



Injections for Knee Osteoarthritis: Corticosteroids, Viscosupplementation, Platelet-Rich Plasma, and Autologous Stem Cells

David M. Levy, M.D., Kyle A. Petersen, M.D.,
Margie Scalley Vaught, C.P.C., C.O.C., C.P.C.-I., C.C.S.-P., M.C.S.-P., A.C.S.-E.M., A.C.S.-O.R.,
David R. Christian, B.S., and Brian J. Cole, M.D., M.B.A.

Abstract: This article reviews the benefits of corticosteroid, viscosupplementation, platelet-rich plasma, and autologous mesenchymal stem cell injections for the treatment of patients with knee osteoarthritis. Integrating injections into both clinical and surgical practices is complicated given existing health insurance reimbursement policies. This review describes the outcomes associated with these interventions and appropriate methods of navigating the existing reimbursement pathways to help providers implement these treatments into their practices.

Osteoarthritis (OA) of the knee is a degenerative condition that affects 38% to 47% of the population aged older than 60 years.¹ OA exacts a significant economic burden on the American health care system. The estimated annual cost of OA per patient is \$5,700,²

and in 2004 alone, the cost of total knee arthroplasty (TKA) to treat OA was \$14.6 billion in the United States.³ OA has an even greater impact on patient function; it is 1 of the top 5 causes of disability in the United States⁴ and is associated with an increase in morbidity and mortality rates.⁵ Men and women with OA have difficulty finding work and performing activities of daily living and have an increased mortality rate due to cardiovascular disease and dementia.⁴

From the Department of Orthopedic Surgery, Rush University Medical Center (D.M.L., K.A.P., D.R.C., B.J.C.), Chicago, Illinois; and Auditing, Coding, Documentation and Compliance Consulting (M.S.V.), Chehalis, Washington, U.S.A.

The authors report the following potential conflict of interest or source of funding: B.J.C. receives support from Aesculap/B. Braun, Geistlich, Medipost, National Institutes of Health (NIAMS and NICHD), Novartis, Sanofi-Aventis. Research support. American Journal of Orthopaedics, American Journal of Sports Medicine, Arthroscopy, Cartilage. Editorial or governing board. Aqua Boom, Biomerix, Gitelescope, Ossio. Stock or stock options. Arthrex. IP royalties, paid consultant, research support. Arthroscopy Association of North America, International Cartilage Repair Society. Board or committee member. Athletico, JRF Ortho, Tornier. Other financial or material support. DJ Orthopaedics, Elsevier Publishing. IP royalties. Flexion. Paid consultant. Journal of Bone and Joint Surgery—American, Journal of Shoulder and Elbow Surgery, Journal of the American Academy of Orthopaedic Surgeons. Editor only: editorial or governing board. Operative Techniques in Sports Medicine, Saunders/Mosby-Elsevier. Publishing royalties, financial or material support. Regentis. Paid consultant. stock or stock options. Smith & Nephew. Other financial or material support, paid consultant. Zimmer. Paid consultant, research support. Full ICMJE author disclosure forms are available for this article online, as [supplementary material](#).

Received December 2, 2017; accepted February 13, 2018.

Address correspondence to Brian J. Cole, M.D., M.B.A., Department of Orthopedic Surgery, Rush University Medical Center, 1611 W Harrison St, Ste 300, Chicago, IL 60612, U.S.A. E-mail: bcole@rushortho.com

© 2018 by the Arthroscopy Association of North America

0749-8063/171498/\$36.00

<https://doi.org/10.1016/j.arthro.2018.02.022>

Although its pathophysiology is not fully understood, OA is defined by irreversible, progressive damage to the articular cartilage of the knee. There are modifiable and nonmodifiable risk factors. Nonmodifiable risk factors include age, race, sex, and potential genetic susceptibility,^{6,7} whereas the key modifiable risk factors include patient weight and activity level.^{6,8} The rate of obesity—defined as a body mass index over 30—continues to rise in the United States, and in a 2012 census, 35% of adults, 57% of black women, and nearly 17% of persons aged younger than 19 years were obese.⁹

Current treatment for OA focuses on relieving symptoms and improving function, and it usually begins with patient education on modifiable risk factors, physical therapy, and oral nonsteroidal anti-inflammatory drugs. Patients who remain unresponsive to these treatments may be indicated for knee injections before being indicated for joint replacement surgery. Today, there are 4 main injection therapies: corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP), and autologous mesenchymal stem

cells (MSCs).¹⁰⁻¹⁶ This article reviews the existing literature evaluating the efficacy of injection therapies in the treatment of knee OA through December 2017.

Injection Therapies

Corticosteroids

Corticosteroids have been used for over 50 years with varying degrees of success (Table 1).¹⁷ The pathophysiology of corticosteroids is more understood than that of most other injectable materials, because corticosteroids alter B- and T-cell immune function and inhibit phospholipase A2 to decrease expression of inflammatory cytokines.¹⁸ There is also evidence to suggest that cortisone increases fluid viscosity and HA concentration within the joint space, which theoretically may help to treat OA.^{17,19}

Synthetic corticosteroids have more anti-inflammatory potency than does native cortisol, and they are derivatives of prednisolone, an analogue of human cortisol.²⁰ Depo-Medrol (Pfizer, New York, NY) is the injectable formulation of methylprednisolone acetate, and the fluorinated derivatives of prednisolone are betamethasone, dexamethasone, and triamcinolone. Triamcinolone (Kenalog; Bristol-Myers Squibb, New York, NY) is frequently used as an injectable for orthopaedic conditions. Methylprednisolone and triamcinolone are the 2 most common injectables used for knee OA. They are equivalent in potency, but triamcinolone is less water-soluble,²⁰ potentially making it a better alternative for patients with diabetes who are at risk of hyperglycemic spurts after injection. Both preparations contain esters, which require hydrolysis by cellular esterases to release the active moiety and last longer than non-ester preparations.²¹ The average duration of benefit ranges from 8 to 56 days for methylprednisolone and 14 to 66 days for triamcinolone.²²⁻²⁴

Corticosteroids for knee OA are almost always administered with local anesthetics. Lidocaine has a rapid onset of action (2-5 minutes) and a duration of 2 or 3 hours, depending on the inclusion of epinephrine.²⁵ Because its anesthetic effect wears off so quickly, clinicians frequently add bupivacaine, which has a slower onset (5-10 minutes) but a longer duration of action (4-8 hours).²⁵ Some clinicians prefer to administer corticosteroid and anesthetics using separate syringes, but Benzon et al.²⁶ have shown that corticosteroid crystals do not change in aggregation or particle size when mixed with local anesthetics. Previous work has shown that continuous infusion of intra-articular anesthetics may lead to chondrolysis,²⁷ but no studies have shown similar long-lasting damage from single injections of physiological doses.²⁸

When pain relief is achieved from a corticosteroid injection, the benefit is usually transient, lasting anywhere from 1 week to 24 months.^{17,29,30} Some

clinicians believe that increased symptoms at baseline and the presence of an effusion or synovitis improve the likelihood of response to cortisone injections.^{20,31} At least 2 studies have suggested that milder OA is a predictor of a positive response,^{32,33} but neither study specified whether Kellgren-Lawrence grades were assessed on posteroanterior flexion (Rosenberg) views, which have been shown to be more sensitive for detecting knee OA.³⁴ Previous research has suggested that different radiographic views may upgrade the diagnosed severity of OA.¹⁵ Therefore, it is important that future trials comparing the severity of knee OA with injection response specify which radiographic views are used as a correlate to clinical outcomes.

Clinicians should always warn patients that post-injection flares may develop in 2% to 25% of patients within a few hours of injection.^{23,35} These flares may last 2 to 3 days but do not predict a poor overall response to therapy.²³ Soft-tissue adverse effects are rare and include skin depigmentation, cutaneous atrophy, and fat necrosis.²⁰ Systemic inhibition of the hypothalamus-pituitary-adrenal axis was shown to last up to 2 weeks in 7 of 10 athletes after intra-articular injection.³⁶ The clinical ramifications of this are most likely negligible, but patients may be cautioned to avoid severe physical stress within 2 weeks of injection. Finally, although there is basic-science evidence that increased numbers of corticosteroid injections may lead to cartilage breakdown,³⁷ the clinical risk of cartilage loss after multiple injections is still very low, at 0.7% to 3.0%.^{38,39} One study found that intra-articular triamcinolone may result in significantly greater cartilage loss and no significant difference in knee pain compared with intra-articular saline solution administration.⁴⁰ However, this study reported relatively low amounts of cartilage volume loss and a dosing frequency that is greater than most clinicians would provide. In addition, patients included in this study had relatively advanced disease at baseline. Furthermore, most clinicians would stop administering intra-articular injections in the absence of efficacy. After thorough consideration of the literature as of 2013, the American Academy of Orthopaedic Surgeons (AAOS) stated that there is inconclusive evidence to recommend for or against the use of intra-articular corticosteroids to treat knee OA.⁴¹ Despite this, physicians continue to liberally use intra-articular corticosteroids to treat patients with symptomatic knee OA.

Senior Author's Clinical Recommendations. In the senior author's (B.J.C.) practice, corticosteroid injections are commonly used as the initial first-line treatment for symptomatic knee OA. We typically use a single injection consisting of 1 mL of methylprednisolone (40 mg) and 9 mL of 1% lidocaine because we find the volume is well tolerated and patients have rapid

Table 1. Corticosteroid Injection Key Points

	Key Points
Composition	<ul style="list-style-type: none"> • The injectable formulation is commonly methylprednisolone or triamcinolone. • Corticosteroids are typically combined with local anesthetic such as lidocaine or bupivacaine.
Mechanism of action	<ul style="list-style-type: none"> • Corticosteroids reduce inflammation by altering B- and T-cell function as well as stimulating HA synthesis.
Efficacy	<ul style="list-style-type: none"> • Synovitis, effusion, or mild OA may predict the therapeutic benefit. • AAOS has stated that there is inconclusive evidence to recommend for or against the use of intra-articular corticosteroids to treat knee OA.
Complications	<ul style="list-style-type: none"> • In 3%-25% of patients, a flare may occur in the days after an injection, but this does not interfere with the therapeutic benefit.

AAOS, American Academy of Orthopaedic Surgeons; HA, hyaluronic acid; OA, osteoarthritis.

initial relief. We typically recommend corticosteroid injections as the first-line treatment for patients presenting with OA that is resistant to other nonsurgical treatments such as nonsteroidal anti-inflammatory medications, physical therapy, weight loss, and an acceptable amount of activity modification. In addition, it is our preference to provide treatment earlier in patients who present with an effusion (which is aspirated at the time of injection) or suspected synovitis with a corticosteroid injection to help alleviate their discomfort. Last, we only allow patients to receive up to 4 injections in a 12-month interval to avoid a potential adverse effect either locally on the articular cartilage or systemically. If a patient does not achieve at least 3 months of meaningful relief, we typically recommend moving on along the continuum of injection therapy. Notably, corticosteroid injections remain a reimbursable, point-of-care service that we typically perform without ultrasound guidance in the knee.

Viscosupplementation

HA is a complex polysaccharide that was first developed in 1934 from cattle vitreous humor (Table 2).⁴² HA is an essential component of proteoglycans, which entangle between collagen fibers and help trap water to

provide compressive strength to articular cartilage.⁴³ High-molecular-weight (HMW) HA was developed for therapeutic use later, in 1971, by Balazs⁴⁴ and was approved for general use by the US Food and Drug Administration (FDA) in 1997. Today, HA is produced *in vitro* by bacterial fermentation or rooster combs.⁴⁵ One of the original studies to show its potentially beneficial anti-inflammatory properties was performed by Rydell and Balazs⁴⁶ and showed decreased synovial inflammation in an animal model.

Arthritic knees have been previously shown to have less endogenous HA than knees without OA,⁴⁷ which helps to explain why exogenous administration may be beneficial.⁴⁸ HA works through a complex mechanism believed to increase the viscosity of intra-articular fluid, decrease oxidative stress within the joint, and inhibit phagocytosis of macrophages, resulting in an anti-inflammatory benefit.⁴⁹ In addition, HA has been shown to inhibit nitric oxide,⁴⁹ which has been associated with OA and causes oxidative stress within the joint space.⁵⁰

In the United States, the 2 primary HA derivatives on the market are Synvisc (Sanofi-Aventis, Bridgewater, NJ) and Orthovisc (Anika Therapeutics, Bedford, MA), which are typically administered once per week for 3 weeks. A recent formulation known as Gel-One

Table 2. Viscosupplementation Injection Key Points

	Key Points
Composition	<ul style="list-style-type: none"> • The solution contains HA, a complex polysaccharide that is an essential component of proteoglycans found in synovial fluid.
Mechanism of action	<ul style="list-style-type: none"> • HA increases the viscosity of intra-articular fluid and entangles between collagen fibers to trap water, providing increased compressive strength to articular cartilage. • HA decreases inflammation by reducing oxidative stress and inhibiting macrophage phagocytosis. • The Synvisc and Orthovisc HA formulations are administered in 3 injections over a period of 3 wk, whereas a more recent formulation, Gel-One, is a single injection.
Efficacy	<ul style="list-style-type: none"> • The existing literature is variable regarding the efficacy of HA injections for knee OA. • HMW HA has been shown to be more efficacious than LMW HA. • The AAOS guidelines do not recommend the use of HA injections for knee OA.
Complications	<ul style="list-style-type: none"> • The local adverse reaction rate is between 2% and 4%. • There is an increased rate of flares and granulomatous inflammation yet a low probability of infection after injection.

AAOS, American Academy of Orthopaedic Surgeons; HA, hyaluronic acid; HMW, high molecular weight; LMW, low molecular weight; OA, osteoarthritis.

(Zimmer, Warsaw, IN) is a 1-time injection. These formulations are considered medical devices as opposed to pharmaceutical agents and are approved by the FDA for the treatment of knee OA in patients in whom conservative nonpharmacologic therapy and simple analgesics have failed.⁴⁷ Clinicians administering intra-articular HA injections typically advise their patients of a local adverse reaction rate of between 2% and 4%.⁴⁸ There is an increased rate of flares⁵¹ and granulomatous inflammation⁵² yet a low probability of infection after HA administration.⁵³ A recent systematic review found no difference in the adverse event rate between single injections of HA and placebo, but there may be an elevated risk with increased numbers of injections.⁵⁴

Many studies have looked into the efficacy of HA in the treatment of knee OA. In 2002 Miltner et al.⁵⁵ showed improved knee function after HA injection, as evidenced by maximum peak torque improvement and changes in Lequesne and visual analog scale (VAS) pain scores. DeCaria et al.⁵⁶ examined functionality after intra-articular HA injections and found no difference in gait velocity compared with placebo but did find that patients treated with HA had improvements in Western Ontario and McMaster Universities Arthritic Index (WOMAC) scores for pain, stiffness, and physical function. In 2010, Chevalier et al.¹⁰ reported significant improvements in WOMAC pain scale scores in patients receiving HA compared with placebo for up to 26 weeks after injection. Kolarz et al.⁵⁷ showed statistically significant improvements in VAS scores, Larson knee joint function, and maximum walking time for as long as 12 months after 5 weekly HA injections. More recently, the efficacy of different HA formulations, specifically HMW and low-molecular-weight HA, has been investigated. Rutjes et al.⁵² performed a systematic review and meta-analysis of clinical trials evaluating HA injections for OA. When all studies were included, a statistically but not clinically significant reduction in pain was observed; however, a subanalysis including only those studies investigating HMW HA showed pain reduction was statistically and clinically significant. In 2007 Waddell and Bricker⁵⁸ studied 1187 grade IV knees injected with HMW HA and found that the period until these patients received a TKA was able to be delayed by a median of over 2 years. In addition, their follow-up study in 2016 found that HMW HA injections delayed knee replacement by greater than 7 years in 75% of patients.⁵⁹ A Cochrane review from 2014 found that viscosupplementation for knee OA provides pain reduction and an improvement of physical function with a low risk of harm.⁶⁰ Furthermore, HMW HA injections have been shown to have a beneficial effect on the biochemistry of articular cartilage. Shah et al.⁶¹ showed increased cartilage proteoglycan content at 6 weeks and 3 months after HMW HA treatment, which correlated with improvement in VAS

pain, WOMAC, and International Knee Documentation Committee (IKDC) outcome scores. In addition, Wang et al.⁶² performed a randomized controlled trial showing preservation of the articular cartilage at 2 years after HMW HA treatment compared with placebo.

Various studies have compared the efficacy of intra-articular corticosteroids with HA for knee OA. A 2006 Cochrane review article found intra-articular HA and intra-articular corticosteroids to be equally efficacious from 1 to 4 weeks, but HA was superior 5 to 13 weeks after injection.⁶³ Another large meta-analysis comparing these 2 treatment options agreed that HA was more effective at providing pain relief but failed to show any difference after 4 weeks.⁶⁴ In fact, these authors showed that intra-articular corticosteroids were more effective from baseline until week 4. This rapid onset of action by corticosteroids is supported by the notion that, when triamcinolone is added to viscosupplementation, improvements in WOMAC and VAS scores are seen after 1 week compared with HA alone.⁶⁵ Nevertheless, after 4 weeks, de Campos et al.⁶⁵ found no difference between HA with or without triamcinolone. Recent trials comparing the 2 treatments have found HA to be more effective at reducing pain and increasing range of motion than triamcinolone alone but have found no difference in gait.⁶⁶

Despite overwhelming evidence supporting HA injections, particularly HMW HA injections, many physicians have questioned their efficacy and utility.⁴⁸ A recent double-blind randomized controlled trial comparing HA versus saline solution found no additional benefit in terms of WOMAC and VAS scores.⁶⁷ In addition, a large meta-analysis concluded that its benefit was clinically irrelevant, with concern for possible increased risk of adverse effects.⁵² This conclusion is similar to that of the AAOS clinical practice guidelines for OA of the knee, which do not recommend using HA for patients with symptomatic knee OA.⁴² Previous research has shown greater pain control and functional improvement with corticosteroids compared with HA injections, particularly in the early stages.⁶⁸ Further studies are needed to address its cost-benefit and long-term safety and efficacy. To date, opinions on the efficacy of HA are highly variable and subject to one's interpretation of the literature.

Senior Author's Clinical Recommendations. The senior author typically elects to use HA injection regimens that are performed as 3 injections over a span of 3 weeks. We recommend HA injections to patients presenting with chronic, low-grade OA that is often localized to the medial, lateral, or anterior compartment. In our experience, patients with mild arthritis often receive significant relief from viscosupplementation and often return to the clinic every 6 to 8 months asking for repeat injections with repeated symptomatic

improvement. We are less likely to recommend HA injections for patients with significant inflammation or suspected synovitis because the anti-inflammatory effects are less potent than those of corticosteroid or PRP injections. Finally, patients with advanced “bone-on-bone” OA and those with symptomatic advanced patellofemoral OA tend to be less responsive, and we often offer alternative injection therapies (i.e., PRP and HA) for those patients.

Platelet-Rich Plasma

PRP has been defined as “a volume of plasma that has a platelet count above baseline” (Table 3).⁶⁹ To obtain PRP, venous blood is drawn from the patient and centrifuged to separate PRP from red blood cells and plasma.⁷⁰ This autologous PRP is then injected into the affected joint. The first reports of PRP preparations were in the 1950s and involved studies investigating coagulation.⁷¹ In recent years, more attention has been given to PRP and its vast array of potential clinical applications.^{14,69,72}

When the platelets degranulate after injection, growth factors such as transforming growth factor β , platelet-derived growth factor, epidermal growth factor, vascular endothelial growth factor, fibroblast growth factor, and insulin-like growth factor are released or related to the presence of PRP.⁷³ These growth factors are believed to have regenerative capacity.^{74,75} More important, in OA, they may inhibit inflammatory effects on chondrocytes by nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and interleukin 1 (IL-1).⁷⁶ Nitric oxide is also inhibited by PRP, which limits the oxidative stress on the joint.⁵¹ Furthermore, PRP has been shown to increase cartilage synthetic activity to a greater degree than HA.⁷⁴ Sundman et al.⁷⁴ evaluated the *in vitro* response of human synovium and cartilage cultured with medium of PRP. They showed that PRP not only stimulated endogenous production of HA but also decreased the production of matrix metalloproteinases responsible for cartilage catabolism. These results suggest a possible chondroprotective element of PRP and are bolstered by other studies in the literature.⁷⁷ Sun

et al.⁷⁵ have shown that growth factors released by platelets stimulate osteochondral formation in rabbits with defects of the patellofemoral groove. Despite the potential for regenerative effects, the likely impact of PRP in a symptomatic patient with knee OA is due to its local and, potentially, systemic anti-inflammatory effects.

Multiple preparations are available that have differing concentrations of platelets, white blood cells, and growth factors. Some studies have shown that leukocyte-rich PRP is associated with an increased rate of death of synoviocytes and greater inflammation,⁷⁸ but the ideal balance is yet to be determined. In addition, other studies have investigated the effect of the leukocyte concentration on clinical efficacy, suggesting that leukocyte-poor preparations are more effective at providing symptomatic relief.⁷⁹ Although not currently FDA approved for injections, PRP is often used off-label and thus not covered by insurance. Most of the reported adverse events are transient pain and localized swelling after PRP injection,^{80,81} but the overall adverse reaction rate is low, with many studies reporting no major adverse reactions.^{11,66} Other studies have shown no increased risk of adverse reactions compared with placebo.⁸² Larger trials are necessary to determine the event rate and possible long-term adverse reactions.

A recent double-blind randomized controlled trial found PRP to be more effective than placebo in the treatment of knee OA.¹⁶ These authors have shown significantly lower WOMAC scores at 6 weeks and 3 months,¹⁶ whereas other authors have shown persistent clinical improvements through 6 and 12 months.^{14,72,81,83} Some studies have found PRP to be more efficacious in younger patients with less cartilage degeneration,^{72,83} and PRP may play a role in delaying the progression of OA and the need for joint replacement.⁸⁴ Halpern et al.¹² have shown that PRP prevented significant worsening of OA in the patellofemoral joint specifically. Similarly, 2 recent systematic reviews have recommended that PRP be considered as part of the initial management of knee OA,^{83,84} with Campbell et al.⁸³ concluding that symptomatic relief can be achieved for up to 12 months.

Table 3. PRP Injection Key Points

	Key Points
Composition	<ul style="list-style-type: none"> • PRP is prepared from the patient’s venous blood, which is centrifuged to separate PRP from red and white blood cells.
Mechanism of action	<ul style="list-style-type: none"> • PRP has been shown to be anti-inflammatory, chondroprotective, and possibly regenerative.
Efficacy	<ul style="list-style-type: none"> • Leukocyte-poor PRP may be more efficacious than leukocyte-rich PRP. • PRP may be more therapeutic in younger patients with mild cartilage loss. • PRP may prevent worsening of the OA, particularly in the patellofemoral joint. • The AAOS guidelines do not recommend for or against the use of PRP for knee OA.
Complications	<ul style="list-style-type: none"> • There are some reports of flares, although the overall adverse reaction rate is low, with many studies reporting no major adverse reactions.

AAOS, American Academy of Orthopaedic Surgeons; PRP, platelet-rich plasma; OA, osteoarthritis.

Many authors have studied the efficacy of intra-articular HA with PRP for the treatment of knee pain. In 2011 Kon et al.¹⁴ showed that younger patients had greater benefit from PRP than did older patients, and as a whole, the study showed longer and greater efficacy of PRP when compared with HA. The suggestion that patients with early OA respond better to PRP has also been indicated by other authors who have found a benefit in lower-grade OA.⁸⁵ In another randomized controlled trial, Sánchez et al.⁸⁶ found the PRP formulation PRGF-Endoret (BTI Biotechnology Institute, Vitoria-Gasteiz, Spain)—plasma rich in growth factors—to be superior to HA in terms of pain relief. Cerza et al.⁸⁷ and Spaková et al.⁸¹ both reported better WOMAC scores after PRP injection for up to 24 weeks and 3 to 6 months, respectively. Furthermore, a separate prospective study of 90 patients found PRP to be less expensive and to be superior to HA at 3 and 6 months regarding functional and pain scores.⁸⁸ Two recent meta-analyses likewise concluded that PRP improved function and pain scores more than did HA.^{24,89} A systematic review by Khoshbin et al.¹³ also found PRP to be more beneficial than HA in terms of IKDC and WOMAC scores. Conversely, a randomized trial in 2015 showed no significant difference in clinical scores or range of motion between PRP and HA.¹¹ Similarly, a 2017 randomized controlled trial found no statistically significant difference in outcome scores, although trends suggested that PRP may be more efficacious than HA and PRP produced a decrease in intra-articular inflammatory cytokine levels.⁹⁰ Despite these findings, recent AAOS guidelines on the management of knee OA have stated that AAOS cannot recommend either for or against the use of PRP,⁴² given the lack of high-quality trials investigating PRP.

Senior Author's Clinical Recommendations. In the senior author's practice, leukocyte-poor PRP is commonly used to treat patients with knee OA if other treatment options have failed. We perform a blood draw of 15 mL of venous blood, which is then centrifuged for 5 minutes to isolate approximately 4 to 6 mL of PRP. We typically recommend a series of 3 injections over a span of 3 weeks. When used in isolation, if patients see no response after the first or second PRP injection, we will typically recommend alternative treatments. If they achieve a modest response early, we encourage consideration of subsequent injections, up to a maximum of 3, over a period of 3 to 4 weeks. Notably, there is virtually no conclusive evidence on the dose or frequency of PRP in the setting of the treatment of knee OA.

More recently, we have chosen to perform a total of 3 weekly combined PRP-HA injections because basic-science research has shown that the combination does

not impair the viscosupplementation effects of HA. In addition, chondrocytes cultured with both PRP and HA showed increased proliferation rates and glycosaminoglycan contents compared with those cultured with HA alone, suggesting that the combined injection may provide a more therapeutic environment.⁹¹⁻⁹⁴ We recommend PRP injections to patients with either chronic, low-grade arthritis or suspected small focal chondral defects. In our clinical experience, patients with advanced arthritis often do not have the same therapeutic benefit as younger patients with early arthritis.

Autologous Stem Cells

In the late 1960s, much attention was drawn to the possibilities of stem cells because of their inherent ability to differentiate into multiple cell lines (Table 4).⁹⁵ More recent studies have shown the capacity of MSCs to differentiate into osteocytes, adipocytes, myocytes, and most importantly for OA treatment, cells of chondrogenic lineage.^{96,97} This ability to regenerate cartilage is believed to be one of the key aspects by which stem cells help patients with OA. In addition, MSCs have the capability to regenerate subchondral bone, which may help in the repair of the osteochondral defects seen in OA.⁹⁸ MSCs can be isolated from various tissues, including bone marrow, adipose tissue, and the umbilical cord.⁹⁹ Given the current regulatory environment, minimally manipulated autologous sources of MSCs must be administered at the time of acquisition and include only bone marrow concentrate and adipose tissue. Notably, the regulatory pathways and FDA position on the use of these sources of MSCs remain a dynamic process specifically related to concerns pertaining to levels of manipulation and homologous use.

Patients with severe OA requiring a TKA have decreased in vitro chondrogenic and adipogenic activity within MSCs when compared with healthy matched individuals, most likely because of their decreased capacity to differentiate into precursor cells.¹⁰⁰ In addition, synovial fluid from patients with OA appears to inhibit the chondrogenic capacity of MSCs from donors.¹⁰¹ The regenerative capability of MSCs may also replenish the proteoglycan lubricant and hyaline-like cartilage that naturally minimizes friction in the patellofemoral joint.¹⁰² Moreover, MSCs have been shown to possess potent immunosuppressive and anti-inflammatory functions⁹⁷ through the suppression of T cells within the joint space and inhibition of the expression of major histocompatibility complex class II antigens.⁹⁶ It is likely that the anti-inflammatory effect rather than the regenerative potential is the mechanism by which symptoms of OA might be reduced after MSC injections.

Table 4. Autologous Stem Cell Injection Key Points

	Key Points
Composition	<ul style="list-style-type: none"> • Autologous stem cells can be derived from bone marrow, adipose tissue, and the umbilical cord.
Mechanism of action	<ul style="list-style-type: none"> • Autologous stem cells can differentiate into osteogenic and chondrogenic cell lines, which may help in the treatment of chondral defects.
Efficacy	<ul style="list-style-type: none"> • Autologous stem cell injections have potent immunosuppressive and anti-inflammatory properties. • Preliminary studies of patients treated with intra-articular injections have shown promising results, especially in those with low-grade OA.
Complications	<ul style="list-style-type: none"> • The rate of adverse reactions was found to be 3.1%, mostly owing to increased pain and swelling. • There is a theoretical risk of being carcinogenic, although this has not been proved.

OA, osteoarthritis.

Before intra-articular MSC injection in humans, multiple animal studies showed its efficacy and mechanism.^{103,104} The first clinical report of MSCs being used to treat OA, in 2002, used culture-expanded MSCs and showed regeneration of extensive unicompartamental articular cartilage defects.¹⁰⁵ Other studies have since shown the efficacy and regenerative capability of intra-articular injections of cultured and stimulated stem cells after microfracture surgery or high tibial osteotomy.^{106,107} Centeno et al.¹⁰⁸ used marrow-derived, culture-expanded MSCs and reported increased range of motion and VAS pain scores at 6 months, as well as increased meniscus volume and, most important, no side effects. Further studies of culture-expanded MSC injections have shown relief from 6 months to greater than 2 years,^{89,109} with improvement in pain, crepitus, and the ability to climb stairs.^{102,109} Orozco et al.⁸⁹ conducted a pilot study of 12 patients with knee OA who were unresponsive to conservative treatment and treated with intra-articular marrow-derived, culture-expanded MSC injections. They showed rapid and progressive improvement in function as well as cartilage quality. More recently, studies have shifted to investigate bone marrow aspirate concentrate (BMAC) as opposed to culture-expanded MSCs because BMAC meets FDA standards as a minimally manipulated autologous source of MSCs. Kim et al.¹¹⁰ investigated BMAC injections for the treatment of knee OA and similarly observed significant improvements in pain and functional outcome scores. It is interesting to note that patients with low-grade OA had significant improvements when compared with patients with higher-grade Kellgren-Lawrence scores. Centeno et al.¹¹¹ retrospectively compared patients with knee OA treated with a BMAC injection and those treated with a BMAC injection and adipose graft. They reported significant symptomatic improvements in both groups at 10 months' follow-up but no difference between groups. Shapiro et al.¹¹² performed a randomized controlled trial of patients with bilateral knee OA treated with a BMAC injection in 1 knee and placebo in the other knee and found significant improvements in both groups. It is interesting to note

that no difference between the BMAC and placebo groups was found at 6 months' follow-up.

Adipose-derived MSCs have also been investigated for the treatment of knee OA. Ceserani et al.¹¹³ performed an in vitro study showing that lipoaspirate has a high concentration of MSCs that may be capable of inhibiting the inflammatory function of macrophages. In addition, an in vitro study by Bosetti et al.¹¹⁴ showed that lipoaspirate induces native chondrocytes to proliferate and produce extracellular matrix, suggesting that adipose-derived MSCs are a viable option for treatment of knee OA. Preliminary clinical studies have also shown promising results. Koh et al.¹¹⁵ reported that patients who underwent arthroscopic lavage and adipose-derived MSC injections had improved or maintained cartilage and that no patients required a TKA at 2 years' follow-up. Russo et al.¹¹⁶ found adipose-derived MSC injections to be a safe treatment option with significant improvements in VAS pain score, IKDC score, Knee Injury and Osteoarthritis Outcome Score, and Tegner-Lysholm functional outcome score at 1 year of follow-up. Hudetz et al.¹¹⁷ investigated the outcome of adipose-derived MSC injections both clinically and radiographically at 12 months postoperatively. Patients reported a significant decrease in VAS pain scores, and delayed gadolinium-enhanced magnetic resonance imaging of cartilage showed a significant increase in articular cartilage glycosaminoglycan content.

In 2013 a systematic review investigated the safety of intra-articular autologous bone marrow MSC injections and found the rate of adverse reactions to be 3.1%, mostly owing to increased pain and swelling.¹¹⁸ Although there is a theoretical concern that autologous MSCs may be carcinogenic,¹¹⁹ this has not been definitively proved, and they are considered a safe treatment option for OA.¹²⁰ Because of a lack of randomized controlled trials of intra-articular injections for OA, there is still uncertainty as to the number of injections, vehicle of injection, size of injections, long-term efficacy, or exact mechanism of action. Recently, Cassano et al.¹²¹ found that BMAC contains high concentrations of IL-1 receptor antagonist, a molecule that inhibits the action of IL-1, which

is a key inflammatory mediator in OA. Despite the basic-science evidence showing a positive impact in an osteoarthritic environment on chondrocytes or synovium and in light of these recent findings, the effects of MSCs in the osteoarthritic knee likely work similarly to the effects of PRP by modulating the local environment with reduced inflammation and pain without any truly identified effects on disease modification.

Senior Author's Clinical Recommendations. The senior author prefers to perform autologous stem cell injections in the operating room with the patient under general anesthesia to ensure patient comfort and sterility during the invasive stem cell harvest. Alternatively, the use of BMAC or adipose tissue (Lipogems, Milano, Italy) can be performed in the office setting. Bone marrow–derived MSCs are more commonly used, although adipose-derived MSCs are becoming more common in our practice and other practices. Autologous MSC injections are not our first-line treatment for knee OA, yet we do use them to treat patients with symptomatic, small focal chondral defects with otherwise intact articular cartilage or those with mild, diffuse cartilage thinning as an adjunct to arthroscopic treatments. The injection is administered intra-articularly after a thorough diagnostic arthroscopy and debridement to remove any potentially symptomatic chondral flaps, loose bodies, or meniscal tears. The use in this setting is currently the subject of a prospective clinical investigation compared with a control group not receiving these adjunct treatments.

Integrating Biologics Into Clinical Practice

Reimbursement for these injections remains a confusing and controversial area. In some regions in the United States, several carriers do not reimburse for HA because of considerations related to the interpretation of outcomes in the literature and the AAOS Appropriate Use Criteria and establishment of clinical practice guidelines published in 2015.¹²² Efforts are currently under way to help reverse these negative payment decisions by orthopaedic specialty societies given the emergence of recent findings in the literature, especially in support of HMW HA injections for the treatment of knee OA.

Office Setting or Stand-alone Procedures

There are rules that govern the use of all the orthobiologics discussed in this article in the office that differ from their use in the operating room. In the office setting, many injectable treatments other than corticosteroids and HA have no formal category I Current Procedural Terminology (CPT) procedure code or a J code for agents or disposables used for purposes of

administering the specific injectable (i.e., PRP, bone marrow aspirate, fat aspiration, or amniotic tissue), and thus there is a “fee-for-service” pathway whereby patients can be considered “self-pay” patients for the purposes of reimbursement. This is true for government-funded insurance plans (Medicare, Medicaid, TriCare, and so on) and most private insurers that do not recognize these injections for OA as a reimbursable service. Unlike bone marrow aspirate, fat aspiration with mechanical processing, and amniotic tissue, if the only procedure being performed is a PRP injection, CPT tracking code 0232T was specifically established to track the use of PRP by the Centers for Medicare & Medicaid Services (CMS). The code as described includes injection of PRP, image guidance, harvesting, and preparation and thus is considered an all-inclusive code. However, there are no relative value units associated with this code, and most payers and carriers have noncoverage policies. Procedurally, physicians should have patients sign an advanced beneficiary notice (ABN) as required by CMS to enable physicians to remain compliant when simultaneously accepting Medicare or other government-payer assignment and billing patients directly for these services.¹²³ A patient-signed ABN should document that the patient understands that he or she is responsible for the cost. Surgeons are urged to check the policies of patients with private insurance to make sure that there is no specific language pertaining to the use and billing for any of these injections outside of their insurance plan in the office setting. Many, in the abundance of caution, will have all patients independent of the payer sign the ABN or waiver of liability, although by design, an ABN was specifically developed by CMS for patients who have Medicare. Thus, a waiver of liability is recommended for non-Medicare patients.

Proper documentation of the procedure, including informed consent, the explanation provided to the patient pertaining to the terms of Medicare or other government programs, reference to the ABN, and a step-by-step procedure note, should be performed and included as part of the patient's medical record. The details of this documentation are beyond the scope of this review.

For non-PRP injections for which no accurate office-based procedure code exists, there is latitude to charge the patient directly, assuming the patient's policy does not dictate otherwise. This would also depend on whether the physician is contracted with the given payer or carrier. If contracted, the provider should determine whether the service is a noncovered procedure. In this case, one may be able to bill for the procedure or substance, the injection, and even image guidance (fluoroscopy or ultrasound) used during the course of the injection. If the provider is contracted with the carrier, then he or she must follow the coverage

guidelines relevant to these injections if such language exists. In a noncoverage situation, the provider could offer a copy of the policy from the carrier to the patient supporting the notion that this can be a self-pay procedure. Notably, the rules are very dynamic, and one should consult with each non-CMS carrier directly before engaging in self-pay policies and procedures. Most payers consider these injections investigational or experimental, given that they lack sufficient published data to determine safety and efficacy.

Surgical Setting and Use of Injections

When performing a bone marrow or adipose aspiration and injection in the operating room as an isolated procedure without other procedures for a patient with CMS or non-CMS coverage and it is considered a non-covered service, obtaining an ABN or equivalent with a detailed procedure note including an explanation related to the billing process can enable the physician to utilize the procedure in its entirety as a self-pay event. Notably, a nuance about the ABN is that Medicare states that it is not really needed for noncovered services and is mainly for services that are covered but for which Medicare has specific medical necessity policies. In general, given the lack of firm scientific evidence related to efficacy and the absence of coding guidelines for these procedures, most carriers will consider them investigational or experimental, so careful documentation is required when implementing a self-pay policy.

When used in a surgical setting, the injection of any substance (PRP, bone marrow aspirate, amniotic tissue, adipose tissue) into the operative site is generally considered inclusive of the operative procedure by CMS guidelines and by the National Correct Coding Initiative guidelines and thus cannot be billed separately. Specifically, the guidelines state that “the placement/injection of cells into the operative site is an inclusive component of the operative procedure and not separately reported.”¹²⁴ The CPT guidelines specifically indicate that correct coding includes selection of a procedure code or service that accurately identifies the service performed. Therefore, creative coding using unlisted codes or other similar codes is highly discouraged. Notably, these guidelines (National Correct Coding Initiative guidelines) apply to CMS and federally funded payers and not routinely to private payers. Thus, similar to office-based assessment for noncoverage, providers should check the patient’s specific policy to ensure that they can directly bill a patient for an otherwise noncovered benefit and should strongly consider having the patient sign a waiver of liability for injections provided as an adjunct to other surgical procedures. There are several *CPT Assistant* articles (April 2017, October 2016, and December 2013) regarding injections during surgical procedures of which one should be aware.

There is a CPT code for bone marrow aspirate harvest from a separate surgical incision for spinal procedures (20939), effective January 1, 2018, and CMS will make separate payments for this code when performed with other spinal surgical procedures. The “-59” modifier may be required, and the multiple-procedure rule would apply with documentation in the medical record supporting the billing. These rules may or may not apply to non-CMS payers. Otherwise, there is no specific CPT code for bone marrow aspirate when used for procedures other than spinal procedures, and CPT directs one to the use of unlisted code 20999. As mentioned, with a government-insured patient, one should not engage in billing the payer or the patient directly when the procedure is performed in the operating room. Similarly, there is a CPT code for fat aspiration (20926), which could be reported as a separate billable event similar to 20939 or 20999. However, this is not a specific code meant to cover the entire procedure of adipose aspiration and processing with injection into the surgical site—the October 2016 *CPT Assistant* article appears to state that 20926 is all-inclusive.

Providers must carefully weigh the risks of charging non-CMS patients for these procedures when performed as adjuncts to a surgical procedure. If the patient’s policy specifically indicates that the policy does not follow CMS guidelines or considers these procedures investigational or experimental, then, with proper documentation and a signed ABN or waiver, one can cautiously conclude that charging the patient directly for these procedures might be allowed. If, however, a private payer’s policy considers these types of injections included in the given surgical procedure, then seeking payment from the patient would be inappropriate.

Conclusions

We sought to highlight the lack of uniformity in the existing literature investigating the reported benefits of corticosteroid, viscosupplementation, PRP, and autologous stem cell injections in patients with knee OA. Implementing the use of these injections into clinical practice is a complicated task given the existing reimbursement environment. This review has provided guidelines for using these treatment modalities, especially those that are not typically covered by current health insurance plans and require alternative reimbursement pathways. In the senior author’s clinical experience, many patients receive significant therapeutic benefits from corticosteroid, HA, PRP, and autologous MSC injections when used in the appropriate patient population.

References

1. Leyland KM, Hart DJ, Javaid MK, et al. The natural history of radiographic knee osteoarthritis: A fourteen-year

- population-based cohort study. *Arthritis Rheum* 2012;64:2243-2251.
2. Maetzel A, Li LC, Pencharz J, Tomlinson G, Bombardier C. The economic burden associated with osteoarthritis, rheumatoid arthritis, and hypertension: A comparative study. *Ann Rheum Dis* 2004;63:395-401.
 3. Kim S. Changes in surgical loads and economic burden of hip and knee replacements in the US: 1997-2004. *Arthritis Rheum* 2008;59:481-488.
 4. Guccione AA, Felson DT, Anderson JJ, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. *Am J Public Health* 1994;84:351-358.
 5. Nüesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Jüni P. All cause and disease specific mortality in patients with knee or hip osteoarthritis: Population based cohort study. *BMJ* 2011;342:d1165.
 6. Cooper C, Snow S, McAlindon TE, et al. Risk factors for the incidence and progression of radiographic knee osteoarthritis. *Arthritis Rheum* 2000;43:995-1000.
 7. Felson DT. Risk factors for osteoarthritis: Understanding joint vulnerability. *Clin Orthop Relat Res* 2004;:S16-S21 (suppl).
 8. Kon E, Filardo G, Drobic M, et al. Non-surgical management of early knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2012;20:436-449.
 9. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA* 2014;311:806-814.
 10. Chevalier X, Jerosch J, Goupille P, et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: A randomised, multicentre, double-blind, placebo controlled trial. *Ann Rheum Dis* 2010;69:113-119.
 11. Filardo G, Di Matteo B, Di Martino A, et al. Platelet-rich plasma intra-articular knee injections show no superiority versus viscosupplementation: A randomized controlled trial. *Am J Sports Med* 2015;43:1575-1582.
 12. Halpern B, Chaudhury S, Rodeo SA, et al. Clinical and MRI outcomes after platelet-rich plasma treatment for knee osteoarthritis. *Clin J Sport Med* 2013;23:238-239.
 13. Khoshbin A, Leroux T, Wasserstein D, et al. The efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis: A systematic review with quantitative synthesis. *Arthroscopy* 2013;29:2037-2048.
 14. Kon E, Mandelbaum B, Buda R, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: From early degeneration to osteoarthritis. *Arthroscopy* 2011;27:1490-1501.
 15. Meyer MA, Leroux TS, Levy DM, et al. Flexion posterior-anterior radiographs affect both enrollment for and outcomes after injection therapy for knee osteoarthritis. *Orthop J Sports Med* 2017;5:2325967117706692.
 16. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: A prospective, double-blind, randomized trial. *Am J Sports Med* 2013;41:356-364.
 17. Hollander JL, Brown EM, Jessar RA, Brown CY. Hydrocortisone and cortisone injected into arthritic joints; comparative effects of and use of hydrocortisone as a local antiarthritic agent. *J Am Med Assoc* 1951;147:1629-1635.
 18. Chatham WW, Kimberly RP. Treatment of lupus with corticosteroids. *Lupus* 2001;10:140-147.
 19. Creamer P. Intra-articular corticosteroid treatment in osteoarthritis. *Curr Opin Rheumatol* 1999;11:417-421.
 20. MacMahon PJ, Eustace SJ, Kavanagh EC. Injectable corticosteroid and local anesthetic preparations: A review for radiologists. *Radiology* 2009;252:647-661.
 21. Wright JM, Cowper JJ, Page Thomas DP, Knight CG. The hydrolysis of cortisol 21-esters by a homogenate of inflamed rabbit synovium and by rheumatoid synovial fluid. *Clin Exp Rheumatol* 1983;1:137-141.
 22. Ostergaard M, Stoltenberg M, Gideon P, Sørensen K, Henriksen O, Lorenzen I. Changes in synovial membrane and joint effusion volumes after intraarticular methylprednisolone. Quantitative assessment of inflammatory and destructive changes in arthritis by MRI. *J Rheumatol* 1996;23:1151-1161.
 23. Hollander JL, Jessar RA, Brown EM. Intra-synovial corticosteroid therapy: A decade of use. *Bull Rheum Dis* 1961;11:239-240.
 24. Blyth T, Hunter JA, Stirling A. Pain relief in the rheumatoid knee after steroid injection. A single-blind comparison of hydrocortisone succinate, and triamcinolone acetonide or hexacetonide. *Br J Rheumatol* 1994;33:461-463.
 25. Swerdlow M, Jones R. The duration of action of bupivacaine, prilocaïne and lignocaine. *Br J Anaesth* 1970;42:335-339.
 26. Benzon HT, Chew TL, McCarthy RJ, Benzon HA, Walega DR. Comparison of the particle sizes of different steroids and the effect of dilution: A review of the relative neurotoxicities of the steroids. *Anesthesiology* 2007;106:331-338.
 27. Gomoll AH, Kang RW, Williams JM, Bach BR, Cole BJ. Chondrolysis after continuous intra-articular bupivacaine infusion: An experimental model investigating chondrotoxicity in the rabbit shoulder. *Arthroscopy* 2006;22:813-819.
 28. Piper SL, Kramer JD, Kim HT, Feeley BT. Effects of local anesthetics on articular cartilage. *Am J Sports Med* 2011;39:2245-2253.
 29. Hollander JL. Intra-articular hydrocortisone in arthritis and allied conditions; a summary of two years' clinical experience. *J Bone Joint Surg Am* 1953;35:983-990.
 30. Valtonen EJ. Clinical comparison of triamcinolonehexacetonide and betamethasone in the treatment of osteoarthrosis of the knee-joint. *Scand J Rheumatol Suppl* 1981;41:1-7.
 31. Gaffney K, Ledingham J, Perry JD. Intra-articular triamcinolone hexacetonide in knee osteoarthritis: Factors influencing the clinical response. *Ann Rheum Dis* 1995;54:379-381.
 32. Arden NK, Reading IC, Jordan KM, et al. A randomised controlled trial of tidal irrigation vs corticosteroid

- injection in knee osteoarthritis: The KIVIS study. *Osteoarthritis Cartilage* 2008;16:733-739.
33. Smith MD, Wetherall M, Darby T, et al. A randomized placebo-controlled trial of arthroscopic lavage versus lavage plus intra-articular corticosteroids in the management of symptomatic osteoarthritis of the knee. *Rheumatology (Oxford)* 2003;42:1477-1485.
 34. Rosenberg TD, Paulos LE, Parker RD, Coward DB, Scott SM. The forty-five-degree posteroanterior flexion weight-bearing radiograph of the knee. *J Bone Joint Surg Am* 1988;70:1479-1483.
 35. Friedman DM, Moore ME. The efficacy of intraarticular steroids in osteoarthritis: A double-blind study. *J Rheumatol* 1980;7:850-856.
 36. Duclos M, Guinot M, Le Bouc Y. Cortisol and GH: Odd and controversial ideas. *Appl Physiol Nutr Metab* 2007;32:895-903.
 37. Mankin HJ, Conger KA. The acute effects of intra-articular hydrocortisone on articular cartilage in rabbits. *J Bone Joint Surg Am* 1966;48:1383-1388.
 38. Raynauld JP, Buckland-Wright C, Ward R, et al. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: A randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2003;48:370-377.
 39. Balch HW, Gibson JM, El-Ghobarey AF, Bain LS, Lynch MP. Repeated corticosteroid injections into knee joints. *Rheumatol Rehabil* 1977;16:137-140.
 40. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: A randomized clinical trial. *JAMA* 2017;317:1967-1975.
 41. Jevsevar DS. Treatment of osteoarthritis of the knee: Evidence-based guideline, 2nd edition. *J Am Acad Orthop Surg* 2013;21:571-576.
 42. Meyer K, Palmer JW. The polysaccharide of the vitreous humor. *J Biol Chem* 1934;107:629-634.
 43. Pearle AD, Warren RF, Rodeo SA. Basic science of articular cartilage and osteoarthritis. *Clin Sports Med* 2005;24:1-12.
 44. Balazs EA. *Hyaluronic acid and matrix implantation: A report on the biologic activity and therapeutic use of hyaluronic acid*, Ed 2. Arlington, MA: Biotrix, 1971.
 45. McArthur BA, Dy CJ, Fabricant PD, Valle AG. Long term safety, efficacy, and patient acceptability of hyaluronic acid injection in patients with painful osteoarthritis of the knee. *Patient Prefer Adherence* 2012;6:905-910.
 46. Rydell N, Balazs EA. Effect of intra-articular injection of hyaluronic acid on the clinical symptoms of osteoarthritis and on granulation tissue formation. *Clin Orthop Relat Res* 1971;80:25-32.
 47. Watterson JR, Esdaile JM. Viscosupplementation: Therapeutic mechanisms and clinical potential in osteoarthritis of the knee. *J Am Acad Orthop Surg* 2000;8:277-284.
 48. Adams ME, Lussier AJ, Peyron JG. A risk-benefit assessment of injections of hyaluronan and its derivatives in the treatment of osteoarthritis of the knee. *Drug Saf* 2000;23:115-130.
 49. Kalaci A, Yilmaz HR, Aslan B, Söğüt S, Yanat AN, Uz E. Effects of hyaluronan on nitric oxide levels and superoxide dismutase activities in synovial fluid in knee osteoarthritis. *Clin Rheumatol* 2007;26:1306-1311.
 50. Abramson SB. Nitric oxide in inflammation and pain associated with osteoarthritis. *Arthritis Res Ther* 2008;10:S2 (suppl 2).
 51. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: A systematic review and meta-analysis. *Ann Intern Med* 2012;157:180-191.
 52. Chen AL, Desai P, Adler EM, Di Cesare PE. Granulomatous inflammation after hylan G-F 20 viscosupplementation of the knee: A report of six cases. *J Bone Joint Surg Am* 2002;84:1142-1147.
 53. Albert C, Brocq O, Gerard D, Roux C, Euller-Ziegler L. Septic knee arthritis after intra-articular hyaluronate injection. Two case reports. *Joint Bone Spine* 2006;73:205-207.
 54. Concoff A, Sancheti P, Niazi F, Shaw P, Rosen J. The efficacy of multiple versus single hyaluronic acid injections: A systematic review and meta-analysis. *BMC Musculoskelet Disord* 2017;18:542.
 55. Miltner O, Schneider U, Siebert CH, Niedhart C, Niethard FU. Efficacy of intraarticular hyaluronic acid in patients with osteoarthritis—A prospective clinical trial. *Osteoarthritis Cartilage* 2002;10:680-686.
 56. DeCaria JE, Montero-Odasso M, Wolfe D, Chesworth BM, Petrella RJ. The effect of intra-articular hyaluronic acid treatment on gait velocity in older knee osteoarthritis patients: A randomized, controlled study. *Arch Gerontol Geriatr* 2012;55:310-315.
 57. Kolarz G, Kotz R, Hochmayer I. Long-term benefits and repeated treatment cycles of intra-articular sodium hyaluronate (Hyalgan) in patients with osteoarthritis of the knee. *Semin Arthritis Rheum* 2003;32:310-319.
 58. Waddell DD, Bricker DC. Total knee replacement delayed with hylan G-F 20 use in patients with grade IV osteoarthritis. *J Manag Care Pharm* 2007;13:113-121.
 59. Waddell DD, Joseph B. Delayed total knee replacement with Hylan G-F 20. *J Knee Surg* 2016;29:159-168.
 60. Evaniew N, Simunovic N, Karlsson J. Cochrane review of CORR: Viscosupplementation for the treatment of osteoarthritis of the knee. *Clin Orthop Relat Res* 2014;472:2028-2034.
 61. Shah RP, Stambough JB, Fenty M, et al. T1rho magnetic resonance imaging at 3T detects knee cartilage changes after viscosupplementation. *Orthopedics* 2015;38:e604-e610.
 62. Wang Y, Hall S, Hanna F, et al. Effects of hylan G-F 20 supplementation on cartilage preservation detected by magnetic resonance imaging in osteoarthritis of the knee: A two-year single-blind clinical trial. *BMC Musculoskelet Disord* 2011;12:195.
 63. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006:CD005328.
 64. Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid

- versus corticosteroids in the treatment of knee osteoarthritis: A systematic review and meta-analysis. *Arthritis Rheum* 2009;61:1704-1711.
65. de Campos GC, Rezende MU, Pailo AF, Frucchi R, Camargo OP. Adding triamcinolone improves viscosupplementation: A randomized clinical trial. *Clin Orthop Relat Res* 2013;471:613-620.
 66. Skwara A, Ponelis R, Tibesku CO, Rosenbaum D, Fuchs-Winkelmann S. Gait patterns after intraarticular treatment of patients with osteoarthritis of the knee—Hyaluronan versus triamcinolone: A prospective, randomized, doubleblind, monocentric study. *Eur J Med Res* 2009;14:157-164.
 67. van der Weegen W, Wullems JA, Bos E, Noten H, van Drumpt RA. No difference between intra-articular injection of hyaluronic acid and placebo for mild to moderate knee osteoarthritis: A randomized, controlled, double-blind trial. *J Arthroplasty* 2015;30:754-757.
 68. Tammachote N, Kanitnate S, Yakumpor T, Panichkul P. Intra-articular, single-shot hylan G-F 20 hyaluronic acid injection compared with corticosteroid in knee osteoarthritis: A double-blind, randomized controlled trial. *J Bone Joint Surg Am* 2016;98:885-892.
 69. Marx RE. Platelet-rich plasma (PRP): What is PRP and what is not PRP? *Implant Dent* 2001;10:225-228.
 70. Howard D, Shepherd JH, Kew SJ, et al. Release of growth factors from a reinforced collagen GAG matrix supplemented with platelet rich plasma: Influence on cultured human meniscal cells. *J Orthop Res* 2014;32:273-378.
 71. Kingsley CS. Blood coagulation; evidence of an antagonist to factor VI in platelet-rich human plasma. *Nature* 1954;173(4407):723-724.
 72. Filardo G, Kon E, Buda R, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2011;19:528-535.
 73. Zhu Y, Yuan M, Meng HY, et al. Basic science and clinical application of platelet-rich plasma for cartilage defects and osteoarthritis: A review. *Osteoarthritis Cartilage* 2013;21:1627-1637.
 74. Sundman EA, Cole BJ, Karas V, et al. The anti-inflammatory and matrix restorative mechanisms of platelet-rich plasma in osteoarthritis. *Am J Sports Med* 2014;42:35-41.
 75. Sun Y, Feng Y, Zhang CQ, Chen SB, Cheng XG. The regenerative effect of platelet-rich plasma on healing in large osteochondral defects. *Int Orthop* 2010;34:589-597.
 76. Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. *Am J Sports Med* 2011;39:2135-2140.
 77. Anitua E, Sánchez M, Nurden AT, et al. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. *Rheumatology (Oxford)* 2007;46:1769-1772.
 78. Braun HJ, Kim HJ, Chu CR, Dragoo JL. The effect of platelet-rich plasma formulations and blood products on human synoviocytes: Implications for intra-articular injury and therapy. *Am J Sports Med* 2014;42:1204-1210.
 79. Riboh JC, Saltzman BM, Yanke AB, Fortier L, Cole BJ. Effect of leukocyte concentration on the efficacy of platelet-rich plasma in the treatment of knee osteoarthritis. *Am J Sports Med* 2016;44:792-800.
 80. Sampson S, Reed M, Silvers H, Meng M, Mandelbaum B. Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: A pilot study. *Am J Phys Med Rehabil* 2010;89:961-969.
 81. Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil* 2012;91:411-417.
 82. Kanchanatawan W, Arirachakaran A, Chaijenkij K, et al. Short-term outcomes of platelet-rich plasma injection for treatment of osteoarthritis of the knee. *Knee Surg Sports Traumatol Arthrosc* 2016;24:1665-1677.
 83. Campbell KA, Saltzman BM, Mascarenhas R, et al. Does intra-articular platelet-rich plasma injection provide clinically superior outcomes compared with other therapies in the treatment of knee osteoarthritis? A systematic review of overlapping meta-analyses. *Arthroscopy* 2015;31:2213-2221.
 84. Laudy AB, Bakker EW, Rekers M, Moen MH. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: A systematic review and meta-analysis. *Br J Sports Med* 2015;49:657-672.
 85. Guler O, Mutlu S, Isyar M, Seker A, Kayaalp ME, Mahirogullari M. Comparison of short-term results of intraarticular platelet-rich plasma (PRP) and hyaluronic acid treatments in early-stage gonarthrosis patients. *Eur J Orthop Surg Traumatol* 2015;25:509-513.
 86. Sánchez M, Fiz N, Azofra J, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy* 2012;28:1070-1078.
 87. Cerza F, Carnì S, Carcangiu A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med* 2012;40:2822-2827.
 88. Say F, Gürler D, Yener K, Bülbül M, Malkoc M. Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. *Acta Chir Orthop Traumatol Cech* 2013;80:278-283.
 89. Orozco L, Munar A, Soler R, et al. Treatment of knee osteoarthritis with autologous mesenchymal stem cells: A pilot study. *Transplantation* 2013;95:1535-1541.
 90. Cole BJ, Karas V, Hussey K, Pilz K, Fortier LA. Hyaluronic acid versus platelet-rich plasma: A prospective, double-blind randomized controlled trial comparing clinical outcomes and effects on intra-articular biology for the treatment of knee osteoarthritis. *Am J Sports Med* 2017;45:339-346.
 91. Russo F, D'Este M, Vadalà G, et al. Platelet rich plasma and hyaluronic acid blend for the treatment of osteoarthritis: Rheological and biological evaluation. *PLoS One* 2016;11:e0157048.

92. Chen WH, Lo WC, Hsu WC, et al. Synergistic anabolic actions of hyaluronic acid and platelet-rich plasma on cartilage regeneration in osteoarthritis therapy. *Bio-materials* 2014;35:9599-9607.
93. Lana JF, Weglein A, Sampson SE, et al. Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. *J Stem Cells Regen Med* 2016;12:69-78.
94. Iio K, Furukawa KI, Tsuda E, et al. Hyaluronic acid induces the release of growth factors from platelet-rich plasma. *Asia Pac J Sports Med Arthrosc Rehabil Technol* 2016;4:27-32.
95. Friedenstein AJ, Piatetzky-Shapiro II, Petrakova KV. Osteogenesis in transplants of bone marrow cells. *J Embryol Exp Morphol* 1966;16:381-390.
96. Barry F, Murphy M. Mesenchymal stem cells in joint disease and repair. *Nat Rev Rheumatol* 2013;9:584-594.
97. Chen FH, Tuan RS. Mesenchymal stem cells in arthritic diseases. *Arthritis Res Ther* 2008;10:223.
98. Hunziker EB, Rosenberg LC. Repair of partial-thickness defects in articular cartilage: Cell recruitment from the synovial membrane. *J Bone Joint Surg Am* 1996;78:721-733.
99. Veronesi F, Giavaresi G, Tschon M, Borsari V, Nicoli Aldini N, Fini M. Clinical use of bone marrow, bone marrow concentrate, and expanded bone marrow mesenchymal stem cells in cartilage disease. *Stem Cells Dev* 2013;22:181-192.
100. Murphy JM, Dixon K, Beck S, Fabian D, Feldman A, Barry F. Reduced chondrogenic and adipogenic activity of mesenchymal stem cells from patients with advanced osteoarthritis. *Arthritis Rheum* 2002;46:704-713.
101. Centeno CJ, Schultz JR, Cheever M, Robinson B, Freeman M, Marasco W. Safety and complications reporting on the re-implantation of culture-expanded mesenchymal stem cells using autologous platelet lysate technique. *Curr Stem Cell Res Ther* 2010;5:81-93.
102. Jo CH, Lee YG, Shin WH, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: A proof-of-concept clinical trial. *Stem Cells* 2014;32:1254-1266.
103. Al Faqeh H, Nor Hamdan BM, Chen HC, Aminuddin BS, Ruzzymah BH. The potential of intra-articular injection of chondrogenic-induced bone marrow stem cells to retard the progression of osteoarthritis in a sheep model. *Exp Gerontol* 2012;47:458-464.
104. Wakitani S, Goto T, Pineda SJ, et al. Mesenchymal cell-based repair of large, full-thickness defects of articular cartilage. *J Bone Joint Surg Am* 1994;76:579-592.
105. Wakitani S, Imoto K, Yamamoto T, Saito M, Murata N, Yoneda M. Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. *Osteoarthritis Cartilage* 2002;10:199-206.
106. Wong KL, Lee KB, Tai BC, Law P, Lee EH, Hui JH. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: A prospective, randomized controlled clinical trial with 2 years' follow-up. *Arthroscopy* 2013;29:2020-2028.
107. Saw KY, Anz A, Siew-Yoke Jee C, et al. Articular cartilage regeneration with autologous peripheral blood stem cells versus hyaluronic acid: A randomized controlled trial. *Arthroscopy* 2013;29:684-694.
108. Centeno CJ, Busse D, Kisiday J, Keohan C, Freeman M, Karli D. Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. *Pain Physician* 2008;11:343-353.
109. Davatchi F, Abdollahi BS, Mohyeddin M, Shahram F, Nikbin B. Mesenchymal stem cell therapy for knee osteoarthritis. Preliminary report of four patients. *Int J Rheum Dis* 2011;14:211-215.
110. Kim JD, Lee GW, Jung GH, et al. Clinical outcome of autologous bone marrow aspirates concentrate (BMAC) injection in degenerative arthritis of the knee. *Eur J Orthop Surg Traumatol* 2014;24:1505-1511.
111. Centeno C, Pitts J, Al-Sayegh H, Freeman M. Efficacy of autologous bone marrow concentrate for knee osteoarthritis with and without adipose graft. *Biomed Res Int* 2014;2014:370621.
112. Shapiro SA, Kazmerchak SE, Heckman MG, Zubair AC, O'Connor MI. A prospective, single-blind, placebo-controlled trial of bone marrow aspirate concentrate for knee osteoarthritis. *Am J Sports Med* 2017;45:82-90.
113. Ceserani V, Ferri A, Berenzi A, et al. Angiogenic and anti-inflammatory properties of micro-fragmented fat tissue and its derived mesenchymal stromal cells. *Vasc Cell* 2016;8:3.
114. Bosetti M, Borrone A, Follenzi A, Messaggio F, Tremolada C, Cannas M. Human lipoaspirate as autologous injectable active scaffold for one-step repair of cartilage defects. *Cell Transplant* 2016;25:1043-1056.
115. Koh YG, Choi YJ, Kwon SK, Kim YS, Yeo JE. Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2015;23:1308-1316.
116. Russo A, Condello V, Madonna V, Guerriero M, Zorzi C. Autologous and micro-fragmented adipose tissue for the treatment of diffuse degenerative knee osteoarthritis. *J Exp Orthop* 2017;4:33.
117. Hudetz D, Borić I, Rod E, et al. The effect of intra-articular injection of autologous microfragmented fat tissue on proteoglycan synthesis in patients with knee osteoarthritis. *Genes (Basel)* 2017;8.
118. Peeters CM, Leijts MJ, Reijman M, van Osch GJ, Bos PK. Safety of intra-articular cell-therapy with culture-expanded stem cells in humans: A systematic literature review. *Osteoarthritis Cartilage* 2013;21:1465-1473.
119. Suzuki K, Sun R, Origuchi M, et al. Mesenchymal stromal cells promote tumor growth through the enhancement of neovascularization. *Mol Med* 2011;17:579-587.
120. Yamasaki S, Mera H, Itokazu M, Hashimoto Y, Wakitani S. Cartilage repair with autologous bone marrow mesenchymal stem cell transplantation: Review of preclinical and clinical studies. *Cartilage* 2014;5:196-202.
121. Cassano JM, Kennedy JG, Ross KA, Fraser EJ, Goodale MB, Fortier LA. Bone marrow concentrate and

- platelet-rich plasma differ in cell distribution and interleukin 1 receptor antagonist protein concentration. *Knee Surg Sports Traumatol Arthrosc* 2018;26:333-342.
122. American Academy of Orthopaedic Surgeons. Surgical management of osteoarthritis of the knee. Evidence-based clinical practice guideline, https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/guidelines/SMOAK%20CPG_4.22.2016.pdf. Published 2015. Accessed November 9, 2017.
 123. Department of Health & Human Services, Centers for Medicare & Medicaid Services. CMS Manual System. Pub 100–103 Medicare national coverage determinations, <http://www.cms.hhs.gov/transmittals/downloads/R83NCD.pdf>. Published 2008. Accessed November 9, 2017.
 124. Chapter 4: Surgery: Musculoskeletal System CPT Codes 20000-29999. *National Correct Coding Initiative Policy Manual for Medicare Services*. Revised January 1, 2018.