begun to offer it, although FDA requires an investigational new drug application for many MSC preparations. Trials for any autologous cell products that are more than "minimally processed" are subject to FDA regulatory approval processes. No company has an FDA-approved autologous MSC product at this point, although one company in Texas has stated intentions to pursue FDA approval. Another company, in Colorado, had offered a cultured, highly processed autologous MSC product, but was ordered by FDA to stop; the company subsequently moved its operations for that product offshore and now offers a "minimally" processed product at its U.S. centers, which continue to expand. Reported total costs for the procedure range from about \$2,900 to \$7,600. Our searches of 11 representative, private, third-party payers that publish their coverage policies online showed that all of the payers listing policies for MSCs for OA consider the therapy investigational at this time and do not cover it.

- **Key Expert Comments:** Experts stated that effective, minimally invasive OA therapies that can prevent or delay joint-replacement surgery are needed. Autologous MSC therapy has potential to be a first-line OA-treatment option if it is shown to reduce pain and regenerate articular cartilage. Experts expressed cautious optimism about the potential impact of autologous MSC therapy for relieving symptoms and regenerating cartilage, wanting to see more outcomes data from well-designed, randomized controlled trials. Although third-party reimbursement for the procedure is limited at this time, diffusion continues as some patients pay out-of-pocket.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Autologous Platelet-Rich Plasma Therapy for Osteoarthritis

- **Key Facts:** Autologous PRP therapy involves processing (centrifuging) the plasma portion of a patient's blood to concentrate and separate out the platelets, which are purported to secrete a wide variety of growth factors and cytokines that purportedly promote tissue regeneration and repair. Some researchers think that because of those characteristics, PRP has potential regenerative effects on cartilage in patients with OA. PRP, collected from the patient and concentrated, is injected directly into the intra-articular space under ultrasound guidance. As with autologous MSC therapy, preparation protocols and injection frequency

vary among treatment centers. The evidence base for PRP lacks sufficiently large, blinded, prospective, randomized controlled trials that compare it to other standard treatments for OA and to autologous MSCs, but it has been used by high-profile athletes trying to speed their recovery after soft-tissue injuries. Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 8 payers that have specific policies denying coverage for the procedure because they consider PRP injections to be experimental or investigational. The cost of PRP therapy has been reported to range from \$500 to \$1,500 per injection, appearing to be less costly than autologous MSC therapy. Sometimes the two are used together, or PRP is administered days after the MSC injection to “feed” the cells. A patient may choose to 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 autologous MSC therapy, several experts stated that if PRP were to be proven effective and become accepted first-line therapy that could regenerate joint cartilage and restore function, it would have a major impact on patient outcomes and costs of treating OA. However, more data and clinical experience are needed to standardize preparation procedures and regimens and test those regimens in randomized controlled trials to determine whether the procedure regenerates cartilage better, has a more durable effect, and leads to less need for additional OA treatment for the affected joint than other, standard therapies for OA.
- **Potential for High Impact:** Lower end of the high-potential-impact range

Osteoarthritis Interventions

Autologous Mesenchymal Stem Cell Therapy for Osteoarthritis

Intervention: Mesenchymal stem cells (MSCs) are adult stem cells that help maintain the relative stability of internal physiologic conditions of many tissue types in the body.¹ As progenitor cells, MSCs purportedly retain the ability to differentiate into a number of cell types, including chondrocytes, which are the cells responsible for maintaining cartilage.^{2,3} Autologous MSCs are derived from the patient and can be isolated, concentrated, cultured, and expanded in vitro and returned to the patient with the intention of treating the large cartilage defects observed in osteoarthritis (OA). However, the mechanism by which these cells lead to cartilage regeneration is unclear.¹ MSCs may differentiate into chondrocytes and fill in a cartilage defect. Additionally, MSCs are known to have effects on the intra-articular environment, including immunomodulation, host cell survival, endogenous tissue progenitor cell proliferation, local angiogenesis, and fibrosis inhibition.¹

The methods used to prepare autologous MSCs have not been standardized; the cells can be isolated from bone marrow, synovium, periosteum, skeletal muscle, or adipose tissue.² MSCs isolated from these different tissues purportedly exhibit differences in their ability to proliferate and their propensity to differentiate into chondrocytes.² To have an adequate number of MSCs for treatment, the cells from a tissue sample must be concentrated by centrifugation and/or expanded in vitro through the culture and addition of growth factors, sometimes including platelets.^{3,4} The method chosen to acquire cells may also influence the nature of the MSCs used for treatment. Additionally, patient characteristics such as age and the severity of OA have been shown to affect the ability of autologous MSCs to differentiate into chondrocytes.^{2,5} Thus, many factors can introduce variability in this procedure. Autologous MSCs have also been given with other therapies, including platelet-rich plasma (PRP) therapy.^{6,7}

Clinical trials: Many case series have been published, but no definitive, well-designed, randomized controlled trials using standardized methods of preparation are available yet.

Results reported from a patient registry (n=539) of a proprietary MSC procedure (Regenexx-SD™) stated more than 70% of patients (n=42 reporting at 24 months; an 8% reporting rate) with knee OA treated with MSC had symptom improvement of greater than 25% from baseline. Mean symptom improvement of all patients who reported outcomes was nearly 60% at 24 months after treatment.⁸

In a randomized controlled trial, patients (n=56) with unicompartmental osteoarthritis of the knee and genu varum who were aged 55 years or younger, were treated with high tibial osteotomy and microfracture. Three weeks after surgery, patients were treated with intra-articular MSC and hyaluronic acid injection (n=28) or hyaluronic acid injection alone (n=28; control group). All patients demonstrated improvements in Tegner, Lysholm, and International Knee Documentation Committee (IKDC) scores. Patients treated with MSCs had an additional improvement of 7.65 (95% confidence interval [CI], 3.04 to 12.26; p=0.001) for the primary endpoint (IKDC score); 7.61 (95% CI, 1.44 to 13.79; p=0.016) for Lysholm scores; and 0.64 (95% CI, 0.10 to 1.19; p=0.021) for Tegner scores. The age-adjusted mean difference in magnetic resonance observation of cartilage repair tissue (MOCART) score 1 year after the surgical intervention was 19.6 (95% CI, 10.5 to 28.6; p<0.001).⁹

In a pilot study (n=12), patients with knee OA were treated with intra-articular injection of autologous, expanded, bone-marrow-derived MSCs. Investigators reported “rapid and progressive improvement of algofunctional indices that approached 65% to 78% by 1 year.” Additionally, the investigators observed “a highly significant decrease of poor cartilage areas (on average, 27%), with

improvement of cartilage quality in 11 of the 12 patients,” as shown by quantitative magnetic resonance imaging (MRI) T2 mapping.¹⁰

In another trial, investigators reported that patients (n=18) who received intra-articular injections of adipose-derived autologous MSC combined with PRP after arthroscopic débridement, for treating knee OA experienced the following:¹¹

- A significant decrease in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores from 49.9 points at baseline to 30.3 points at the mean followup of 24.3 months (p<0.001)
- Improved Lysholm scores from a mean baseline value of 40.1 points to 73.4 points at the last followup (p<0.001)
- Improved mean VAS (visual analog scale, a measure of pain) score from 4.8 at baseline to 2.0 at the last followup (p=0.005)
- Improved whole-organ MRI score from 60.0 points at baseline to 48.3 points at the last followup (p<0.001) (clinical significance uncertain)
- Improved cartilage whole-organ MRI score from 28.3 points at baseline to 21.7 points at the last followup (p<0.001) (clinical significance uncertain)

Improved clinical and MRI results were purportedly positively related to the number of stem cells injected.¹¹

In patients with knee OA and a Kellgren-Lawrence status of 2, 3, or 4 (n=23) 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 for patients at 6-month (n=12) and 12-month (n=10) followup. The investigators reported that patients treated with MSC therapy experienced the following:⁴

- Improved pain from baseline, as measured on a VAS, of 34% and 25% at 6 and 12 months, respectively
- Improved patient global assessment of disease of 33% from baseline at both 6 and 12 months
- Improved physician global assessment of 51% and 53% from baseline at 6 and 12 months, respectively
- Improved 50-foot walk pain of 26% and 17% from baseline at 6 and 12 months, respectively
- Improved WOMAC scores of 20% and 8% from baseline at 6 and 12 months, respectively
- Mean improved patellofemoral cartilage thickness at seven standardized points of 0.4 mm and 0.8 mm from baseline to 6 months and 12 months, respectively

Manufacturer and regulatory status: FDA categorizes therapeutic stem cell-based products as human cells, tissues, and cellular and tissue-based products (HCT/Ps), which it defines as “articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.”¹²

Whether an HCT/P is subject to FDA regulation as a biological product, drug, or device depends on how much it has been manipulated after collection. These products are regulated under the authority of both the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act (FDCA).¹³ FDA contends that most of the autologous MSCs used for OA “are highly processed, are used for other than their normal function, are combined with non-tissue components, or are used for metabolic purposes” and are subject to regulation.^{12,13} Thus, they are subject to requirements for filing as an investigational new drug, investigational device exemption, or new biologic, depending on how FDA categorizes the product and which division has product oversight. Considerations addressed in FDA’s decision to regulate HCT/Ps include the following:¹⁴

- Has the product been more-than-minimally manipulated (i.e., processing has altered the biological characteristics)?
- Is the product intended for homologous function?
- Has the product been combined with any nontissue or noncellular components?
- Does the product's overall effect on the physiology depend on the body's metabolism?

In 2010, FDA filed an injunction against Regenerative Sciences, Inc., of Broomfield, CO, asserting that its stem cell products were considered drugs. FDA asserted that the company was manufacturing these agents without its approval, without following good manufacturing practice, and without proving the treatment's safety and efficacy.¹⁵ The company contended that its autologous MSC therapy represented a "practice of medicine" under Colorado state law, and so was not subject to FDA oversight.^{16,17} On July 23, 2012, the U.S. District Court for the District of Columbia ruled that the company's ex vivo expansion and manipulation of autologous MSCs exceeded minimal processing and, thus, was subject to FDA regulatory oversight.¹⁶ The court also stated that the presence of the antibiotic doxycycline (which had been shipped in interstate commerce and was added to the cell culture) made the cell product subject to regulation under the FDCA and the Public Health Service Act.¹⁶ The court granted FDA a permanent injunction against Regenerative Sciences for use of Regenexx[™] MSCs unless the company completes the required FDA regulatory approval processes.¹⁶

The company continues to offer a modified Regenexx same-day procedure (Regenexx-SD). Regenexx-SD consists of prolotherapy 2 days before the injection of bone marrow-derived MSCs which are collected, processed, and injected the same day. Two days after the MSC injection, an intra-articular PRP injection is administered; patients are also instructed on a physical therapy protocol, as well as diet and hormone counseling as needed.⁶ The manufacturer states that the new Regenexx procedure offered in the United States is compliant with Code of Federal Regulations 21 Part 1271, which sets forth HCT/P regulations,¹⁸ falling under part 1271.15 (b), which exempts establishments that remove HCT/Ps from an individual and implant them into the same individual during the same surgical procedure.^{19,20} At least 22 medical facilities in the United States offer the Regenexx procedure.²¹

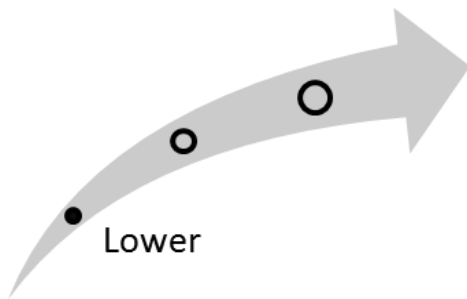
Diffusion and cost: Although the efficacy of autologous MSCs treating OA has not yet been established, the treatment can conceivably be performed at any suitably equipped health care center, and scores of centers have begun to offer it as a treatment.^{6,22} One center in Connecticut has quoted a price of \$2,900–\$3,700 for the total costs of a bone marrow-derived MSC injection and related procedures (e.g., prolotherapy and PRP injections).⁷ Another center, in Arizona, quoted a price of \$7,600 for all costs related to an adipose-derived stem cell injection.²³ Our searches of 11 representative, private, third-party payers that publish their coverage policies online (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 deny coverage for MSC therapy for OA, stating that MSC therapy is investigational because of insufficient evidence or insufficient long-term safety or efficacy outcomes.²⁴⁻²⁸

Clinical Pathway at Point of This Intervention

Patients with OA are often 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 using prescription painkillers, corticosteroid injections, or viscosupplementation. For patients with severe, persistent symptoms despite optimal treatment, clinicians can recommend surgery, including joint replacement.²⁹ 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 and who do not want to undergo knee replacement.

Figure 1. Overall high-impact potential: autologous mesenchymal stem cell therapy for osteoarthritis



Experts commenting on this technique stated that effective, minimally invasive OA therapies that can prevent or delay joint-replacement surgery are needed. Autologous MSCs have the potential to be the first treatment for OA that could regenerate articular cartilage and could provide additional benefit compared with PRP therapy. However, data are limited regarding the ability of autologous MSCs to improve OA symptoms and regenerate cartilage, and experts were cautious in their assessment of MSC therapy's potential impact. Additionally, the current lack of third-party payer coverage and high out-of-pocket costs for patients are expected to temper the impact of autologous MSC therapy for OA until more evidence accumulates to demonstrate its clinical benefit. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts with clinical, research, health devices, health systems, and health administration backgrounds, offered perspectives on this intervention.³⁰⁻³⁵ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Current OA therapies treat only the symptoms and do not restore cartilage or joint function, the experts stated; thus, a significant unmet need exists for treatments that can restore cartilage and obviate or delay the need for joint replacement.

In terms of health outcomes, preliminary data were encouraging, the experts said, and they were cautiously optimistic about the potential of MSCs to improve patient health outcomes. They thought MSCs could potentially relieve symptoms and regenerate cartilage, providing a novel treatment option to reverse the disease course of OA, reducing the need for additional therapies. Patients who are physically inactive due to OA or who were physically inactive and developed OA could be motivated to adopt a more active lifestyle if MSC can effectively relieve their symptoms, improving health outcomes, one health devices expert noted.³¹

Acceptance and adoption: The current evidence would not convince most clinicians that the procedure is effective, noted one expert representing a research perspective.³⁴ However, the experts opined that more clinicians would accept MSC therapy if the procedure were to be found safe and effective in larger, randomized controlled trials, because MSC therapy is less invasive than joint-replacement surgery. However, one expert representing a clinical perspective stated that some clinicians are very skeptical of any biologic therapy in general.³³ Additionally, two experts representing a research perspective theorized that concern regarding the development of cancerous growths could limit clinician acceptance.^{32,34} One expert representing health systems perspective

noted that additional training for the procedure and lack of third-party reimbursement could be barriers to clinician acceptance.³⁵

Patients with OA have a great need for effective treatment and some patients are currently paying out of pocket for treatments such as PRP, thus patient acceptance would likely be high, noted one clinical expert.³³ Additionally, the advantages compared with conservative treatment are considerable, and the reported adverse events appear minimal, which could lead to high patient acceptance, one health systems expert opined.³⁵ The largest barrier to patient acceptance would be reimbursement, noted two health systems experts.^{30,35} One research expert identified the potential for developing malignancies as an additional barrier to patient acceptance.³²

Health care delivery infrastructure and patient management: Changes in infrastructure, such as buying equipment and creating facilities to handle and isolate MSCs in an FDA-compliant manner, will be needed in many locations where there may already be demand for the procedure, even though MSC injection is similar to other injections used to treat OA, some experts stated.^{32,34,35}

Some experts stated that MSC therapy could reduce the cost of care if the procedure can reduce or delay the need for joint-replacement surgery.^{31,35} Other experts thought MSC injections would add costs to the system.^{30,33} According to one health systems expert, patients with OA spend about \$2,600 in out-of-pocket costs annually to manage their symptoms; thus, a treatment that restores cartilage could have a significant financial impact compared with the cost of long-term conservative symptom management.³⁵ However, another expert representing a research perspective stated joint replacement surgery could cost less than the total cost of repeat MSC therapy, depending on the number of treatments required.³⁴

In terms of patient management, experts were divided on the role MSC therapy may play in treating OA. The therapy could provide a major advance in treatment for many patients if it becomes the first therapy shown to regenerate joint cartilage and restore function, stated two experts, representing health device and health systems perspectives.^{31,35} They thought individuals using MSC therapy could avoid the cost, complications, and recovery time of joint-replacement surgery.^{31,35}

Health disparities: If the procedure is adjunctive to current therapies it could increase health disparities by adding to costs. Some 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 treating OA.^{30-32,34,35}

Autologous Platelet-Rich Plasma Therapy for Osteoarthritis

Intervention: PRP involves processing a plasma portion of a patient's blood 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.³⁶ As such, PRP is thought by some investigators and clinicians to have potential to address the underlying pathology of OA rather than only ameliorating symptoms of the disease.³⁷ PRP has been used in a number of hemostatic applications as well as for treating soft-tissue injuries such as tendinitis and chronic wounds.³⁶

In PRP, patient blood is collected and centrifuged to concentrate platelets in a small volume of plasma (about 5 mL) for each injection; clinicians inject it into the patient's intra-articular space under ultrasound guidance.³⁷⁻⁴⁰ Typically, multiple injections are given over the course of several weeks.

Clinical trials: In one prospective trial (n=150 knees), patients with bilateral early knee OA received a blinded, single intra-articular PRP injection (Group A; n=54 knees), two PRP injections 2–3 weeks apart (Group B; n=50 knees), or saline injection (Group C; n=46 knees). Followup evaluation was performed at 3 weeks, 3 months, and 6 months by a blinded, independent observer. Significant improvement in all WOMAC parameters ($p<0.05$) were noted in both PRP-injection groups beginning at about 2–3 weeks with a trend of slight symptom worsening at the 6 month followup.⁴¹ The percentage benefit from baseline to each followup time point was greater in patients in both PRP-injection groups compared with benefit in the saline-injection group ($p<0.001$). No significant difference in clinical improvement was observed between patients treated with single or dual PRP injections. Patients treated with PRP reported mild adverse events, including sweating, which occurred within 30 minutes and could be attributed to platelet dosage; nausea; and headache.⁴¹

In a prospective, randomized controlled trial, patients (n=49) aged 40–50 years with early OA and cartilage lesions less than 4 cm² were treated with arthroscopic microfracture. Then patients (n=24) were treated with PRP injection or untreated (control; n=25) and evaluated with VAS, IKDC score preoperatively and postoperatively at 1, 6, 12, and 24 months. Significant clinical improvements were observed in both the PRP and control groups from preoperative to 2 years ($p=0.017$). Also in the 2 years after treatment, significant clinical improvements were observed in the PRP group compared with the control group ($p=0.012$). Cartilage hardness and elasticity degree was significantly better in the PRP group compared to the control group at 4–6 months postoperatively.⁴²

In another trial, patients (n=120) with knee OA of Kellgren-Lawrence grade 1, 2, or 3 were treated with three intra-articular injections of either PRP or hyaluronic acid. Statistically significant improvements in the WOMAC and Numeric Rating Scale scores were observed in patients who received PRP injections at 3- and 6-month followup. No severe adverse events were observed by the investigators.⁴³

In a randomized, double-blind, controlled trial, patients (n=109) with knee OA of Kellgren-Lawrence grade 1, 2, or 3 were treated with three weekly injections of PRP or hyaluronic acid and evaluated at 12-month followup. Both groups showed clinical improvement at followup with no statistical difference between groups. The authors reported a “trend” for improvement in the PRP group patients with low-grade articular degeneration (Kellgren-Lawrence score up to 2). No serious adverse events were reported. Mild pain and effusion after the injections were reported, more in the PRP group than in the hyaluronic acid group ($p=0.039$).⁴⁴

In a study (n=261) of patients with knee OA with Outerbridge grades I–IV and symptoms of more than 3 months' duration who were treated with three intra-articular PRP injections every 2 weeks, 6-month followup showed statistically significant improvements in the PRP group for pain, stiffness, and functional capacity ($p<0.0001$).⁴⁵ No adverse events were reported.

In another trial (n=100 patients, 115 knees), patients with knee OA received three intra-articular PRP injections. Statistically significant improvements in all clinical scores (International Knee Documentation Committee form, EQ [EuroQol] VAS quality-of-life score) were reported between the baseline evaluation, the end of the therapy, and between baseline and 6- and 12-month followup ($p<0.0005$). In the trial, the results declined significantly by and after 12-month followup ($p=0.02$) but were still better than at baseline ($p<0.0005$).³⁸ By 24-month followup, all evaluated outcomes were significantly lower than those observed at 12-month followup. Better results were obtained in younger patients ($p=0.0001$) and in patients with lesser degrees of cartilage degeneration ($p<0.0005$). The median duration of the clinical improvement provided by PRP for knee OA was 9 months.⁴⁰

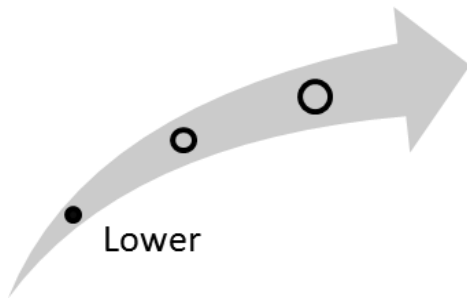
Manufacturer and regulatory status: Autologous PRP is not considered a drug or a therapeutic substance by FDA; therefore, the preparation is not subject to regulatory marketing approval. The patient undergoes apheresis to collect blood to yield the plasma that is centrifuged to concentrate platelets 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.³⁶ Many devices have FDA marketing approval for use in preparing PRP.³⁸

Diffusion and cost: The therapy's cost reportedly is from \$500 to \$1,500 per injection.⁴⁶ One sports medicine clinic in Connecticut lists the total cost of a PRP injection ranging from \$700 to \$1,100 per treatment, depending on the complexity of the procedure.⁴⁷ Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 8 payers that have policies denying coverage for the procedure because they consider PRP injections to be experimental or investigational.⁴⁸⁻⁵⁵

Clinical Pathway at Point of This Intervention

Patients with OA are frequently prescribed 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 using prescription analgesics, corticosteroid injections, or viscosupplementation. For patients with severe, persistent symptoms despite optimal treatment, clinicians can recommend surgery, including joint replacement.²⁹ If proven effective for treating 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: autologous platelet-rich plasma therapy for osteoarthritis



Overall, experts commenting on this intervention were divided on the impact that PRP might have on OA treatment. Treatment options that can restore cartilage and bridge the gap between pain relief and joint replacement are needed. PRP could become standard first-line therapy if the treatment is shown to regenerate joint cartilage and restore function. The experts thought that preventing joint replacement surgery or reversing pathogenesis could have a large impact on patient outcomes and be a major cost-saving advance in OA treatment. Improved reimbursement in the future could increase diffusion because PRP has been shown to be more effective than hyaluronic acid injections and is less costly than some hyaluronic acid injections. However, they called for more data and clinical experience 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 lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.⁵⁶⁻⁶¹ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Current therapies for OA treat only the symptoms and do not restore cartilage or joint function, the experts stated. Thus, a significant and growing unmet need exists for noninvasive treatments that can restore joint cartilage and function and delay or eliminate the need for joint replacement surgery.

Experts were cautiously optimistic about PRP therapy's potential to improve patient health outcomes by relieving symptoms, but they were less certain about the treatment's ability to regenerate cartilage or prevent or delay joint-replacement surgery. Most experts stated that large, randomized, double-blind controlled trials with longer follow up are needed to better understand PRP's effects on knee OA.⁵⁷⁻⁶¹

Acceptance and adoption: Clinicians are likely to accept the PRP procedure because it offers a minimally invasive option, minimal learning curve, is low cost to implement, and has a low risk of adverse events, based on PRP study outcomes, the experts noted. Lack of reimbursement and patients' high out-of-pocket costs were seen as barriers to physician acceptance. Experts generally agreed that additional data to confirm efficacy will be required for payer coverage and broader diffusion.

Patients are also expected to have high acceptance if the procedure is found to be effective and safe and delays the need for knee replacement, the experts opined. Patients were also expected to prefer the minimally invasive nature of PRP injections over surgery. One health systems expert stated that a segment of patients with knee OA exists who highly value health and function and would be willing to spend discretionary income on PRP injections, while most patients will want

their insurers to cover the procedure.⁶⁰ Other experts stated patients would prefer PRP injections over joint replacement surgery or corticosteroid injections.⁵⁷⁻⁵⁹ One health systems expert pointed out that many patients currently pay more in out-of-pocket costs for hyaluronic acid injections than the cost for PRP injections, which could increase patient acceptance of PRP.⁶⁰ If PRP can eliminate the need for joint-replacement surgery in some patients, PRP injections are expected to be cost saving, which would increase acceptance and diffusion, clinical, systems, and research experts thought.^{58,59,61}

Health care delivery infrastructure and patient management: Because some patients with OA are already being treated with intra-articular knee injections, minimal changes in infrastructure and patient management would be seen with implementing PRP, experts thought. However, changes in patient management and infrastructure might occur because of fewer joint-replacement surgeries, which would cause many inpatient procedures to be handled as outpatient procedures, reducing costs, two experts noted.^{58,59} Additionally, three experts thought some equipment may need to be purchased for preparing PRP, and staff would need training in handling blood collection and preparing PRP.^{57,59,60}

Health disparities: The effect of this intervention on health disparities is unclear. Most experts did not foresee a significant effect on health care disparities.^{56,57,59,61} However, a health systems expert opined that although the current costs of PRP injections and lack of reimbursement are likely to increase health care disparities, the lower costs and greater symptom relief of PRP over hyaluronic acid injections will eventually lead to favorable reimbursement, which would allow more patients to be treated with PRP who are unable to pay for it out of pocket.⁶⁰ Additionally, minorities are less likely to have joint replacement surgery and could be more accepting of minimally invasive PRP injections, one clinical expert stated.⁵⁸

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