

Prolotherapy and Platelet Rich Plasma Therapies (for Indiana Only)

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[Instructions for Use](#)

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Related Policy
<ul style="list-style-type: none"> Skin and Soft Tissue Substitutes (for Indiana Only)

Application

This Medical Policy only applies to the state of Indiana.

Coverage Rationale

Due to insufficient evidence of efficacy, the following are unproven and not medically necessary for any condition or indication due to insufficient clinical evidence of efficacy:

- Prolotherapy
- Platelet-Rich Plasma

Note: Refer to the Medical Policy titled [Skin and Soft Tissue Substitutes \(for Indiana Only\)](#) for information related to amnion-derived fluid injections/therapy.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed

CPT Code	Description
0481T	Injection(s), autologous white blood cell concentrate (autologous protein solution), any site, including image guidance, harvesting and preparation, when performed

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HCPCS Code	Description
G0460	Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment
M0076	Prolotherapy
P9020	Platelet-rich plasma, each unit
S9055	Procuren or other growth factor preparation to promote wound healing

Description of Services

According to the National Institute of Health, prolotherapy is an injection-based complementary and alternative medical (CAM) therapy for chronic musculoskeletal pain. A relatively small volume of an irritant or sclerosing solution is injected at sites on painful ligament and tendon insertions, and in adjacent joint space over the course of several treatment sessions (Rabago et al., 2010). Prolotherapy is the injection of any substance that promotes growth of normal cells, tissues, or organs. Also known as proliferative therapy, non-surgical ligament and tendon reconstruction and regenerative joint injection, prolotherapy is an orthopedic procedure that stimulates the body's healing processes to strengthen and repair injured and painful joints and connective tissue (American Osteopathic Association of Prolotherapy Regenerative Medicine [AOAPRM]).

There are three types of prolotherapy. Growth factor injection prolotherapy involves the injection of a complex protein that stimulates growth of a certain cell line. Growth factor stimulation prolotherapy causes the body to produce growth factors via dextrose injections. Inflammatory prolotherapy is the injection of a substance that causes activation of the inflammatory cascade to produce growth factors using dextrose, phenol-containing-solutions, and sodium-morrhuate-containing solutions (American Association of Orthopaedic Medicine [AAOM]).

Platelet rich plasma (PRP) is a concentrate of platelets and plasma proteins derived from a patient's whole blood, centrifuged to remove red blood cells and other unwanted components. It has a greater concentration of growth factors than whole blood and has been used as an autologous tissue injection in a variety of disciplines, including dentistry, orthopedic surgery, and sports medicine (Taber's, 2017).

Procuren® an autologous PRP product that has been used as treatment in the past for chronic wound healing, but it is no longer manufactured or commercially available.

Clinical Evidence

Prolotherapy

The available studies on prolotherapy are limited to those that include short to medium term follow-up with no significant functional improvement compared to placebo. Additional studies are needed to further define treatment parameters and to determine whether a clinically significant improvement is achieved.

Low Back Pain (LBP)

A systematic review by Chou et al. (2009) included 174 articles of which 97 met criteria to assess the benefits and harms of nonsurgical interventional therapies for low back and radicular pain. Of the 97, only five addressed prolotherapy. Three of these studies found no difference between prolotherapy and either saline or local anesthetic control injections for short- or long-term (up to 24 months) pain or disability. One higher quality trial found prolotherapy associated with increased likelihood of short-term improvement in pain or disability versus control injection, but both treatment groups received a number of co-interventions including spinal manipulation, local injections, exercises, and walking. In the fifth trial, effects of prolotherapy could not be determined because the prolotherapy group received strong manipulation and the control injection group only light

manipulation. The authors concluded that prolotherapy has not been found to be effective for the treatment of low back and radicular pain.

A systematic review by Dagenais et al. (2008) of articles on prolotherapy published from 1997 to 2007 concluded that that prolotherapy is one of a number of treatments recommended for CLBP. Prolotherapy has a long history of use, a reasonable but not proven theoretical basis, a low complication rate, and conflicting evidence of efficacy. It is considered contraindicated in patients with metastatic cancer, non-musculoskeletal pain, spinal anatomical defects, systemic inflammation, morbid obesity, bleeding disorders, low pain threshold, inability to perform post treatment exercises, chemical dependency, or whole-body pain. Because high doses of a prolotherapy solution containing dextrose 12.5%, glycerin 12.5%, phenol 1.0%, and lidocaine 0.25% may produce a temporary increase in hepatic enzymes, it may not be prudent to not administer these solutions to patients with pre-existing hepatic conditions.

In a 2007 Cochrane Review on prolotherapy injections for CLBP, Dagenais et al. concluded that there is conflicting evidence regarding the efficacy of prolotherapy injections for patients with CLBP. When used alone, prolotherapy is not an effective treatment for this condition. When combined with spinal manipulation, exercise, and other co-interventions, prolotherapy may improve CLBP and disability. Conclusions are confounded by clinical heterogeneity amongst studies and by the presence of co-interventions.

Osteoarthritis (OA)

Krstičević and colleagues conducted a systematic review on the efficacy and safety of proliferative injection therapy (prolotherapy) for treatment of knee and hand OA. Seven RCTs were included, with 393 participants aged 40-75 years having joint pain ranging from three months to eight years. Dextrose was the most commonly used agent, with follow-up ranging from 12 weeks to 12 months. All studies concluded that prolotherapy was effective treatment for OA and no serious AEs were reported. The authors concluded that current data about prolotherapy for OA should be considered preliminary and that future high-quality trials are warranted since these low-quality studies did not provide reliable evidence (2017).

In a systematic review and meta-analysis, Hung and colleagues (2016) compared the effectiveness of dextrose prolotherapy versus control injections and exercise in the management of OA pain. Searching PubMed and Scopus from the earliest record until February 2016, one single-arm study and five RCTs were included (n=326). The investigators estimated the effect sizes of pain reduction before and after serial dextrose injections and compared the values between dextrose prolotherapy, comparative regimens, and exercise six months after the initial injection. Regarding the treatment arm using dextrose prolotherapy, the effect sizes compared with baseline were 0.65, 0.84, 0.85, and 0.87 after the 1st, 2nd, 3rd, and 4th or more injections, respectively. The overall effect of dextrose was better than control injections, demonstrating superiority when compared with local anesthesia and exercise. There was an insignificant advantage of dextrose over corticosteroids which was only estimated from one study. The authors concluded that dextrose injections decreased pain in OA patients; but did not exhibit a positive dose-response relationship following serial injections. Dextrose prolotherapy was found to provide a better therapeutic effect than exercise, local anesthetics, and probably corticosteroids when patients were re-tested six months following the initial injection. The researchers also noted that the effect of prolotherapy did not differ between hand and knee OA. This study had several drawbacks, including but not limited to the minimal number of trials eligible for meta-analysis, as well as heterogeneity in the patient populations, injection protocols, comparative regimens, and outcome assessment.

Knee (KOA)

Rahimzadeh et al (2018) investigated the effect of injecting intra-articular platelet-rich plasma (PRP) versus prolotherapy (PRL) on pain and function in knee osteoarthritis. In this randomized, double-blind trial, 42 patients with knee OA received intra-articular injections. "Patients in the PRP therapy group received 7 mL PRP solution and those in the PRL group received 7 mL 25% dextrose. Using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), levels of pain and knee function were evaluated and recorded for each patient immediately prior to the first injection as well as at one month (immediately prior to the second injection), two months (a month after the second injection), and six months later. During the first and second months, a rapid decrease in the overall WOMAC score was observed in both groups. The overall WOMAC score increased at the sixth month, but was lower than the overall WOMAC score in the first month. Statistical analysis indicated that the overall WOMAC score significantly decreased in both groups of patients over six months." The authors concluded that this study suggests a positive change in WOMAC score indicated an improvement in the quality or life of patients receiving either injection after the first injection, and that PRP is more effective than PRL in the treatment of OA of the knee. However they acknowledge that this study had limitations, e.g., "lack of a control group receiving placebo; lack of

morphological assessment of cartilage, soft tissue, and structures in and around the knee joint; small sample size; and limited timeframe for patient assessment.”

Sit et al. (2016) conducted a systematic review with meta-analysis to synthesize clinical evidence on the effect of prolotherapy for KOA. Of 134 citations identified, three randomized controlled trials (RCTs) with moderate risk of bias and one quasi-randomized trial met inclusion criteria with data from a total of 258 patients. The primary outcome of interest was change in the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) score. In the meta-analysis of two eligible studies, prolotherapy was superior to exercise alone by a standardized mean difference of 0.81, 0.78, and 0.62 on the WOMAC composite scale and WOMAC function and pain subscale scores, respectively. Moderate heterogeneity and risk of bias existed in all cases. The authors concluded that prolotherapy demonstrated a positive and significant beneficial effect in the treatment of KOA. Limitations of the review included the limited number of studies and their relatively small sample size. Larger, long-term trials with uniform outcomes and high methodological standards are needed for more a more comprehensive assessment of the overall treatment effect of prolotherapy.

van Drumpt et al. (2016) conducted an open label, prospective trial (NCT01773226) assessing safety and efficacy of an injection therapy for individuals with early to moderate OA. Using an Autologous Protein Solution (APS) called nSTRIDE®, 11 participants who had failed at least one other type of conservative therapy received the injection. Assessment for adverse events (AE) and clinical response outcomes occurred at one week, two weeks, one month, three months, and six months postinjection. Long-term follow up lasted an average of 18 months. Only mild AEs were reported. Postinjection pain scores were reduced by 83% and 90% at three and six months, respectively. At 18 months, mean WOMAC Index function scores reflected 61% improvement. The authors concluded that a single injection of APS for treatment of early to moderate KOA had very positive outcomes and that well-controlled, randomized multicenter clinical studies to confirm efficacy are warranted. Study limitations include the lack of a control group and small sample size, although the study design was deemed adequate to determine feasibility.

Kon et al. (2017) conducted a multicenter, double-blind, RCT to investigate if one intra-articular injection of APS can reduce pain and improve function in patients affected by KOA (NCT02138890). Forty-six patients with unilateral KOA were randomized into the APS group, which received a single ultrasound-guided injection of APS, and the saline (control) group, which received a single saline injection. Patient-reported outcomes and AE were collected at two weeks and at one, three, six, and 12 months through a variety of assessment tools including the visual analog scale (VAS), WOMAC Index, and Knee injury and Osteoarthritis Outcome Score (KOOS). There were no significant differences in frequency and severity of AEs between groups. The improvement from baseline to two weeks and to one, three, and six months was similar between treatments as well. At 12 months, improvement in WOMAC pain score was 65% in the APS group and 41% in the saline group. There were no significant differences in VAS pain improvement between groups. Significant differences between groups were detected in changes from baseline to 12 months in bone marrow lesion size as assessed on magnetic resonance imaging (MRI) and osteophytes in the central zone of the lateral femoral condyle, both in favor of the APS group. There were no significant differences between the APS and control group in other measured secondary endpoints. The authors concluded that this study supports that a single injection of APS is safe and demonstrates clinical improvement at one-year in patients affected by KOA. Treatment with APS or a saline injection provided significant pain relief over the course of the study with differences becoming apparent at between 6 and 12 months after treatment. Study limitations include the need for longer follow up as well as small sample size.

O'Shaughnessey et al. (2014) conducted a multi-center controlled feasibility study (NCT01050894) to determine if blood from OA patients (n=105) could be mechanically processed to form an APS with preferentially increased concentrations of anti-inflammatory versus inflammatory cytokines. Through examination of whole blood taken from control donors and OA donors, it was identified that the APS device system does preferentially increase anti-inflammatory cytokines over inflammatory cytokines. The study also identified that results were no different when using blood from the control or from the OA donors. The authors concluded that these results, combined with findings in previous studies, provide strong support for further investigation of APS as a promising therapy for OA.

A partially blinded controlled trial was performed by Rabago et al. (2013) to assess the relationship between KOA relative to quality of life (QOL) and intra articular cartilage volume in participants treated with prolotherapy over a 52-week period. It was noted that prolotherapy is an injection therapy reported to improve KOA-related QOL to a greater extent than blinded saline injections and at-home exercise, but its mechanism of action is unclear. It was noted that the prolotherapy showed improvement in the QOL in those with KOA compared with the controlled group over the 52-week period. The study authors concluded that prolotherapy may have a pain-specific disease modifying effect, but still requires further research and testing.

The findings are limited by lack of randomization and appropriate blinding to the study interventions, which could have introduced a bias in the findings.

In a follow up to the above trial, Rabago et al. assessed long-term effects of prolotherapy on knee pain, function and stiffness among adults with KOA through a post clinical-trial, open-label follow-up case series. Participants (n=65) received 3-5 monthly interventions and were assessed using the validated WOMAC index at baseline, 12, 26, 52 weeks, and 2.5 years. Progressive improvement in WOMAC scores were reported at all time intervals. The authors concluded that prolotherapy resulted in safe, significant, progressive improvement of knee pain, function and stiffness scores among most participants through a mean follow-up of 2.5 years and may be an appropriate therapy for patients with KOA refractory to other conservative care (2015). Findings are limited by lack of comparison group for the long-term findings.

In an Evidence-based Practice Center Systematic Review Protocol for the Treatment of KOA, the Agency for Healthcare Review and Quality (AHRQ) does not address intra-articular injected agents such as prolotherapeutic substances (Newberry et al., 2017).

There are several active clinical trials involving the APS nStride® (Zimmer Biomet) for KOA. For more information, refer to www.clinicaltrials.gov. (Accessed October 28, 2020)

Fingers

Jahangiri et al. compared the advantages of prolotherapy in the treatment of first carpometacarpal OA with those of corticosteroid local injection in a double-blind RCT. Sixty participants (60 hands) with OA of the first carpometacarpal joint were assigned equally to two groups. For the corticosteroid group, after two monthly saline placebo injections, a single dose of 40 mg methylprednisolone acetate (0.5 ml) mixed with 0.5 ml of 2% lidocaine was injected. For the dextrose (DX) group, 0.5 ml of 20% DX was mixed with 0.5 ml of 2% lidocaine and the injection was repeated monthly for three months. Pain intensity, hand function and the strength of lateral pinch grip were measured at the baseline and at one, two, and six months post-treatment. The two groups were comparable at two months, but significantly different at one month (better results for corticosteroid), and at six months (more favorable outcome for DX). After six months of treatment, both groups increased functional level, but DX seemed to be more effective. The authors concluded that for the long term, DX seemed to be more advantageous, while the two treatments were comparable in the short term. Further research with a large sample size is needed to compare possible complications of corticosteroid/lidocaine vs DX/lidocaine injections in the management of OA (2014).

Lateral Epicondylitis (LE)

A randomized clinical trial was conducted by Bayat et al (2019) comparing the efficacy of dextrose prolotherapy to steroid injection in the treatment of chronic lateral epicondylitis. Thirty subjects were randomly assigned to either the hypertonic dextrose group or the methylprednisolone group. “Participants were assessed through Quick DASH and VAS scores, once before injection, and then after one- and three-months follow-up. Two patients were excluded due to not completing the follow-up timepoints.” “In both groups VAS scores revealed significant improvement during the first month follow-up [mean difference (MD) = 1.9±3.3, versus 1.5±1.9 for the prolotherapy and steroid groups, respectively]. This declining trajectory continued at the third month visit in the prolotherapy group and MD reached 4.4±2.9, while it did not change remarkably in the steroid group (MD=1.9±3.4). In fact, comparing VAS scores between the 1st- and 3rd-month time points did not reveal a significant improvement in the steroid group (p=0.6). Also, the Quick DASH index showed a similar pattern and improved remarkably in both groups during the first visit. However, only the efficacy in the prolotherapy group persisted after three-month follow-up (MD = 9.5±21.6, p=0.044). One month after injections no preference between the two interventions was observed (p=0.74 for VAS and 0.14 for Quick DASH score). However, the third-month follow-up revealed a meaningful superiority (p=0.03 for VAS and p=0.01 for Quick DASH score) favoring the prolotherapy method.” The authors concluded that while both methods appeared to be effective in the short-term treatment of chronic lateral epicondylitis, the dextrose prolotherapy injections appeared to be slightly more efficacious over a longer period. This study is limited by the small study population and suboptimal data analysis.

Dong et al. (2015) conducted a systematic review and Bayesian network meta-analysis comparing many injection therapies (including prolotherapy) for LE. All of the injection treatments showed a trend towards better effects than placebo, and the study authors concluded prolotherapy’s superiority would need to be confirmed by more research. The findings are limited by the inherent indirectness of network meta-analyses.

Sims et al. (2014) conducted a systematic review of RCTs examining 11 non-surgical treatments for LE which included prolotherapy. They concluded that the existing literature does not provide conclusive evidence that there is one preferred method of non-surgical treatment for this condition.

A pilot study was conducted assessing dextrose prolotherapy (PrT) for chronic LE. The study design was three-arm RCT. Twenty-six adults (32 elbows) with chronic lateral epicondylitis for three months or longer were randomized to ultrasound-guided PrT with dextrose solution, ultrasound-guided PrT with dextrose-morrhuate sodium solution, or watchful waiting (“wait and see”). The primary outcome was the Patient-Rated Tennis Elbow Evaluation (PRTEE) (100 points) at 4, 8, and 16 weeks (all groups) and at 32 weeks (PrT groups). The secondary outcomes included pain-free grip strength and MRI severity score. The participants in both PrT groups reported improved PRTEE composite and subscale scores at 4, 8, and/or 16 weeks compared with those in the wait-and-see group. At 16 weeks, compared with baseline, the PrT with dextrose and PrT with dextrose-morrhuate groups reported improved composite PRTEE scores by a mean of 18.7 and 17.5 points, respectively. The grip strength of the participants receiving PrT with dextrose exceeded that of other two groups 8 and 16 weeks. There were no differences in MRI scores. Satisfaction was high and there were no AE. PrT resulted in safe, significant improvement of elbow pain and function compared with baseline status and follow-up data and the wait-and-see control group. This pilot study suggests the need for a definitive trial to validate these results across a larger population. (Rabago et al., 2013)

There are several open clinical trials involving the use of prolotherapy in the treatment of LE. For more information, refer to www.clinicaltrials.gov. (Accessed October 28, 2020)

Rotator Cuff (RC) Tendinopathies

A retrospective case series by Ryu et al (2018) investigated prolotherapy with polydeoxyribonucleotide (PDRN) as a possible viable treatment option for chronic rotator cuff tendinopathy. “The records of patients with chronic rotator cuff tendinopathy (n=131) were reviewed retrospectively, and the patients treated with PDRN prolotherapy (n=32) were selected. The main outcome of the shoulder pain and disability index score on a numerical rating scale of average shoulder pain was measured. The authors concluded that compared to baseline data, significant improvements were shown in the shoulder pain and disability index and pain visual analog scale scores at one week after the end of treatment at one month and three months later.” They also concluded that “additional randomized multidisciplinary effectiveness trials that include imaging outcomes such as ultrasound are required to verify the effect of PDRN for chronic RCT compared with current therapies, including prolotherapy with PDRN.” The findings are limited by lack of comparison group.

Seven et al. (2017) evaluated the efficacy of prolotherapy in treating chronic refractory RC lesions through a randomized prospective comparative trial. Individuals with chronic RC lesions and symptoms that persisted for > six months were divided into two groups: the control group (n=60), treated with exercise three times weekly for 12 weeks; and the prolotherapy group (n=60), receiving 2 to 6 ultrasound-guided prolotherapy injection sessions in addition to the three times weekly home exercise program. A total of 101 patients out of 120 were included in the results. Clinical assessment of shoulder function was performed using a VAS for pain, Shoulder Pain and Disability Index (SPADI), Western Ontario Rotatory Cuff (WORC) Index, patient satisfaction, and shoulder range of motion (ROM). Participants were examined at baseline, weeks 3, 6, and 12, and last follow-up (minimum of one year). At one year, 92.9% versus 56.8% of participants reported excellent or good outcomes overall in the prolotherapy and control groups, respectively. No AEs were reported. Limitations of this study included but were not limited to small sample size and lack of a placebo control. The investigators concluded that prolotherapy is an easily applicable and satisfying auxiliary method in the treatment of partial RC lesions, reducing pain and improving both shoulder function and patient satisfaction. Larger studies with longer follow-up times are needed.

Bertrand and colleagues (2016) compared the effect of dextrose prolotherapy on pain levels and degenerative changes in painful RC tendinopathy. In this blinded RCT, 72 participants who received three monthly injections of 0.1% lidocaine with dextrose prolotherapy (entheses dextrose [Enth-Dex group]) or one of two control injections (entheses saline injection without dextrose [Enth-Saline group] or superficial saline injection [Superfic-Saline group]) were included in the 9-month follow-up data. All participants received concurrent physical therapy. The primary outcome measure was achieving an improvement in maximal current shoulder pain ≥ 2.8 (twice the minimal clinically important difference for VAS pain score). At nine months, the Enth-Dex group maintained a 2.9-point improvement in pain in comparison with 1.8 and 1.3 for the Enth-Saline and Superfic-Saline groups, respectively. The use of prolotherapy in the Enth-Dex group reported a significant improvement compared to the Superfic-Saline group (16 [59%] vs. 7 [27%]); however, the difference between the Enth-Dex group and the Enth-Saline group did not reach clinical significance. The authors concluded that prolotherapy may provide an effective and welcome addition to the

management of patients with painful RC tendinopathy. Additional, larger clinical trials with more complete functional assessment tools are required to determine the clinical utility of this technology.

In a retrospective, observational study, Lee and colleagues (2015) examined the effectiveness of prolotherapy for non-traumatic refractory RC disease in 151 patients who were unresponsive to three months of aggressive conservative treatment. Of the patients, 63 received prolotherapy with 16.5 % dextrose 10-ml solution (treatment group), and 63 continued conservative treatment (control group). Main outcome measures included VAS score of the average shoulder pain level for the past one week, SPADI score, isometric strength of the shoulder abductor, active ROM of the shoulder, maximal tear size on ultrasonography, and number of analgesics required per day. Over one-year follow-up, 57 patients in the treatment group and 53 in the control group were analyzed. There was no significant difference between the two groups in age, sex, shoulder dominance, duration of symptoms, and ultrasonographic findings at pre-treatment. The average number of injections in the treatment group was 4.8. Compared with the control group, outcome measures showed significant improvement in the treatment group. There were no AEs. The authors concluded that prolotherapy can be an option for patients with refractory chronic RC disease who showed no response to other treatments. They stated that prospective RCTs are needed to further demonstrate efficacy. The only limitation cited was the non-randomized retrospective study design.

Groin Pain

A case series by Topol and Reeves (2008) evaluated the use of prolotherapy in 75 athletes with chronic groin/abdominal pain. Participants received monthly injections of 12.5% dextrose in 0.5% lidocaine for two months. Average number of treatments received was three (range 1–6). Outcomes were measured using VAS and Nirschl pain phase scale (NPPS). Seventy-two athletes completed the full treatment. Follow-up occurred at an average of 26 months (range 6–73). VAS and NPPS improved 82% and 79% respectively. Sixty-six of 72 athletes returned to full sport, and all but two of the 66 athletes returned to full sport pain free. The authors found that 81% of the athletes had improvement in pain with 92% returning to unrestricted sports. The study is limited by small sample size and study design which did not provide a comparison group. Additional studies are needed to validate these results across a larger and more diverse population.

Temporomandibular Joint (TMJ) Hypermobility

A randomized controlled trial conducted by Louw et al (2019) studied the effect of hypertonic dextrose injection (prolotherapy) for the treatment of temporomandibular dysfunction. Forty-two participants (54 joints) were randomized to three monthly intra-articular injections of 20% dextrose/0.2% lidocaine or to 0.2% lidocaine. This was followed by injections of dextrose/0.2% lidocaine as needed through one year. Facial pain and jaw dysfunction, maximal interincisal opening, percentage of joint with 50% or more improvement in pain/function, and patient satisfaction were the primary and secondary outcome measures. “Randomization produced a control group with more female participants ($P=.03$), longer pain duration ($P=.01$), and less MIO ($P=.01$). Upon 3-month analysis, including pertinent covariates, dextrose group participants reported decreased jaw pain (4.3 ± 2.9 points vs 1.8 ± 2.7 points; $P=.02$), jaw dysfunction (3.5 ± 2.8 points vs 1.0 ± 2.1 points; $P=.008$), and improved MIO (1.5 ± 4.1 mm vs -1.8 ± 5.1 mm; $P=.006$). Control group participants received dextrose injections beginning at three months. No between-group differences were noted at 12 months; pooled data suggested that jaw pain, jaw function, and MIO improved by 5.2 ± 2.7 points (68%), 4.1 ± 2.8 points (64%), and 2.1 ± 5.5 mm, respectively. Pain and dysfunction improved by at least 50% in 38 of 54 (70%) and 39 of 54 (72%) jaws, respectively.” The authors concluded that prolotherapy resulted in substantial improvement in jaw pain, function and maximal interincisal opening compared with masked control injection at three months; with clinical improvements enduring to 12 months. This study is limited by the small patient population and suboptimal data analysis/reporting.

Cömert Kiliç et al. (2016) conducted a RCTI involving 30 adult patients with bilateral TMJ hypermobility referred for treatment. They were divided randomly into two treatment groups using either saline (placebo group) or dextrose injections (study group). The solution was injected into five different TMJ areas in three sessions at monthly intervals. The predictor variable was the treatment technique. The outcome variables were VAS evaluations and maximum inter-incisal opening (MIO). Outcome variables were recorded preoperatively and at 12 months postoperatively. The follow-up sample was comprised of 26 subjects, 12 in the placebo group and 14 in the study group. Masticatory efficiency increased and general pain complaints and joint sounds decreased significantly in both groups. MIO decreased significantly only in the study group. Insignificant changes in the other parameters were found for both groups. The authors concluded that after estimating differences between follow-up and baseline outcomes, the mean change in primary outcome variables showed no statistically significant difference between the two groups, suggesting that dextrose prolotherapy is no more effective than placebo for TMJ hypermobility.

Zhou and colleagues conducted a single center case series of 45 patients, introducing a modified technique of prolotherapy using an injection of lignocaine and 50% dextrose at a single site in the posterior periarticular tissues. The criteria for inclusion in this study were open lock of the jaw > twice in the past six months, and no long-standing dislocation of the TMJ. Patients were followed for at least one year. There were appreciable improvements in the number of episodes of dislocation and clicking after the injection. The overall success rate, defined as the absence of any further dislocation or subluxation for more than six months, was 41/45 (91%). Of the 41 rehabilitated patients, 26 (63%) required a single injection, 11 (27%) had two treatments, and four (10%) needed a third injection. All patients tolerated the injections well. The authors concluded that the modified dextrose prolotherapy is simple, safe, and cost-effective for the treatment of recurrent dislocation of the TMJ. Study limitations include small study size and the lack of a control group (2014).

Refai, et al. (2011) conducted a prospective, double-blind RCT with 12 patients to assess the efficacy of dextrose prolotherapy for the treatment of TMJ hypermobility. While therapeutic results were promising, the authors concluded that continued research into prolotherapy's effectiveness with large sample sizes and long-term follow-up is needed.

Lower Limb Tendinopathies

Because their efficacy and potential AEs are unclear, Morath et al. (2018) conducted a systematic review and meta-analysis of available published literature on sclerotherapy and prolotherapy for treating Achilles tendinopathy (AT) in athletes. While the initial search yielded 1,104 entries, only 13 were human studies. Four RCTs were ranked as having a low risk of selection bias. Three of those reported a statistically significant drop in the VAS score. Positive results regarding pain relief and patient satisfaction were identified in 12 of the 13 studies. The authors stated that the meta-analysis was clearly in favor of the intervention. Only one serious AE and two minor AEs were reported in the entire body of literature. The researchers concluded that both sclerotherapy and prolotherapy are safe and may be effective treatment options for AT; however, long-term studies and RCTs are still needed to support their recommendation. The conclusions are limited by a mix of human and animal studies, controlled and uncontrolled studies, and questionable choice of comparison groups.

A systematic review by Sanderson and Bryant (2015) evaluated the effectiveness and safety of prolotherapy injections for management of lower limb tendinopathy and fasciopathy. While no AEs following prolotherapy injections were reported in any study in this review, the authors found limited evidence that prolotherapy injections are a safe and effective treatment for AT, PF, and Osgood-Schlatter disease. More robust research using large, methodologically-sound RCTs is required.

Platelet Rich Plasma (PRP) Therapies

While some available studies are promising, the majority of evidence on platelet-derived blood or plasma therapies compared to other standard treatment is highly variable with regard to efficacy or improved health outcomes for a wide range of conditions. Higher quality studies with longer follow-up as well as standardization of best practices are needed to determine the benefit of this technology.

Osteoarthritis (OA)

Knee (KOA)

A randomized, double-blind, triple-parallel, placebo-controlled trial by Lin and colleagues (2019) prospectively compared the efficacy of intraarticular (IA) injections of PRP and hyaluronic acid (HA) with a sham control group (normal saline solution [NS]) for KOA. A total of 87 osteoarthritic knees (53 patients) were assigned to one of three groups receiving three weekly injections of either LP-PRP (31 knees), HA (29 knees), or NS (27 knees). The WOMAC Index score and International Knee Documentation Committee (IKDC) subjective score were collected at baseline and at 1, 2, 6, and 12 months after treatment. All three groups showed statistically significant improvements in both outcome measures at one month; however, only the PRP group sustained the significant improvement in both the WOMAC and IKDC scores at 12 months, showing improvement of 21% and 40%, respectively. There was no significant difference in both functional outcomes between the HA and NS groups at any time point. Only the PRP group reached the minimal clinically important difference in the WOMAC score at every evaluation. Study limitations included small sample size and that the trial did not include imaging studies for the evaluation of joint cartilage post-injection. The authors concluded that IA injections of LP PRP can provide clinically significant functional improvement for at least one year in patients with mild to moderate KOA.

Future long-term studies of larger sample sizes encompassing all stages of degeneration with the inclusion of imaging evaluation and biomarker analysis of the knee joints are warranted to further elucidate these findings. These findings need to be reproduced in additional large high-quality studies to assess the implications for clinical care.

Delanois and colleagues conducted a systematic review and analysis of reports evaluating: (1) PRP injections; (2) bone marrow-derived mesenchymal stem cells (BMSCs); (3) adipose-derived mesenchymal stem cells (ADSCs); and (4) amnion-derived mesenchymal stem cells (AMSCs) in management of KOA. Of 1009 studies identified within the last five years, 123 met inclusion criteria. Although the majority of PRP reports demonstrated improvements in pain and/or function, some revealed no substantial improvements. Similar findings were noted for the other therapy. The reviewers concluded that although some promising early results for PRP, BMSC, ADSC, and AMSC therapies were identified, the majority of level I studies have multiple problems including but not limited to small sample sizes, potentially inappropriate control cohorts, and short-term follow-up. Despite the limitations, they indicate that there still appears to be evidence justifying their use for KOA management. More high-level, larger human studies utilizing standardized protocols are needed (2019).

Annaniemi et al. (2018) conducted a retrospective study with 190 participants to compare PRP versus viscosupplements in terms of symptom relief and time to arthroplasty in patients with KOA. Subjects received either IA injections of PRP (94 patients), which the authors label as “an experimental treatment in osteoarthritis”, or HA (86 patients) between January 2014 and October 2017. WOMAC, VAS, and range of motion (ROM) were measured before injection, at 15 days, six months, 12 months, and at final follow-up. Individuals treated with HA experienced a higher arthroplasty rate (36% vs 5.3%), lower ROM, worse VAS and WOMAC Index scores, and increased risk of any arthroplasty occurrence than those treated with PRP. Cox proportional hazards analysis revealed a tendency to decrease the risk of knee arthroplasty for the participants treated by PRP. When adjusted for propensity score in matched pairs (n=78), the PRP group still showed significant improvement over the HA group in arthroplasty rate (12.8% vs 41%), VAS and WOMAC scores, but not in ROM during the mean follow-up of 16.7 months. Authors found that in comparison to HA, IA injections of PRP are associated with better outcomes, prolonged time to arthroplasty, and a valid therapeutic option in select KOA patients who are unresponsive to conventional treatments. A limitation of retrospective study design was cited by the authors, who concluded that further larger studies are needed to validate this promising treatment modality. Additionally, the findings are limited by lack of randomization between interventions, which could have introduced biases and multiple comparisons.

A blinded, comparative RCT by Di Martino and colleagues (2018) evaluated long-term clinical outcomes provided by IA injections of either PRP or HA to treat knee degenerative disease. One hundred ninety-two patients underwent three blinded weekly IA injections of either PRP or HA. Patients were prospectively evaluated pre-injection, and then at two, six, 12, and 24 months with a mean of 64.3 months of follow-up. Primary outcomes were based on subjective IKDC evaluation, secondary outcomes based on EuroQol VAS and Tegner scores. One hundred sixty-seven participants reached the final evaluation. Both treatments were effective in improving knee functional status and symptoms over time. Mean IKDC subjective score improved significantly for both groups and remained stable over time up to 24 months and at final evaluation. A comparative analysis showed no significant intergroup difference in any of the clinical scores at any follow-up point. The median duration of patient subjective perception of symptomatic relief was nine months for HA and 12 months for PRP, which was considered insignificant. The only significant difference was observed in the rate of reintervention at 24 months, which was significantly lower in the PRP group (22.6% vs 37.1%). While both treatments were effective in improving knee functional status and symptoms over time, researchers concluded that PRP did not provide an overall superior clinical improvement compared with HA in terms of either symptomatic-functional improvement at different follow-up points or effect duration (ClinicalTrials.gov identifier NCT01670578).

A systematic literature review and meta-analysis if possible were performed by Laudy et al. to evaluate the effectiveness of PRP injections for KOA based on decreasing pain, improving function, global assessment and changes regarding joint imaging. Ten trials were included. Most of these compared PRP to HA and were observational. The author identified only one RCT comparing PRP to placebo (Patel, et al. 2013), which is also review with newer studies in the systematic review by Delanois, et al. (2019). In the studies reviewed by Laudy, et al., IA PRP injections were more effective for pain reduction compared with placebo or HA, but the level of evidence was limited due to a high risk of bias. (2015).

A comparative effectiveness review of PRP for KOA stated that IA-PRP is a minimally invasive treatment associated with few complications that may be appealing when more conservative therapies (e.g., oral medications, PT), are contraindicated, unavailable, or fail to provide adequate relief. Current evidence suggests limited difference in efficacy from IA-HA at up to six months, but that IA-PRP may be associated with better outcomes at one-year follow-up. If IA-PRP can be conclusively shown to

provide benefits over IA-HA at one year, it has the potential to displace IA-HA. Future research should consider the role of PRP preparation protocols upon efficacy, as they vary considerably across studies. There is no standardization or consensus as to best practices, nor is there clear understanding of which steps and factors (if any) are associated with better outcomes. These factors are likely to bear upon acceptance of PRP as an alternative to IA-CS or IA-HA in the future (Hayes, 2018).

National Institute for Health and Clinical Excellence (NICE)

NICE's 2019 interventional procedures guidance on PRP injections for KOA states that the technology raises no major safety concerns however, the evidence on efficacy is limited in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Further research should be in the form of RCTs with medium- to long-term follow-up, including validated measures of knee function and patient-reported outcomes.

Hip Osteoarthritis (HOA)

A Hayes report of published literature on the use of PRP for the treatment of HOA identified 4 RCTs representing 303 patients who were treated with intra-articular (IA)-PRP or IA-HA. They stated that the small body of low-quality evidence suggests that pain and function outcomes may improve after treatment with ultrasound-guided IA-PRP and remain better than pretreatment status up to one year. IA-PRP outcomes do not appear to be different from those obtained with IA injection with IA-HA, a common treatment alternative for which there is uncertainty regarding the clinical significance of treatment benefits. There is insufficient evidence available to draw firm conclusions about safety; the limited published evidence indicates that IA-PRP is safe and well tolerated. Long-term effects of PRP therapy beyond one year have not been established. The report concludes that there is potential but unproven benefit of PRP for HOA. Future studies may help determine whether IA-PRP is more efficacious than placebo or other active treatments and provide additional information regarding potential harms (2019).

Dallari et al. (2016, included in the Hayes review cited above) conducted a comparative, blinded, RCT to compare therapeutic efficacy of autologous PRP, HA, or a combination of both (PRP+HA) in HOA. Participants (n=111) were assigned to three groups and received three weekly injections of either PRP (44 patients), PRP+HA (31 patients), or HA (36 patients). The primary outcome measure was a change in pain intensity as assessed by the VAS at 2, 6, and 12 months after treatment. Secondary outcome measures included the WOMAC Index. The PRP group had the lowest VAS scores at all follow ups. In particular, the mean VAS score in the PRP, PRP+HA, and HA groups was 21, 35, and 44 at six months, respectively. The WOMAC score of the PRP group was significantly better at two- and six- month follow-ups, but not at 12 months. The authors concluded that these results indicated that IA PRP injections offer a significant clinical improvement in patients with HOA without relevant side effects. The benefit was significantly more stable up to 12 months as compared with the other tested treatments. The addition of PRP+HA did not lead to a significant improvement in pain symptoms.

Dold and colleagues conducted a systematic review of PRP for articular cartilage pathology. Literature search was conducted for studies published up to October 2012 that assessed clinical outcomes of the use of PRP for the treatment of chondral and osteochondral pathology, excluding those including concomitant management of acute fractures or ligament reconstruction. Ten studies were included in the final analysis, but only one addressed use of PRP for HOA and was only level IV evidence (2014).

Battaglia et al. (2013, included in the Hayes review cited above) conducted a randomized comparative study of PRP vs HA with 12 months of follow-up in patients with HOA. One hundred subjects received PRP (group A) and or HA administered via IA US-guided injections (group B). Patients were evaluated at baseline and after one, three, six, and 12 months using the Harris Hip Score and VAS. An overall improvement was detected in both groups between one- and three-month follow-up. Despite a slightly progressive worsening between six- and 12-month follow-up, the final clinical scores remained higher compared with baseline with no significant differences between PRP and HA. The authors concluded that injections of PRP are efficacious in terms of functional improvement and pain reduction but are not superior to HA in patients with symptomatic hip OA at 12-month follow-up.

Soft Tissue (Tendon, Joint and other Soft Tissue Areas of the Body)

Balasubramaniam et al. (2015) systematically reviewed the literature regarding PRP therapy in chronic tendinopathy. A total of 389 articles were reviewed from Feb 2010 to April 2014, with 9 RCTs meeting inclusion criteria. Each article was reviewed independently by two authors. Each article was analyzed using the Cochrane Criteria checklist. The review found that PRP was most effective in patellar and lateral epicondylar tendinopathy, with both RCTs in the patellar section of the study supporting the use of PRP in pain reduction at three and 12 months, whereas two of four studies in the lateral epicondylar section showed

improvements in pain and disability at six and 12 months. There was a lack of evidence to support the use of PRP in Achilles and RC tendinopathy. The authors concluded that although the results of this review showed promise for the use of PRP in chronic tendinopathy, the analysis highlighted the need for more controlled clinical trials comparing PRP with placebo. The findings are limited by the small number of quality studies for each indication and inconsistent results of the intervention.

Moraes et al. (2014) conducted a Cochrane review to assess the effect of platelet rich therapy (PRT) for musculoskeletal soft tissue injuries. Nineteen studies were found that compared PRT with placebo, autologous whole blood, DN or no PRT (n=1,088). The trials covered eight types of injury, some of which were treated surgically: RC tears, shoulder impingement syndrome, tennis elbow, knee ligament reconstruction using autologous and donor grafts, PT, AT, and acute rupture of the Achilles tendon. The available evidence base comprised a diverse collection of small trials that applied PRT in various ways for treating tendinopathies or as an augmentation procedure for surgically treated soft tissue injuries. There was very low-quality evidence from a subset of the trials for a marginal short-term benefit in pain from PRT; however, other very low-quality evidence indicated that using PRT did not appear to have a clinically relevant effect on short-term or long-term function. Very low-quality evidence showed no difference in AEs between the PRT and the various control interventions. Overall, and for the individual conditions, researchers concluded there is currently insufficient evidence to support the use of PRT for treating these injuries.

In 2016, the Washington State Health Care Authority (WSHCA) conducted a technology assessment to evaluate the safety and efficacy of PRP and/or ABI for the treatment of various musculoskeletal and orthopedic conditions. As part of the technology assessment, a total of 54 RCTs and eight cohort studies were included and reviewed. Limitations of the studies noted by the Committee generally included small sample populations, short-term follow-up, inconsistency of measured outcomes, potential for risk bias, and lack of high-quality evidence. The authors concluded there was insufficient evidence to draw strong conclusions regarding safety and efficacy. Moreover, the Committee reported despite its current use, standardization of PRP preparation is lacking, and although the technology to obtain PRP is FDA-approved, PRP is currently not indicated for direct injection.

Knee

A Hayes comparative effectiveness review on PRP for treatment of ligament injuries and tendinopathies of the knee identified 1 good-quality systematic review and meta-analysis with findings from four RCTs and two quasi-RCTs assessing the efficacy of PRP versus no PRP in anterior cruciate ligament reconstruction (ACLR) surgery or at the patellar graft donor site. Two additional primary RCTs were identified that supplemented these data. Two primary RCTs were identified that examined the use of PRP versus no PRP in patients with PT. No studies of PRP use in medial collateral ligament (MCL) injuries were found. The use of PRP in ACLR may not yield different functional outcomes from ACLR without PRP. However, limited evidence from patients who received PRP for patellar donor site morbidity suggests that function may improve more by 12 months compared with patients who did not receive PRP treatment and that use of PRP may reduce graft donor site pain more than no PRP. With regard to PT, limited and conflicting evidence precludes conclusions regarding functional improvement and pain reduction for PRP relative to some active controls. There is a paucity of evidence regarding the use of PRP to treat other ligament injuries or tendinopathies of the knee. The overall quality rating of the evidence was low to very low due to study limitations and inconsistency in the data and the report concluded that there was no proven benefit for this indication (2017; reviewed 2020).

Dragoo and colleagues (included in the Hayes review cited above) conducted a blinded RCT with 23 participants with patellar tendinopathy (PT) to compare clinical outcomes after a single US-guided, LR-PRP injection versus dry needling (DN). After failing non-operative treatment, participants were randomized to receive US-guided DN alone (DN group; n=13) or with injection of LR-PRP (PRP group; n=10), along with standardized eccentric exercises. The subjects completed patient-reported outcome surveys before and at 3, 6, 9, 12, and ≥ 26 weeks after treatment during follow-up visits. The primary outcome measure was the Victorian Institute of Sports Assessment (VISA) score for PT at 12 weeks. Secondary measures included the VAS for pain, Tegner activity scale, Lysholm knee scale, and Short Form (SF-12) questionnaire at 12 and ≥ 26 weeks. Patients who were dissatisfied at 12 weeks were allowed to cross over into a separate unblinded arm. At 12 weeks post-treatment, the PRP group had improved significantly more than the DN group, but the differences were not statistically significant at ≥ 26 weeks. Lysholm scores were not significantly different between groups at 12 weeks, but significantly improved in the DN group at ≥ 26 weeks. At 12 weeks, 3 patients in the DN group failed treatment and subsequently crossed over into the PRP group. These patients were excluded from the primary ≥ 26 -week analysis. There were no treatment failures in the PRP group, and no AEs were reported. Recruitment for the trial was stopped because interim analysis demonstrated statistically significant and clinically important results. While a therapeutic regimen of standardized eccentric exercise and US-guided LR-PRP injection with DN accelerated the recovery from PT compared to exercise and US-guided DN alone, the authors stated that the apparent benefit

of PRP dissipated over time. Limitations to this study include small sample size, short follow up period, and lack of intention to treat analysis beyond 12 weeks (2014).

Achilles Tendinitis (AT) and Plantar Fasciitis (PF)

In a 2019 comparative effectiveness review, Hayes concluded that while PRP is a minimally invasive treatment that is associated with very few complications, available evidence from randomized trials does not indicate better functional outcomes after AT repair (compared with no PRP), and evidence for use of PRP in AT is limited and inconclusive. For treatment of PF, PRP may lead to better functional and pain-related outcomes compared with corticosteroid injection but evidence for other comparators is limited. They identified that PRP development protocols varied considerably across studies; there was no consensus regarding best practices nor was there clear understanding of which steps and factors (if any) are associated with better outcomes.

Usuelli et al. (2018, included in the Hayes review cited above) conducted a prospective RCT comparing the efficacy of PRP and stromal vascular fraction (SVF) injection for the treatment of non-insertional Achilles tendinopathy (AT). A total of 44 participants were assigned to the PRP group (n=23) or the SVF group (n=21), for a total of 28 tendons per group. Outcomes were measured using the VAS pain scale, the VISA-Achilles (VISA-A), the American Orthopaedic Foot & Ankle Society (AOFAS) Ankle-Hindfoot Score and the SF-36 form, assessing pre-operatively and at 15, 30, 60, 120, and 180 days from treatment. Patients were also evaluated by US and magnetic resonance (MR) before treatment and after 4 (US only) and six months. Comparing the two groups, VAS, AOFAS and VISA-A scored significantly better at 15 and 30 days in the SVF in comparison to the PRP group. At remaining assessment points, the scores were not significantly different between the two groups; and no correlation was found between clinical and radiological findings. The researchers concluded that both PRP and SVF were safe and effective treatments for recalcitrant AT. The patients treated with SVF obtained faster results, thus suggesting that such a treatment should be taken into consideration for those individuals who require an earlier return to daily activities or sport. Limitations to this study include small sample size and limited follow up period, as well as a comparison of PRP to a non-established treatment.

Boesen et al. (2017, included in the Hayes review cited above) conducted an RCT to determine whether eccentric training in combination with high-volume injection (HVI) or PRP injections improves outcomes in AT. A total of 60 men with chronic (> 3 months) AT were included and followed for six months (n=57). All participants performed eccentric training combined with either (1) one HVI (steroid, saline, and local anesthetic), (2) four PRP injections each 14 days apart, or (3) placebo (a few drops of saline under the skin). Randomization was stratified for age, function, and symptom severity on the VISA-A. Outcomes included function and symptoms (VISA-A), self-reported tendon pain during activity using VAS, tendon thickness and intratendinous vascularity using US imaging and Doppler signal, and muscle function via heel-rise test. Outcomes were assessed at baseline and at 6, 12, and 24 weeks of follow-up. VISA-A scores improved in all groups at all time points, with greater improvement in the HVI group. VAS scores improved in all groups at all time points, with overall greater decrease in HVI and PRP versus placebo. Tendon thickness showed a significant decrease only in HVI and PRP groups during the intervention. Muscle function improved in the entire cohort with no difference between the groups. The researchers concluded that treatment with HVI or PRP in combination with eccentric training in chronic AT seems more effective in reducing pain, improving activity level, and reducing tendon thickness and intratendinous vascularity than eccentric training alone. HVI may be more effective in improving outcomes of chronic AT than PRP in the short term. Study limitations include small sample size and short term follow up

Gogna and colleagues (2016, included in the Hayes review cited above) conducted a comparative RCT evaluating PRP versus low dose radiation as treatment for PF. All consecutive sportspersons presenting with clinical diagnosis of PF underwent treatment consisting of stretching exercises, activity modification, and non-steroidal anti-inflammatory drugs for six months. The first 40 patients who did not respond to treatment were divided randomly into two groups of 20 patients each: Group A (PRP) and Group B (low dose radiation [LDR]) and were monitored for six months. Outcome measurements were mean improvement in the pain score using VAS and AOFAS, as well as evaluation of PF thickness on US. Significant improvement in all three parameters was noted at the time of final follow up within both groups, with differences in outcomes for both groups being statistically insignificant. The researchers concluded that PRP is equivalent to LDR in patients with chronic recalcitrant PF not responding to PT. Limitations cited include study design, lack of standardized protocols for PRP injections, and lack of placebo group comparison.

Jain et al. (included in the Hayes review cited above) compared the efficacy of PRP to that of steroid for individuals with chronic PF resistant to traditional non-operative management in a randomized comparative study. Sixty heels with intractable PF who

had failed conservative treatment received either PRP or steroid injection. Primary outcomes were assessed via the Roles-Maudsley (RM) Score, VAS for pain and the AOFAS score. Data was collected prospectively on the cohort, pre-treatment, at three, six- and 12-months post injection. Pre-injection and at three and six months, both groups were well matched with no statistically significant differences. At 12 months, the RM, VAS and AOFAS scores in the PRP arm (1.9, 3.3 and 88.5) were significantly better than the steroid arm (2.6, 5.3 and 75). The authors concluded that PRP is as effective as steroid injection at achieving symptom relief at three and six months after injection. However, at 12 months, PRP is significantly more effective making it more durable than cortisone injection. The limitation of this study was use of the AOFAS score as the only outcome measure, which may not have been the best tool for this condition and apparent lack of masking of the participants or investigators to the assigned intervention, which could have resulted in biases (2015).

Shoulder

A 2018 Hayes comparative effectiveness review on PRP for treatment rotator cuff (RC) repairs, tendinopathies, and related conditions identified one good-quality systematic review/meta-analysis with findings from 15 RCTs, along with six additional primary RCTs, assessing the use of PRP in arthroscopic RC repair. Two RCTs were identified that examined PRP injections for treatment of partial RC tears or RC tendinopathy, and two RCTs were identified that examined PRP use with arthroscopic acromioplasty (AA) or needling for calcific tendinitis. Compared with no PRP, the use of PRP in arthroscopic RC repair may provide short-term benefits for functional improvement and pain reduction, but data were conflicting for this finding and benefits did not persist long term. Taken together, these findings provide some preliminary evidence that PRP may accelerate recovery from arthroscopic RC repair in the short term, but PRP treatment does not change long-term functional or pain outcomes. Limited evidence finds no difference in functional improvement with PRP injections for non-arthroscopic treatment of partial RC tears or tendinopathy, but findings were inconsistent with regard to pain. Finally, limited evidence suggests no difference in functional improvement after AA or needling for RC tendinopathy, along with no difference in pain relief after AA. The overall quality rating of this body of evidence is considered low to very low.

An RCT by Ebert et al. (2017, included in the Hayes review cited above) investigated whether the midterm clinical and radiographic outcomes of arthroscopic supraspinatus repair are enhanced after repeated postoperative applications of PRP. A total of 60 patients (30 control; 30 PRP) were initially randomized to receive two US-guided injections of PRP to the tendon repair site at seven and 14 days after double-row arthroscopic supraspinatus repair or not. A total of 55 patients (91.7%) underwent a clinical review and magnetic resonance imaging (MRI) at a mean of 3.5 years after surgery. Patient-reported outcome measures (PROMs) included the Constant score, Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) questionnaire, Oxford Shoulder Score (OSS), and VAS for pain. Global rating of change (GRC) scale and patient satisfaction scores were evaluated. Structural integrity of the surgical repair was assessed via MRI using the Sugaya classification system. At the midterm review, there was no difference between the groups for any of the PROMs. No differences between the groups were demonstrated for the subjective and ROM subscales of the Constant score, although a significantly higher Constant strength subscale score was observed in the PRP group. There was no evidence for any group differences in MRI scores or retear rates, with 66.7% of PRP patients and 64.3% of control patients rated as Sugaya grade 1. Two control patients had symptomatic retears (both full thickness) within the first 16 weeks after surgery compared with 2 PRP patients, who suffered symptomatic retears (both partial thickness) between 16 weeks and a mean 3.5-year follow-up. Significant postoperative clinical improvements and high levels of patient satisfaction were observed in patients at the midterm review after supraspinatus repair. The researchers concluded that while pain-free, maximal abduction strength was greater in the midterm in the PRP treatment group. Repeated applications of PRP delivered at 7 and 14 days after surgery provided no additional benefit to tendon integrity.

Pandey and colleagues (included in the Hayes review cited above) conducted a RCT to determine whether application of PRP improve outcomes after arthroscopic repair of RC tear. Subjects (PRP group n=52, control group n=50) with medium-sized and large degenerative posterolateral tears were included for arthroscopic repair with a minimum follow-up of two years. Patients were evaluated with clinical scores (VAS, Constant-Murley score, University of California-Los Angeles (UCLA) score, and American Shoulder and Elbow Surgeons score) and US to assess retear and vascularity pattern of the cuff. VAS scores were significantly lower in the PRP group than in controls at one, three and six months but not later. Constant-Murley scores were significantly better in the PRP group compared with controls at 12 and 24 months, whereas UCLA scores were significantly higher in the PRP group at 6 and 12 months. The American Shoulder and Elbow Surgeons score in both groups was comparable at all the times. At 24 months, retear in the PRP group (n=2; 3.8%) was significantly lower than in the control group (n=10; 20%). Doppler US examination showed significant vascularity in the PRP group repair site at three months postoperatively and in peribursal tissue until 12 months. The researchers concluded that application of moderately concentrated PRP improves clinical and structural outcome in large RC tears and enhances vascularity around the repair site in

the early phase. Study limitations included the lack of standardized procedures to ensure a consistent PRP preparation. Future research should include RCTs with larger sample sizes to evaluate PRP in large tears (2016).

Flury et al. (2016, included in the Hayes review cited above) investigated whether an intraoperative pure PRP injection compared with a local anesthetic injection improved patient-reported outcomes at three and six months after arthroscopic RC repair through a blinded RCT. Between January 2011 and November 2012, a total of 120 patients who underwent arthroscopic double-row repair of a supraspinatus tendon rupture were randomized to receive either pure PRP by an injection at the footprint (n=60) or ropivacaine injected in the subacromial region (control group; n=60). Concomitant tears were present in 78% of patients. Clinical parameters and various outcome scores (Constant-Murley shoulder score; OSS; patient American Shoulder and Elbow Surgeons score; QuickDASH score; EuroQol 5 dimensions) were documented preoperatively and at three, six, and 24 months postoperatively. The repair integrity was assessed by MRI or US at 24 months. Furthermore, a pain diary was completed within the first 10 postoperative days, and AEs recorded. The final follow-up rate was 91%. An associated tear of the subscapularis tendon was diagnosed in 23% of PRP-treated patients and 36% of control patients. At three months post-surgery, the mean OSS was 32.9 ± 8.6 versus 30.7 ± 10.0 in PRP-treated and control patients, respectively. No significant differences were noted for other outcome parameters at 6 and 24 months. Pain for both groups decreased from postoperative day one to 10 without any significant group difference. Recurrent supraspinatus tendon defects were diagnosed in the PRP and control groups at 6 and 11, respectively. Localized AEs were experienced by 22 PRP-treated and 18 control group participants during the 24-month follow up period. The authors concluded that patients treated with pure PRP showed similar safety and efficacy at three, six, and 24 months following arthroscopic repair compared with control patients receiving ropivacaine.

In a prospective RCT, Verhaegen et al. (included in the Hayes review cited above) investigated the evolution of RC calcification and the role of PRP supplementation on the healing process. Patients (n=40) were evenly randomized to either group 1 (PRP) or group 2 (no PRP [control group]). Group 1 received a perioperative PRP infiltration during RC repair, whereas the control group did not. Patients were assessed preoperatively and postoperatively at six weeks, three and six months, and one year. The Constant score, Simple Shoulder Test, and QuickDASH were used as outcome measures. The evolution of the cuff defect was evaluated with US at three and six months and with MRI after one year. All patients improved significantly after surgery and there was no difference in clinical outcome or RC healing between groups. A high rate of persistent RC defects after one year was observed in both groups, and the presence of residual cuff defects did not influence the clinical outcome. The authors concluded that while they believed in the need for biologic enhancement in orthopedic surgery and RC healing specifically, this study could not identify any beneficial effect of the addition of PRP on RC healing (2016).

The clinical and tissue effects of the co-application of PRP injection with arthroscopic acromioplasty (AA) in patients with chronic RC tendinopathy was investigated by Carr et al. (2015, included in the Hayes review cited above) in a RCT of 60 individuals. The authors reported there was no significant difference in the OSS between AA alone and AA + PRP at any time point in the study. The authors noted that PRP significantly alters the tissue characteristics in tendons after surgery with reduced cellularity and vascularity and increased levels of apoptosis and the co-application of PRP may have potential deleterious effects on healing tendons.

National Institute for Health and Clinical Excellence (NICE)

NICE's 2013 interventional procedures guidance on PRP injections for tendinopathy states that the technology raises no major safety concerns however, the evidence on efficacy is limited in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Further research is encouraged comparing autologous blood injections (ABI) (with or without techniques to produce PRP) against established non-surgical methods for managing tendinopathy. Trials should clearly describe patient selection (including the site of tendinopathy, duration of symptoms and any prior treatments) and document whether a 'dry needling' technique is used. Outcomes should include specific measures of pain, QOL and function, and whether subsequent surgical intervention is needed.

Lateral Epicondylitis (LE)

In a comparative effectiveness review by Hayes, prolotherapy using PRP is identified as a minimally invasive treatment option for patients with persistent LE that is unresponsive to other conservative measures. Current evidence suggests that PRP may yield some long-term benefits that are not apparent before six months, particularly when compared with corticosteroid injection. Once PRP preparations are standardized and best practices are established, trials can identify which factors are associated with better outcomes, yielding more effective PRP preparations and patient selection criteria (2017; reviewed 2019).

In 2017, Merolla and colleagues conducted a prospective comparative randomized study to compare the efficacy of autologous PRP injections and arthroscopic lateral release in treating chronic LE. A total of 101 patients received arthroscopic release (n=50) or US-guided PRP injections (n=51). Outcomes were assessed using VAS for pain, the Patient-Rated Tennis Elbow Evaluation (PRTEE), and a calibrated hand dynamometer for grip strength. Follow up assessment intervals were at week 2, 4, 8, 12, 24, and at 1 and 2 years for the PRP group. While unable to be assessed at weeks two and four due to immobilization and rehabilitation, the arthroscopy group was evaluated at the same intervals. Both groups experienced significant improvement in all measures. The PRP group experienced significantly improved grip strength at week 8; all other significant differences were in favor of arthroscopy. Consumption of rescue pain medication was not significantly different between the groups. Authors concluded that while both procedures were safe and well accepted, arthroscopic release ensured better long-term outcomes than PRP injection. The findings are limited by lack of comparison to a placebo injection and active intervention in the non-PRP group.

A prospective double blind RCT was conducted by Schöffl et al. (included in the Hayes review cited above) comparing autologous conditioned plasma (ACP) to placebo in 50 patients with LE. The group was divided equally to receive either one round of injection therapy with ACP (PRP) or a placebo of normal saline with re-evaluation at four weeks and six months post-injection. Out of the 50, 18 patients from each group qualified for reevaluation. The difference between the DASH scores of the treatment and placebo groups was statistically insignificant at both four weeks and six months. The authors concluded that while a therapeutic effect was achieved in both groups, there was no therapeutically significant difference between ACP and placebo treatments. ACP/PRP injections need to be investigated in future studies (2017).

Foot Injuries

Görmeli and colleagues (2015) conducted a prospective, blinded RCT to compare the effects of HA and PRP as adjunct therapies after arthroscopic microfracture in osteochondral lesions (OCLs) of the talus. Patients with talar OCLs in their ankle joints (n=40) were treated with arthroscopic debridement and a microfracture technique. Thirteen randomly selected patients received PRP, 14 patients received HA, and the remaining 13 patients received saline as a control group. The participants were assessed using AOFAS and VAS scores after a 15-month follow-up. Postoperatively, all the groups exhibited significantly increased AOFAS scores and decreased VAS scores compared with their preoperative results. The AOFAS scores were significantly increased in the PRP group versus the HA and control groups, although the increased AOFAS scores in the HA group versus the control group were also significant. Similar to the AOFAS scores, the decrease in the VAS scores was significantly lower in the PRP group versus the HA and control groups. The HA group had significantly lower VAS scores than the control group. The authors concluded that both PRP and HA injections improved the clinical outcomes of patients who underwent surgery for talar OCLs in the midterm period and can be used as adjunct therapies for these patients. Because a single dose of PRP provided better results, they recommended PRP as the primary adjunct treatment option in the talar OCL postoperative period. Limitations to this study include small sample size, short follow up period, and no masking of the participants to the intervention, which could have introduced biases.

Mei-Dan et al. (2012) evaluated the short-term efficacy and safety of PRP versus HA in reducing pain and disability caused by OCLs of the ankle in an RCT with 32 patients. Participants were divided into the HA (group 1) or PRP (group 2). Thirty OCLs, 15 per arm, received three consecutive IA therapeutic injections and were followed for 28 weeks. Outcomes were measured using the AOFAS Ankle-Hindfoot Scale, VAS, and the subjective global function score. The authors found that while OCLs of the ankle treated with IA injections of PRP and HA both resulted in a decrease in pain scores and an increase in function for at least six months with minimal AEs, PRP treatment led to a significantly better outcome than HA. Study limitations include small sample size, short follow up period, suboptimal randomization, and lack of masking, which could have introduced biases.

Low Back Pain (LBP)

A 2018 Hayes Search and Summary (archived) found very limited peer-reviewed, published literature specific to the use of PRP to treat spinal ligaments or facet joints. Ten abstracts were retrieved, including a prospective randomized comparison study, a prospective uncontrolled study, a retrospective uncontrolled study, a case series, literature reviews, and review articles. They concluded there is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management of the use of PRP to treat thoracic and lumbar spinal pain.

A randomized study by Wu et al. (included in the Hayes review cited above) compared efficacy and safety between autologous PRP and local anesthetic (LA)/corticosteroid IA injection for the treatment of lumbar facet joint syndrome. Forty-six patients were randomized into group A (IA injection with PRP) and group B (IA injection with LA/corticosteroid). Outcomes were

assessed via the VAS, the Roland-Morris Disability Questionnaire (RMQ), Oswestry Disability Index (ODI), and modified MacNab criteria for pain relief and applications of post-treatment drugs, and were performed prior to injection, at one week, and at one, two, three, and six months post-injection. No significant difference between groups was observed at baseline. Compared with pretreatment, both group A and group B demonstrated statistical improvements in the pain VAS score at rest or during flexion, the RMQ, and the ODI. For group B, subjective satisfaction based on the modified MacNab criteria and objective success rate were highest (80% and 85%) after one month, but only 50% and 20%, respectively after six months. However, for group A, they increased over time. No treatment-related complications were reported by either group. The authors concluded that both autologous PRP and LA/corticosteroid for IA injection are effective, easy, and safe enough in the treatment of lumbar facet joint syndrome. However, autologous PRP was considered superior due to longer duration of efficacy. Limitations to this study include short follow up period and small sample size (2017).

Singla and colleagues (2017) conducted a prospective randomized open blinded end point (PROBE) study to assess the efficacy and safety of PRP compared with methylprednisolone in US-guided sacroiliac joint (SIJ) injection for LBP. Patients (n=40) with chronic LBP and SIJ pathology were randomly allocated into two groups. Group S received 1.5 mL of methylprednisolone (40 mg/mL) and 1.5 mL of 2% lidocaine with 0.5 mL of saline, while Group P received 3 mL of leukocyte-free PRP with 0.5 mL of calcium chloride into US-guided SIJ injection. VAS scores, Modified Oswestry Disability Questionnaire (MODQ) scores, Short Form (SF-12) Health Survey scores, and complications (if any) were evaluated at 2, 4, 6, and 12 weeks. Intensity of pain was significantly lower in Group P at six and 12 weeks as compared to Group S. The efficacy of steroid injection was reduced to only 25% at three months in Group S, while it was 90% in Group P. Patients receiving PRP also showed a reduction of VAS \geq 50% from baseline when other factors were controlled. The MODQ and SF-12 scores were improved initially for up to four weeks but deteriorated further at three months in Group S, while both the scores improved gradually in Group P for the entire follow up period. Authors concluded that PRP injection is an effective treatment modality in LBP involving the SIJ. Limitations include small study group size and short follow up period

A prospective, double-blind, RCT was conducted by Tuakli-Wosornu et al. (2016) to determine whether single injections of autologous PRP into symptomatic degenerative intervertebral disks will improve participant-reported pain and function. Adults (n=46) with chronic (\geq six months), moderate-to-severe lumbar diskogenic pain that was unresponsive to conservative treatment were randomized to receive intradiskal PRP (n=29) or contrast agent (n=18). Main outcome measures included the Functional Rating Index, Numeric Rating Scale for pain, the pain and physical function domains of the SF-36 Health Survey, and the modified North American Spine Society Outcome Questionnaire. Data on pain, physical function, and participant satisfaction were collected at one week, four weeks, eight weeks, six months, and one year. Participants in the control group who did not improve at eight weeks were offered the option to receive PRP and subsequently followed. Over eight weeks of follow-up, there were statistically significant improvements in participants who received intradiskal PRP with regards to pain, function, and patient satisfaction compared with controls. No AEs of disk space infection, neurologic injury, or progressive herniation were reported following the injection of PRP. The authors concluded that intradiskal PRP injection resulted in significant improvements in function, pain, and patient satisfaction scores over eight weeks compared with controls. Those who received PRP maintained significant improvements functional scores through at least one year of follow-up. Study limitation cited was the very limited follow up time of only eight weeks for the randomized portion of the study and differential exclusion of participants after randomization. The authors concluded that although these results are promising, further studies are needed to define the subset of candidates most likely to respond to biologic intradiskal treatment and the ideal cellular characteristics of the intradiskal PRP injectate.

Wounds

Moneib et al. (2018) performed a study to compare the clinical efficacy of PRP in the management of chronic VLU vs conventional treatment. Subjects (n=40) were equally randomized to treatment with autologous PRP weekly for six weeks (Group A) or treated conventionally for six weeks (compression and dressing/Group B). Treatment results were calculated by percentage of improvement in area of the ulcer. The authors reported that compared to conventional therapy, a highly significant improvement in the ulcer size was observed post-PRP therapy. Subjective improvement in pain associated with the ulcer was noted by all patients. They concluded that PRP is a safe nonsurgical procedure for treating chronic VLUs. Additional studies with larger sample size and longer follow-up periods are required to confirm or refute the findings. The findings are limited by lack of masking to the intervention allocation, which could have introduced biases and unclear randomization method.

A systematic review was performed by Miron et al. (2017) to analyze studies utilizing platelet-rich fibrin (PRF) for soft tissue regeneration, augmentation, and/or wound healing. Thirty-one clinical studies were included; a total of 8 reported the effects of

PRF in a RCT, with five additional studies (13 total) reporting appropriate controls. Fifty-eight percent of clinical studies reported positive wound healing events associated with the use of PRF. Twenty-seven of the 31 studies (87%) supported the use of PRF for soft tissue regeneration and wound healing for a variety of procedures in medicine and dentistry. The findings of the RCT were conflicting with a number of studies showing no benefit of PRP. While the authors concluded that the currently available literature supports soft tissue regeneration after soft tissue regenerative procedures utilizing PRF, they stated there is a lack of appropriate controls with which to conduct comparative analyses. The authors note that it is imperative that the next wave of research utilizing PRF as an adjunct to soft tissue regenerative therapies designs appropriate studies with necessary controls to further evaluate the regenerative potential of PRF for soft tissue wound healing.

The primary objective of a case series performed by Suthar et al. (2017) was to assess the efficacy of PRP in wound/ulcer healing by evaluating the percentage reduction in wound/ulcer size over the 24 weeks follow-up period by visual inspection. The secondary objectives included safety and feasibility of autologous PRP injections, time to wound/ulcer healing, improvement in pain or discomfort, and QOL. Twenty-four patients with non-healing ulcers of different etiologies were treated with a single dose of a combination of autologous PRP gel and subcutaneous injections of PRP in and around the wound periphery. All the patients showed signs of wound healing with reduction in wound size, and the mean time duration to ulcer healing was 8.2 weeks. Reduction in pain was observed in all the patients' post-treatment and the patients' QOL significantly improved. The authors concluded that PRP is a safe and effective treatment modality for chronic non-healing ulcers and recommended that further research with prospective RCTs on larger patient population are necessary to validate the results. Limitations include study design with no comparison group, small sample size, and short follow up.

In a meta-analysis, Martinez-Zapata et al. (2016) examined whether autologous PRP promotes the healing of chronic wounds. Ten RCTs that compared autologous PRP with placebo or alternative treatments for any type of chronic wound in adults were included (n=442). Four RCTs recruited people with a range of chronic wounds; three RCTs recruited people with VLU and three RCTs studied foot ulcers in people with diabetes. The median length of treatment was 12 weeks. The authors concluded that the results were non-conclusive as to whether autologous PRP improves the healing of chronic wounds generally compared with standard treatment. Autologous PRP may increase the healing of foot ulcers in people with diabetes compared with standard care, but it is unclear if autologous PRP has an effect on other types of chronic wounds. Three studies reported wound complications such as infection or dermatitis, but results showed no difference in the risk of AEs in people treated with PRP or standard care. These findings are based on low quality evidence due to the small number of studies and patients included, and their poor methodological quality.

Escamilla Cardenosa et al. (2017) conducted an unblinded randomized control trial to analyze the efficacy and safety of using platelet rich in growth factor (PRGF) as a local treatment for venous ulcers. The study included 58 patients (n=102 ulcers) who were randomly assigned to the study group (application of PRGF) or the control group (wet-to-dry dressing changes with saline) over a 24-week period. The average percentage healed area in the platelet rich plasma (PRP) group was 67.7% (vs 11.2% in the control group). PRP group members had greater reduction in pain. No adverse effects were observed in either of the two treatment groups. The authors concluded that the study results reveal that application of plasma rich in platelets is an effective and safe method to speed up healing and reduce pain in venous ulcers. The small sample size and lack of blinded assessment are factors compromising the quality of the evidence.

Carter et al. (2011) conducted an industry-sponsored systematic review and meta-analysis to evaluate the use platelet rich plasma (PRP) for the treatment of cutaneous wounds compared to standard wound care. Twenty-four studies met inclusion criteria. These studies included three systematic reviews, 12 randomized controlled trials, two prospective cohort studies, three prospective comparative studies and four retrospective reviews. The results of the meta-analysis suggested that PRP therapy can positively impact wound healing and associated factors such as pain and infection in cutaneous wounds. Limitations of the studies included heterogeneous patient populations, lack of long-term follow-up, pooling of data on different types of PFG products and regimens, and possible conflicts of interest. Several of the studies included in the meta-analysis had conflicting results.

National Institute for Health and Clinical Excellence (NICE)

In a diabetic inpatient clinical guideline, NICE recommends that autologous PRP gel should not be offered as treatment for diabetic foot problems unless part of a clinical trial (2016).

Clinical Practice Guidelines

American Academy of Orthopaedics (AAOS)

The AAOS indicated that guidelines and standards are in development on the conduct and reporting requirements associated with PRP as well as characterized and uncharacterized cell products. Those guidelines are expected to address candidate biologic targets and clinical outcome metrics including imaging metrics for treatment of chronic tendon injuries, acute ligament and muscle injuries, surgical soft tissue repairs, and KOA (2018).

Wound Healing Society

In guidelines for the treatment of venous ulcers, the Wound Healing Society states that cytokine growth factors [includes platelet-derived growth factor] have yet to be shown to demonstrate sufficient statistically significant results of effectiveness to recommend any of them for treatment of venous ulcers, although isolated reports suggest their potential usefulness (Level I) (Marston et al., 2016).

American College of Physicians (ACP)

ACP published 2015 guidelines on the treatment of pressure ulcers. The guidelines noted that “although low quality evidence suggests that dressings containing Platelet derived growth factors (PDGF) promote healing, ACP supports the use of other dressings such as hydrocolloid and foam dressings, which are effective at promoting healing and cost less than PDGF dressings.”

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Prolotherapy and platelet rich plasma therapy are procedures and, therefore, not subject to FDA regulation. However, any medical devices, drugs, biologics, or tests used as a part of these procedures may be subject to FDA regulation.

Two sclerosing agents have been approved by the FDA: sodium tetradecyl sulfate (Sotradecol®) and ethanolamine (Ethamolin®) for the treatment of varicose veins and esophageal varices. The agents used in the reviewed studies, such as dextrose and lidocaine, are approved for injection by the FDA but are not specifically approved for prolotherapy for joint and ligamentous injections, making such use off-label.

Another agent, sodium morrhuate (Scleromate®), is not currently listed as an approved sclerosing agent per the FDA.

NStride® (Zimmer Biomet), an autologous protein solution device, does not have FDA approval and is limited to investigational use. Additional information, under active ingredient name sodium tetradecyl sulfate and ethanolamine, is available at:

- <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=040541>
- <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>

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Policy History/Revision Information

Date	Summary of Changes
08/01/2021	<p>Template Update</p> <ul style="list-style-type: none"> Replaced content sub-heading titled “Professional Societies” with “Clinical Practice Guidelines” in <i>Clinical Evidence</i> section <p>Coverage Rationale</p> <ul style="list-style-type: none"> Added instruction to refer to the Medical Policy titled <i>Skin and Soft Tissue Substitutes (for Indiana Only)</i> for information regarding amnion-derived fluid injections/therapy; removed reference link to the Medical Policy titled <i>Bone or Soft Tissue Healing and Fusion Enhancement Products (for Indiana Only)</i> <p>Supporting Information</p> <ul style="list-style-type: none"> Archived previous policy version CS103IN.01

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This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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