Prolotherapy and Platelet Rich Plasma Therapies

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Instructions for Use

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Related Community Plan Policy

- Skin and Soft Tissue Substitutes

Commercial Policy

- Prolotherapy and Platelet Rich Plasma Therapies

Application

This Medical Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	None
Kentucky	Prolotherapy and Platelet Rich Plasma Therapies (for Kentucky Only)
Louisiana	Prolotherapy and Platelet Rich Plasma Therapies (for Louisiana Only)
Nebraska	Prolotherapy and Platelet Rich Plasma Therapies (for Nebraska Only)
New Jersey	Prolotherapy and Platelet Rich Plasma Therapies (for New Jersey Only)
Pennsylvania	Prolotherapy and Platelet Rich Plasma Therapies (for Pennsylvania Only)
Tennessee	Prolotherapy and Platelet Rich Plasma Therapies (for Tennessee Only)

Coverage Rationale

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

- Prolotherapy
- Platelet-Rich Plasma

Note: Refer to the Medical Policy titled Skin and Soft Tissue Substitutes 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

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HCPCS Code	Description
G0460	Autologous platelet rich plasma for nondiabetic chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment
G0465	Autologous platelet rich plasma (PRP) for diabetic chronic wounds/ulcers, using an FDA-cleared device (includes administration, dressings, phlebotomy, centrifugation, and all other preparatory procedures, per treatment)
M0076	Prolotherapy
P9020	Platelet-rich plasma, each unit

Description of Services

Prolotherapy (Proliferative Therapy), also known as Non-Surgical and Ligament and Tendon Reconstruction and Regenerative Joint Injection, is an orthopedic procedure that stimulates the body's healing processes to strengthen and repair injured and painful joints and connective tissue. Prolotherapy is injection of any substance (i.e., dextrose, saline, sarapin and procaine or lidocaine) that promotes growth of normal cells, tissues, or organs by stimulating the body's natural healing mechanisms to lay down new tissue in the weakened area. This is done by a very directed injection to the injury site, "tricking" the body to repair again. The mild inflammatory response which is created by the injection encourages growth of new, normal ligament or tendon fibers, resulting in a tightening of the weakened structure. Additional treatments repeat this process, allowing a gradual buildup of tissue to restore the original strength to the area. In the last several years newer formulas include Platelet Rich Plasma (PRP) and autologous (from the same person) adult stem cell sources, typically taken from bone marrow or adipose (fat) tissue. Each treating physician tailors the selection of the appropriate formula according to the patient's need. The three types of prolotherapy are: 1) Growth factor injection prolotherapy; 2) Growth factor stimulation prolotherapy; and 3) Inflammatory prolotherapy (AOAPRM, 2020; AAOM, 2020).

Platelet rich plasma (PRP) is an autologous blood preparation with a high platelet concentration and concentrated platelet-derived growth factors and other cytokines, which may be the primary contributors to the benefits of PRP therapy. Introducing PRP to tissues with low healing potential, these growth factors and cytokines may stimulate regeneration and promote tissue repair. PRP preparations are not standardized and exhibit wide variability in platelet and white blood cell concentrations. It is unclear how these variations in PRP composition may affect clinical outcomes (Hayes, 2021).

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)

Gul et al. (2020) performed a randomized controlled trial (RCT) to determine the efficacy of prolotherapy injections versus exercise in the treatment of osteoarthritis secondary to developmental dysplasia of the hip. The study consisted of 41 patients divided into two groups: treated with prolotherapy (n = 20) and exercise (control group; n = 21). Clinical outcomes were evaluated at baseline, 3 weeks, 3 months, 6 months, and a minimum of 1-year follow-up. Prolotherapy injection recipients outperformed exercise controls for Visual Analog Scale (VAS) pain change score at 6 months (−4.6 ±2.6 versus −2.8 ±2.5; p = 0.016), and 12 months (−4.5 ±2.4 versus −2.9 ±2.5; p = 0.017) and for HHS at 6 months (24.2 ±14.0 versus 14.8 ±12.4; p = 0.007) and 12 months (24.3 ±13.4 versus 16.5 ±11.3; p = 0.018). The authors concluded that prolotherapy is superior to exercise and may delay surgery. Limitations include a small sample size which makes it difficult to decide whether these conclusions can be generalized to a larger population. Well designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes. Further investigation is needed before clinical usefulness of this procedure is proven.

Sit et al. (2020) performed a single-center, parallel-group, blinded, randomized controlled trial (RCT) comparing the efficacy of intra-articular hypertonic dextrose prolotherapy versus normal saline injection for knee osteoarthritis (OA). A total of 76 patients were enrolled in the study and randomized into two groups of 38 each (prolotherapy: n = 38; normal saline: n = 38) over a 52-week period. Improvement in the DPT group compared with NS group on the primary outcome of WOMAC pain score at 52 weeks was noted. Beneficial effects were also demonstrated in WOMAC function, WOMAC composite, VAS pain intensity, and EuroQol-5D VAS and index scores. The composite WOMAC score improvement in the DPT group exceeded the minimal clinical important difference of 12 points at 52 weeks. No adverse events were reported. The authors concluded that use of intra-articular dextrose prolotherapy injections may be a safe and effective treatment for patients with KOA. Prolotherapy injections reduced pain and improved function and quality of life compared with blinded saline injections. Long-term follow-up and direct comparison with other injection therapies is needed to determine the clinical relevance of these findings.

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 3 months to 8 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, 1 single-arm study and 5 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 6 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 6 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)

Bae et al. (2020) performed a systematic review and meta-analysis to evaluate the effectiveness of prolotherapy compared with alternative treatment options for chronic musculoskeletal pain. Alternative options included steroid injections, saline injections, platelet-rich plasma (PRP) injections, exercise, and extracorporeal shock wave therapy. The review included ten randomized controlled trials, involving a total of 750 patients including a prolotherapy group and comparator groups using exercise, saline, PRP, and steroid injection. The primary outcome was pain score change during daily life. Pain scores from 6 months to 1 year after dextrose prolotherapy were reduced compared to saline injection (standardized mean difference [SMD] -0.44; 95% confidence interval [CI] -0.76 to -0.11, P = 0.008) and exercise (SMD -0.42; 95% CI -0.77 to -0.07, P = 0.02). There was no difference in pain scores for prolotherapy compared to PRP or steroid injection. The authors concluded that prolotherapy is a more effective treatment for chronic pain compared to saline injection or exercise. The available evidence is limited with overall poor-quality methodology and design, and diversity in reporting outcome measures. Therefore, no conclusions can be made regarding the relative efficacy, effectiveness, or safety of treatment.

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 1 month (immediately prior to the second injection), 2 months (a month after the second injection), and 6 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 6 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.

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).

Fingers

Jahangiri et al. (2014) 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 3 months. Pain intensity, hand function and the strength of lateral pinch grip were measured at the baseline and at 1, 2, and 6 months post-treatment. The two groups were comparable at 2 months, but significantly different at 1 month (better results for corticosteroid), and at 6 months (more favorable outcome for DX). After 6 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.

Lateral Epicondylosis (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 1- and 3-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 3-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 3rd-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 Baysian 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 a three-arm RCT. Twenty-six adults (32 elbows) with chronic LE for 3 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 AEs. 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).

Rotator Cuff (RC) Tendinopathies

Chang et al. (2021) performed a double-blinded, randomized controlled trial (RCT) to determine whether dextrose prolotherapy offers clinical benefits in patients with shoulder pain and bursitis. The study consisted of patients (n = 50) in an outpatient rehabilitation department of a single medical center with a diagnosis of shoulder pain and bursitis. Participants were randomly assigned to 15% dextrose injection (D15W) [Group 1], and placebo [Group 2] to receive either D15W or normal saline injection. The primary outcome was maximal pain relief while performing activities. The secondary outcomes included resting pain level, function, and disability assessment results, and ultrasonographic parameters. Participants were followed up for three months post treatment. Following observation of time effects for all outcome parameters minus elastographic parameters, the authors concluded that dextrose bursal injection was not associated with greater improvements in clinical outcomes compared to normal saline injection. Data, however, indicated a greater increase in tissue stiffness of the supraspinatus tendon with bursal dextrose injection. Limitations include small sample size and short duration of follow-up.

Giovannetti de Sanctis et al. (2021) performed a systematic review to compare injectable corticosteroids with other drugs in the treatment of partial rotator cuff tears and the effectiveness in terms of pain and shoulder functionality. Nine prospective, randomized controlled trials were included in the review with a total of 494 patients. Of the 494 patients, 232 underwent corticosteroid infiltration, 90 with platelet-rich plasma (PRP), 47 with glucose prolotherapy, and 125 underwent an infiltrative cycle with lidocaine or other local anesthetic as placebo. Corticosteroid Visual Analog Scale (VAS) scores: Pre-op: 5.6 ±0.66; short-term: 2.73 ±1.08; mid-term: 2.93 ±0.89; and long-term: 4.09 ± 0.38. PRP VAS scores: Pre-op: 6.2 ±1.2; short-term: 3.51 ±1.86; mid-term: 3.9; and long-term: 2.04 ±0.76. Prolotherapy VAS scores: Pre-op: 5.3 ±0.81; short-term: 4.37 ±1.16; mid-term: 4.27 ±1.36; and long-term: 3.1 ±1.52. The authors concluded that all treatments showed improvement compared to baseline, however, there were no differences in terms of pain control. PRP was better in terms of shoulder function. Prolotherapy could not be analyzed due to the small number of studies. Limitations include a small sample size which makes it difficult to decide whether these conclusions can be generalized to a larger population. The findings of this study need to be validated by well-designed studies and further investigation is needed before clinical usefulness of these procedures is proven.

Nasiri et al. (2021) performed a randomized controlled trial (RCT) to compare the effectiveness of prolotherapy injection(s) with corticosteroid injection(s) in patients with rotator cuff dysfunction. Thirty-three patients were randomly allocated in two groups: prolotherapy group: n = 17 and corticosteroid group: n = 16. Visual analog scale (VAS) and Shoulder Pain and Disability Index (SPADI) were evaluated for both groups at baseline, 3 and 12 weeks after injections. Improvement in VAS and SPADI scores in 3 and 12 weeks after injections compared with preinjection times was shown in both groups. The authors concluded that both therapies, when administered with a home exercise program, are effective in the management of pain related to rotator cuff dysfunction. However, due to side effects from corticosteroids, prolotherapy is the suggested alternative. Limitations include small sample size and short duration of follow-up. Well designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

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 > 6 months were divided into 2 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 3 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 Rotator 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 9 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. seven [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 3 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 1 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 1-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

Bisciotti et al. (2020) performed a systematic review of conservative treatment for long standing adductor-related groin pain syndrome (GPS). The review consisted of 19 studies and 440 patients. Seven types of therapeutic interventions were reviewed including compression clothing therapy, manual therapy combined with strengthening exercise, prolotherapy, corticoid injection, platelet-rich plasma (PRP) therapy, intra-tissue percutaneous electrolysis, and pulse-dose radiofrequency. Prolotherapy, described in two studies, was performed on 24 patients with long-standing GPS. Follow-up assessments were completed at 6 months and 32 months. Visual Analog Scale (VAS) was assessed for pain during sports activity, and Nirschl Pain Phase Scale (NPPS) was assessed for functional impairment caused by pain. Thirty-two months after therapy, VAS scores improved from 6.3+/-1.4 to 1.0+/2.4 ($p < .001$), and NPPS scores 5.3+/-0.7 to 0.8+/-1.9 ($p < .001$). Only one study reviewed platelet rich plasma for GPS with a total of 41patients. The authors concluded that strength of evidence for prolotherapy is a moderate level (C), and a recommendation of conflicting strength (D) for PRP. The available data are relatively weak and inconclusive and derived primarily from uncontrolled or poorly controlled studies. Well designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

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 2 months. Average number of treatments received was 3 (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

Sit et al. (2021) performed a systematic review of randomized controlled trials (RCTs) to determine the efficacy of hypertonic dextrose prolotherapy (DPT) for temporomandibular joint (TMJ) disorders. Ten full-text RCTs were included in the study with sample sizes ranging from 12 to 72, with a total of 336 patients. The study period ranged from four weeks to 1-year post enrollment. The primary outcome was pain intensity. Secondary outcomes included maximum interincisal mouth opening (MIO) and disability score. Meta-analysis of five RCTs revealed decreased TMJ pain compared to placebo (Standardized Mean Difference: -0.76; 95% CI -1.19 to -0.32, I^2 = 0%). No statistical differences were noted for changes in maximum inter-incisal mouth opening (MIO) and functional scores. Cochrane risk of bias (RoB) assessment tool 2 revealed “some” to “high” risk of bias. The authors concluded that prolotherapy had a positive effect on TMJ pain compared to placebo injections. The significance of this study is limited by small sample size and short follow-up period.

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 1 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 3 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 3 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 RCT 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 (2014) 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 6 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 6 months, was 41/45 (91%). Of the 41 rehabilitated patients, 26 (63%) required a single injection, 11 (27%) had 2 treatments, and 4 (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.

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 larger 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 comparation 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)

An ECRI Clinical Evidence Assessment (2020) report on platelet-rich plasma therapy (PRP) for knee osteoarthritis (KOA) was published following systematic review and meta-analysis. The report concentrated on PRP's effectiveness and safety compared with those of hyaluronic acid (HA) and corticosteroids. Pain relief, knee function, and adverse events were assessed. Pain relief: meta-analysis of data from 30 RCTs reported that PRP yielded better pain score improvements than HA, corticosteroids, and placebo at 3, 6, and 12 months. Knee function: PRP had better Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores than HA, corticosteroids, and placebo at 3, 6, and 12 months. No serious AEs occurred. More complications with PRP alone than with PRP plus HA were reported as well as more local AEs with leukocyte-rich PRP. The authors concluded that there was insufficient comparative data and evidence is inconclusive. Limitations included varied PRP preparation, injection methods, and number of injections. Time between injections varied (weekly to monthly). Analysis was limited to 3-, 6-, and 12-month outcomes; data were not available for longer follow-up. Other limitations within the evidence base included lack of blinding in some studies, need for long-term follow-up, primarily single-center focus, and no reporting on a treatment's ability to postpone knee replacement (ECRI, 2020).

Trams et al. (2020) performed a systematic review and meta-analysis to evaluate platelet-rich plasma (PRP) efficacy in the recovery of knee disorders and during knee surgery. A total of 83 clinical studies with 5,323 patients were included in this review. Mean follow-up period was 12 months (ranging from 10 days to 3 years) and the mean number of patients included was 62 (ranging from 20 to 315). The study included patellar tendinitis (4 studies/137 patients), muscle injuries around the knee (4 studies/224 patients), high tibial osteotomy (HTO) (2 randomized controlled trials (RCTs)/80 patients), total knee arthroplasty (TKA) (6 RCTs/621 patients), arthroscopy (4 RCTs/199 patients), anterior cruciate ligament reconstruction (ACL) (16 RCTs/740 patients), meniscal repair (2 RCTs/5 non-RCTs), and osteoarthritis (38 studies/2,962 patients). In total, seven areas of meta-analysis reported a positive effect of PRP. Among them, 10 sub-analyses revealed differences in favor of PRP when compared to the control groups ($p < 0.05$). The study showed positive effects of PRP, both on the recovery of knee disorders and during

knee surgery. The authors concluded that PRP improves outcomes in osteoarthritis applications, arthroscopic treatment of cartilage degeneration. meniscus healing, faster return to sport after muscle injuries, and reduces blood loss after total knee replacement. Limitations include the need for further prospective and randomized studies with a higher number of subjects with lower biases.

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 1 of 3 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 1 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 1 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 (2019) 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 5 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.

Annaniemi et al. (2018) conducted a retrospective study with 190 participants to compare PRP versus visco supplements 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, 6 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 systematic literature review and meta-analysis if possible were performed by Laudy et al. (2015) 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.

A 2018 Hayes comparative effectiveness review of platelet-rich plasma (PRP) for knee osteoarthritis (KOA) stated that intra-articular (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 6 months, but that IA-PRP may associated with better outcomes at 1-year follow-up. If IA-PRP can be conclusively shown to provide benefits over IA-HA at 1 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). The 2021 annual review identified five new key RCT studies. The evidence remains unchanged (Hayes, 2021). (Author Di Martino A et al. (2018) previously cited in this policy, is included in this review).

Hip Osteoarthritis (HOA)

Gazendam et al. (2020) performed a systematic review and network meta-analysis of randomized controlled trials (RCTs) to compare the efficacy of various intra-articular (IA) injectable treatments in treating hip osteoarthritis at up to 6 months of follow-up. The intra-articular injectables included: corticosteroids (CCS), hyaluronic acid (HA), and platelet-rich plasma (PRP). Eleven studies which included 1,353 patients were reviewed. Treatment groups included IA placebo injection with or without local anesthetic (n = 314), HA (n = 596), CCS (n = 237), PRP (n = 155), a combined HA and PRP injection (HA+PRP, n = 31), and a control group with no injection (n = 20). There was high risk of bias due to deviations from the intended interventions and missing outcome data. Results revealed that none of the hip injections demonstrated improvement in pain or function scores compared with saline hip injection at 2-4 months, and 6 months except for HA+PRP and the control group. The authors concluded that no treatment was found to have a clinically meaningful benefit beyond placebo. Limitations included small sample size. Well designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

A 2019 Hayes Health Technology Assessment 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 1 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 1 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 (Hayes, 2019). The October 19, 2020 annual review identified four new abstracts which included one randomized controlled trial and three systematic reviews and meta-analyses. The evidence remains unchanged (Hayes, 2020). (Authors Dallari et al. (2016) and Battaglia et al. (2013) which were previously cited in this policy are included in this report).

Dold and colleagues (2014) 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.

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

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.

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 3 and 12 months, whereas 2 of 4 studies in the lateral epicondylar section showed improvements in pain and disability at 6 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.

Knee

An ECRI Clinical Evidence Assessment (2021) on platelet-rich plasma (PRP) for patellar tendinopathy assessed one systematic review with randomized controlled trials (RCTs) and 2 RCTs not included in the systematic review. PRP safety and effectiveness was compared with alternative therapies. Primary outcomes were Pain, function, and adverse events. The authors reported no significant differences in PRP-treated patients compared with saline-treated patients after 1 year and with dry needling patients after 6 months. PRP-treated patients had greater pain relief than those undergoing extracorporeal shockwave therapy at 1 year and high-volume-image-guided saline injections at 6 months. A meta-analysis of all four RCTs found no significant differences for pain. PRP with autologous expanded bone marrow mesenchymal stem cells revealed pain improved in both groups after 6 months, with no differences between groups. The authors reported no significant differences in function, measured using Victorian Institute of Sports Assessment-Patella (VISA-P) scores in PRP-treated patients compared with saline-treated patients after 1 year and with dry needling patients after 6 months. Two other RCTs reported PRP-treated patients had greater function improvement compared with patients undergoing extracorporeal shockwave therapy at 1 year and high-volume-image-guided saline injections at 6 months. A meta-analysis of all 4 RCTs found no significant differences in VISA-P. No adverse events were reported. The authors concluded that PRP injections may improve pain and function in individuals with patellar tendinopathy based on inconclusive evidence. Limitations include small study size, short follow-up period and potential bias risks. Larger RCTs with longer follow-up comparing PRP with other treatments treating patellar tendinopathy and reporting patient-oriented outcomes are needed (ECRI, 2021).

Lopez-Royo et al. (2020) performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to determine the effectiveness of minimally invasive techniques (MIT) in patients with patellar tendinopathy. The study included a total of 10 RCTs and 326 patients. Five RCTs were included in the meta-analysis. The primary outcome was functionality using the VISA-p questionnaire. Secondary outcome was focused on pain. The study revealed MIT including PRP, skin-derived tenocyte-like cells, and dry needling combined with exercise lasting over 6 weeks obtained better results in pain and functionality than other short-term treatments. Long term results revealed that skin-derived tenocyte-like cells, and dry needling are more effective than PRP. The authors conclude that while PRP was effective at post-treatment, the improvements were not maintained over time and may have secondary effects. In addition, the authors concluded that it will be necessary to develop RCTs analyzing not only the effect but also comparing efficacy between different MITs. Limitations include the short-term follow-up which did not allow for assessment of intermediate and long-term outcomes. Further investigation is needed before clinical usefulness of this procedure is proven.

A 2017 Hayes comparative effectiveness review on PRP for treatment of ligament injuries and tendinopathies of the knee identified one 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. (Author Dragoo et al. (2014) which was previously cited in this policy, is included in this review). The 2020 annual review identified one new key RCT study. The evidence remains unchanged (Hayes, 2020).

Achilles Tendinitis (AT) and Plantar Fasciitis (PF)

Fei et al. (2021) performed a systematic review and meta-analysis to compare the effectiveness of platelet-rich plasma (PRP) versus steroid injection to relieve pain and improve foot and ankle function in patients with plantar fasciitis (PF). The study included a total of 12 randomized controlled trials (RCTs) involving 653 patients performed between 2012 and 2019. The primary goals were pain relief and improved function. Visual Analog Scale (VAS) of the PRP group was lower than that of the steroid group at 6 months ($p = 0.02$), 1 year ($p = 0.02$), and 1.5 years ($p < 0.00001$) follow-up. American Orthopedic Foot and Ankle Society (AOFAS) scores of the PRP group were higher than that of the steroid group at 1 year ($p = 0.005$) follow-up. The authors concluded that PRP injection is more effective in relieving pain and improving foot and ankle function compared to steroid injection at mid-term follow-up. Limitations include small sample size and short duration of follow-up, high heterogeneity between studies, and subjective outcome measures.

In a 2019 Hayes comparative effectiveness review the effectiveness of PRP for treatment of conditions of the Achilles tendon and plantar fascia was assessed based on measures of functional improvement and pain relief, along with rates of adverse events. The report 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. The authors concluded 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. A 2021 annual review identified seven new RCTs. The studies were low quality of evidence and did not change the previous conclusion (Hayes, 2021). (Authors Usuelli et al. (2018), Boesen et al. (2017), Gogna et al. (2016), Jain et al. (2015) which were previously cited in this policy, are included in this Hayes report).

Shoulder

An ECRI Health Technology Assessment (2020) on platelet-rich plasma to aid healing after rotator cuff surgery included one systematic review (n = 781) and two randomized controlled trials (RCTs) (n = 87) to compare rotator cuff surgery with PRP and rotator cuff surgery without PRP. Pain and function were assessed. No studies reported on adverse events, re-treatment rates, or symptom resolution. A single study addressing PRP use after rotator cuff surgery does not support its use. Findings revealed surgery with PRP reduced incomplete tendon healing (measured via imaging) compared with no PRP One RCT reported that patients treated with or without PRP did not differ in shoulder functional status. One RCT reported that Constant scores and pain (VAS) did not differ statistically between surgery with delayed PRP treatment (10- to 14-days post-surgery) and surgery without PRP. The authors concluded that rotator cuff surgery plus PRP yielded small incremental benefits in shoulder function and pain compared with surgery without PRP but are too small to be clinically significant. Limitations include small sample size and moderate risk of bias due to single-center focus (ECRI, 2020).

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 2 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. (Authors Ebert et al. (2017), Pandey et al. (2016), Flury et al. (2016), Verhaegen et al (2016), Carr et al. (2015) which were previously cited in this policy, are included in this review). A 2020 annual review identified two key RCTs. The evidence remains unchanged (Hayes, 2020).

Lateral Epicondylitis (LE)

An ECRI Clinical Evidence Assessment (2021) on platelet-rich plasma therapy (PRP) for lateral epicondylitis (LE) included 2 systematic reviews that included 25 RCTs and 5 additional randomized controlled trials (n = 2,033) to compare PRP with alternative treatments (i.e., saline or corticosteroid injections) or placebo. Pain, function, and adverse events were assessed. Findings revealed that saline injection, PRP injection, and steroid injections all provided comparable pain relief and functional improvement up to 3-months post-treatment. By 3-months, however, PRP provided better pain relief than steroid injection. PRP combined with surgery revealed improved pain in both groups up to 1-year post-treatment. At 24-weeks post-treatment, however, PRP provided better pain control compared to physical therapy. Transient post-injection pain was the most reported adverse reaction and no serious adverse events. The authors concluded that evidence is inconclusive with mixed results for PRP as treatment of LE. Limitations included wide variations in how PRP is prepared and used as well as varied patient characteristics and symptoms of LE (ECRI, 2021).

In a 2017 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 6 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. (Author Schöffl et al. (2017) which was previously cited in this policy, is included in this review). The 2021 annual review identified three new RCTs. The evidence remains unchanged (Hayes, 2021).

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 2 and 4 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.

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 6 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 randomized study by Wu et al. (2017) 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 1 week, and at 1-, 2-, 3-, and 6-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 1 month, but only 50% and 20%, respectively after 6 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.

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 2 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 6 and 12 weeks as compared to Group S. The efficacy of steroid injection was reduced to only 25% at 3 months in Group S, while it was 90% in Group P. Patients receiving PRP also showed a reduction of VAS ≥ 50% from baseline when other factors were controlled. The MODQ and SF-12 scores were improved initially for up to 4 weeks but deteriorated further at 3 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 included 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 (≥ 6 months), moderate-to-severe lumbar discogenic pain that was unresponsive to conservative treatment were randomized to receive intradiscal 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 1 week, 4 weeks, 8 weeks, 6 months, and 1 year. Participants in the control group who did not improve at 8 weeks were offered the option to receive PRP and subsequently followed. Over 8 weeks of follow-up, there were statistically significant improvements in participants who received intradiscal 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 intradiscal PRP injection resulted in significant improvements in function, pain, and patient satisfaction scores over 8 weeks compared with controls. Those who received PRP maintained significant improvements functional scores through at least 1 year of follow-up. Study limitation cited was the very limited follow up time of only 8 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 intradiscal treatment and the ideal cellular characteristics of the intradiscal PRP injectate.

Wounds

A 2021 Hayes Health Technology Assessment report focused on the efficacy and safety of platelet-rich plasma (PRP) for treatment of venous leg ulcers (VLUs). Individuals enrolled in the reviewed studies were adult men and women who had VLUs that had not responded adequately to conventional treatment with an average VLU duration range from 3 months to 6 years. The studies included were eight randomized controlled trials (RCTs) and one comparative cohort study that evaluated PRP for treatment of VLUs. PRP was administered as either a gel, topical liquid, or injected liquid in conjunction with standard wound care, and compared with standard wound care alone. Findings from seven studies suggested that PRP may significantly improve healing of VLUs, one study found no benefit and the other study did not perform between-group statistical analyses. Six studies reported that no complications occurred. Two studies reported the following complications: cellulitis prompting antibiotic treatment (8%), superficial minute ulceration (4%), and pain (unidentified number of patients). No deaths related to PRP treatment were identified. There was variation in protocols for preparation and administration of PRP, small treatment groups, heterogenous study populations, and variability in number of PRP treatment sessions. The authors concluded that the results of the reviewed studies suggested that PRP is reasonably safe for treatment of VLUs. Additional RCTs with large study populations and appropriate controls to avoid potential bias of results are needed to confirm that PRP improves VLU healing and to determine the optimal method for administration of PRP (Hayes, 2021). (Authors Escamilla Cardenosa et al. (2017) and Moneib et al.(2018) which were previously cited in this policy are included in this review).

An ECRI Clinical Evidence Assessment (2020) on platelet-rich plasma (PRP) therapy for chronic wounds included two systematic reviews (SRs) and eight randomized controlled trials (RCTs). The efficacy of PRP treatment for chronic wounds including diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), and pressure ulcers (PUs) was evaluated. Wound healing rates, wound size reduction rates, and adverse events were assessed. The studies reported higher complete DFU wound healing (12 weeks) and shorter healing times (8 weeks) with PRP compared to standard treatment. VLU wound healing and area reduction revealed no differences statistically between PRP and standard treatment. One RCT revealed PU scale scores for exudate and area reduction were better with PRP than standard treatment at 2-months. The authors concluded that the quality of most studies was very low because of high risk of bias and there was a lack of a standard procedure for producing PRP, differences in platelet concentrations, frequency of PRP application to the wound, and follow-up times (ECRI, 2020).

Qu et al. (2020) completed a systematic review and meta-analysis to evaluate the efficacy of autologous platelet-rich plasma (PRP) in individuals with lower extremity diabetic ulcers (DUs), lower extremity venous ulcers (VUs), and pressure ulcers (PUs). A total of 27 (22 randomized and 5 comparative observational) studies with 1,796 patients were included in the review: DUs = 15; VUs = 11; and PUs = 2. Follow-up post-treatment ranged from no follow-up to 11 months. PRP therapy increased healing and complete wound closure in lower extremity DUs compared to treatment without PRP (Relative Risk (RR): 1.20; 97% CI: 1.09 to 1.32, moderate strength of evidence (SOE)). PRP therapy also shortened the time to complete wound closure and reduced wound area and depth (low SOE). There were no significant changes found in terms of wound infection, amputation, wound recurrence, or hospitalization. Evidence related to VUs and PUs was insufficient to estimate effect on critical outcomes. There was no statistically significant difference in death, total adverse events, or serious adverse events between PRP and management without PRP. The authors concluded that autologous PRP based on moderate SOE increases complete wound closure/healing, and low SOE shortens healing time and reduces wound size in patients with lower extremity DUs. The evidence is insufficient regarding VUs and PUs. Limitations included a lack of standard reporting of PRP formulation techniques, PRP concentration, formulation and volume used, lower extremity DU off-loading procedures and periprocedural restrictions, and patient recruiting methods. In addition, the available data are relatively weak and inconclusive and derived primarily from uncontrolled or poorly controlled studies with significant methodological flaws.

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 eight 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 of 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 VLUs 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.

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.

Clinical Practice Guidelines

American Academy of Orthopaedics (AAOS)

A 2021 AAOS clinical practice guideline on management of osteoarthritis of the knee states that platelet-rich plasma (PRP) may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee. This recommendation is based on evidence from one or more low quality studies with consistent findings or evidence from a single moderate quality study recommending for or against the intervention. AAOS recommends that future research in this area should include detailed osteoarthritis characterization including sub-group analyses and osteoarthrosis severity stratification (AAOS, 2021).

A 2020 AAOS clinical practice guideline on management of glenohumeral joint osteoarthritis is based on a systematic review of published studies. There is lack of evidence of the utilization of platelet rich plasma in the treatment of osteoarthritis of the glenohumeral joint and it cannot be recommended. AAOS concluded that better standardization and high-quality evidence from clinical trials is needed to provide definitive evidence on the efficacy of biologics in glenohumeral OA (AAOS, 2020).

A 2019 AAOS clinical practice guideline on the management of rotator cuff injuries makes the following recommendations:

- Limited evidence does not support the routine use of platelet rich plasma for the treatment of rotator cuff tendinopathy or partial tears
- Strong evidence does not support biological augmentation of rotator cuff repair with platelet-derived products on improving patient reported outcomes; however, limited evidence supports the use of liquid platelet rich plasma in the context of decreasing re-tear rates
- Lack of supporting evidence does not support the routine use of platelet rich plasma in the non-operative management of full-thickness rotator cuff tears (AAOS, 2019)

American Association of Hip and Knee Surgeons

The American Association of Hip and Knee Surgeons 2019 position statement on biologics for advanced hip and knee arthritis stated "It is our position that biologic therapies, including stem cell and PRP injections, cannot currently be recommended for the treatment of advanced hip or knee arthritis. With unproven benefits, high out-of-pocket costs for patients, and clear safety concerns, we do not support the routine clinical use of these therapies. While we do recognize the potential benefit of biologic therapies, we encourage rigorous, well-designed clinical trials to establish the safety, efficacy, and cost-effectiveness of these potential treatments prior to widespread adoption" (Browne et al., 2019).

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."

American College of Rheumatology

A 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee made the following recommendations:

- Prolotherapy is conditionally recommended against in patients with knee and/or hip OA
- Platelet-rich plasma treatment is strongly recommended against in patients with knee and/or hip OA

(Kolasinski et al., 2019)

American Society of Interventional Pain Physicians (ASIPP)

A 2019 ASIPP guideline on the management of low back pain stated that after review of evidence there is Level III evidence for intradiscal injections of PRP, whereas the evidence is considered Level IV for lumbar facet joint, lumbar epidural, and sacroiliac joint injections of PRP, (on a scale of Level I through V) (Navanit et al., 2019).

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.

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, updated 2019).

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.

Veterans Affairs/Department of Defense (VA/DoD)

The VA/DoD 2020 clinical practice guideline for the non-surgical management of hip and knee osteoarthritis made the following statement: There is insufficient evidence to recommend for or against platelet-rich plasma injections for the treatment of osteoarthritis of the hip or knee. The quality of evidence reviewed was very low given the serious inconsistency and imprecision with study designs, lack of standardization (e.g., dose, frequency, preparation technique), and outcome measures.

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).

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.

For additional information, search product codes KSS, ORG, or JQC at the following website: 510(k) Premarket Notification (fda.gov). (Accessed October 20, 2021)

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.

References

American Academy of Orthopaedic Surgeons. Management of Glenohumeral Joint Osteoarthritis Evidence-Based Clinical Practice Guideline. Published March 23, 2020.

American Academy of Orthopaedic Surgeons. Management of Osteoarthritis of the Knee (NonArthroplasty) Evidence-Based Clinical Practice Guideline. August 31, 2021. https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf. Accessed November 10, 2021.

American Academy of Orthopaedic Surgeons. Management of Rotator Cuff Injuries Evidence Based Clinical Practice Guideline. Published March 11, 2019.

American Academy/Association of Orthopedic Medicine (AAOM). Prolotherapy injections for pain. 2020. https://www.aaomed.org/Prolotherapy-injections-for-pain. Accessed October 26, 2021.

American College of Physicians. Treatment of Pressure Ulcers: A Clinical Practice Guideline 2015.

American Osteopathic Association of Prolotherapy Regenerative Medicine (AOAPRM). What is Prolotherapy? WHAT IS PROLOTHERAPY? The American Osteopathic Association of Prolotherapy Regenerative Medicine (prolotherapycollege.org). Accessed October 26, 2021.

Annaniemi JA, Pere J, Giordano S. Platelet-rich plasma versus hyaluronic acid injections for knee osteoarthritis: A propensity-score analysis. Scand J Surg. 2018 Nov 25:1457496918812218.

Bae G, Kim S, Lee S, et al. Prolotherapy for the patients with chronic musculoskeletal pain: systematic review and meta-analysis. Anesth Pain Med (Seoul). 2021 Jan;16(1):81-95.

Balasubramaniam U, Dissanayake R, Annabell L. Efficacy of platelet-rich plasma injections in pain associated with chronic tendinopathy: A systematic review. Phys Sportsmed. 2015.

Battaglia M, Guaraldi F, Vannini F, et al. Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics. 2013 Dec;36(12):e1501-8.

Bayat M, Raeissadat SA, Mortazavian Babaki M, Rahimi-Dehgolan S. Is dextrose prolotherapy superior to corticosteroid injection in patients with chroniclateral epicondylitis?: a randomized clinical trial. Orthop Res Rev. 2019;11:167-175. Published 2019 Nov 5.

Bertrand H, Reeves KD, Bennett CJ, et al. Dextrose prolotherapy versus control injections in painful rotator cuff tendinopathy. Arch Phys Med Rehabil. 2016; 97(1):17-25.

Bisciotti GN, Chamari K, Cena E, et al. The conservative treatment of longstanding adductor-related groin pain syndrome: a critical and systematic review. Biol Sport. 2021 Mar;38(1):45-63.

Boesen AP, Hansen R, Boesen MI, et al. Effect of high-volume injection, platelet-rich plasma, and sham treatment in chronic midportion Achilles tendinopathy: a randomized double-blinded prospective study. Am J Sports Med. 2017 Jul;45(9):2034-2043.

Browne JA, Nho SJ, Goodman SB, Della Valle CJ. American Association of Hip and Knee Surgeons, Hip Society, and Knee Society Position Statement on biologics for advanced hip and knee arthritis. J Arthroplasty. 2019 Jun;34(6):1051-1052.

Carr AJ, Murphy R, Dakin SG, et al. Platelet-rich plasma injection with arthroscopic acromioplasty for chronic rotator cuff tendinopathy: A randomized controlled trial. Am J Sports Med 2015;43(12):2891-7.

Carter MJ, Fylling CP, Parnell LK. Use of platelet rich plasma gel on wound healing: a systematic review and meta-analysis. Eplasty. 2011;11:e38.

Chang YJ, Chang FH, Hou PH, et al. Effects of hyperosmolar dextrose injection in patients with rotator cuff disease and bursitis: a randomized controlled trial. Arch Phys Med Rehabil. 2021 Feb;102(2):245-250.

Chou R, Atlas SJ, Stanos SP, et al. Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline. Spine (Phila Pa 1976). 2009 May 1;34(10):1078-93.

Cömert Kiliç S, Güngörmüş M. Is dextrose prolotherapy superior to placebo for the treatment of temporomandibular joint hypermobility? A randomized clinical trial. Int J Oral Maxillofac Surg. 2016 Jul;45(7):813-9.

Dagenais S, Mayer J, Haldeman S, et al. Evidence-informed management of chronic low back pain with prolotherapy. Spine J. 2008 Jan-Feb;8(1):203-12.

Dagenais S, Yelland MJ, Del Mar C, et al. Prolotherapy injections for chronic low-back pain. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD004059.

Dallari D, Stagni C, Rani N, et al. Ultrasound-guided injection of platelet-rich plasma and hyaluronic acid, separately and in combination, for hip osteoarthritis: a randomized controlled study. Am J Sports Med. 2016 Mar;44(3):664-71.

Delanois RE, Etcheson JI, Sodhi N, et al. Biologic therapies for the treatment of knee osteoarthritis. J Arthroplasty. 2019 Apr;34(4):801-813.

Di Martino A, Di Matteo B, Papio T, et al. Platelet-rich plasma versus hyaluronic acid injections for the treatment of knee osteoarthritis: Results at 5 years of a double-blind, randomized controlled trial. Am J Sports Med. 2018 Dec 13:363546518814532.

Dold AP, Zywiel MG, Taylor DW, et al. Platelet-rich plasma in the management of articular cartilage pathology: a systematic review. Clin J Sport Med. 2014 Jan;24(1):31-43.

Dong W, Goost H, Lin X, et al. Injection therapies for lateral epicondylalgia: a systematic review and Bayesian network meta-analysis. Br J Sports Med. 2015 Sep 21. pii: bjsports-2014-094387.

Dragoo JL, Wasterlain AS, Braun HJ, et al. Platelet-rich plasma as a treatment for patellar tendinopathy: a double-blind, randomized controlled trial. Am J Sports Med. 2014 Mar;42(3):610-8.

ECRI. Platelet-rich plasma therapy for chronic wounds. Plymouth Meeting (PA): ECRI; 2020 Sep 22. (Clinical Evidence Assessment).

ECRI. Platelet-rich plasma for knee osteoarthritis. Plymouth Meeting (PA): ECRI; 2020 Dec 15. (Clinical Evidence Assessment).

ECRI. Platelet-rich plasma therapy for lateral epicondylitis. Plymouth Meeting (PA): ECRI; 2021 Apr. (Clinical Evidence Assessment).

ECRI. Platelet-rich plasma therapy for patellar tendinopathy. Plymouth Meeting (PA): ECRI; 2021 May. (Clinical Evidence Assessment).

ECRI Institute. Platelet-rich plasma to aid healing after rotator cuff surgery. Plymouth Meeting (PA): ECRI Institute; 2020 Feb 20. (Custom Rapid Responses).

Ebert JR, Wang A, Smith A, et al. A midterm evaluation of postoperative platelet-rich plasma injections on arthroscopic supraspinatus repair: a randomized controlled trial. Am J Sports Med. 2017 Nov;45(13):2965-2974.

Escamilla Cardenosa M, Dominguez-MaldonadoG, Cordoba-Fernandez A. Efficacy and safety of the use of platelet-rich plasma to manage venous ulcers. Journal of Tissue Viability. 2017 May;26(2):138-43.

Fei X, Lang L, Lingjiao H, et al. Platelet-rich plasma has better mid-term clinical results than traditional steroid injection for plantar fasciitis: a systematic review and meta-analysis. Orthop Traumatol Surg Res. 2021 Oct;107(6):103007.

Flury M, Rickenbacher D, Schwyzer HK, et al. Does pure platelet-rich plasma affect postoperative clinical outcomes after arthroscopic rotator cuff repair? A randomized controlled trial. Am J Sports Med. 2016 Aug;44(8):2136-46.

Gazendam A, Ekhtiari S, Bozzo A, et al. Intra-articular saline injection is as effective as corticosteroids, platelet-rich plasma and hyaluronic acid for hip osteoarthritis pain: a systematic review and network meta-analysis of randomised controlled trials. Br J Sports Med. 2021 Mar;55(5):256-261.

Giovannetti de Sanctis E, Franceschetti E, De Dona F, et al. The efficacy of injections for partial rotator cuff tears: a systematic review. J Clin Med. 2020 Dec 25;10(1):51.

Görmeli G, Karakaplan M, Görmeli CA, et al. Clinical effects of platelet-rich plasma and hyaluronic acid as an additional therapy for talar osteochondral lesions treated with microfracture surgery: a prospective randomized clinical trial. Foot Ankle Int. 2015 Aug;36(8):891-900.

Gogna P, Gaba S, Mukhopadhyay R, et al. Plantar fasciitis: a randomized comparative study of platelet rich plasma and low dose radiation in sportspersons. Foot (Edinb). 2016 Aug;28:16-19.

Gül D, Orsçelik A, & Akpancar S. Treatment of osteoarthritis secondary to developmental dysplasia of the hip with prolotherapy injection versus a supervised progressive exercise control. Med Sci Monit. 2020 Feb 11;26:e919166.

Hayes, Inc., Health Technology Assessment. Platelet-rich plasma for wound treatment in venous leg ulcers. Lansdale, PA: Hayes, Inc; October 26, 2021.

Hayes, Inc., Medical Technology Directory. Comparative Effectiveness Review of Platelet-Rich Plasma for Knee Osteoarthritis: A Review of Reviews. Lansdale, PA. Hayes, Inc. December 2017. Updated March 19, 2021.

Hayes, Inc., Medical Technology Directory. Comparative Effectiveness Review of Platelet-Rich Plasma for Tendinopathies or Ligament Injuries of the Knee. Lansdale, PA. Hayes, Inc. December 2017 Updated December 21, 2020.

Hayes, Inc., Medical Technology Directory. Comparative Effectiveness Review of Platelet-Rich Plasma for Rotator Cuff Repairs, Tendinopathies, and Related Conditions: A Review of Reviews. Lansdale, PA. Hayes, Inc. September 15, 2020.

Hayes, Inc., Medical Technology Directory. Platelet-Rich Plasma for Hip Osteoarthritis. Lansdale, PA: Hayes, Inc.; June 14, 2019. Updated October 19, 2020.

Hayes, Inc., Medical Technology Directory. Platelet-Rich Plasma for Treatment of Conditions of the Achilles Tendon and Plantar Fascia. Lansdale, PA: Hayes, Inc.; June 1, 2020. Updated May 12, 2021.

Hayes, Inc., Medical Technology Directory. Platelet-Rich Plasma for Treatment of Lateral Epicondylitis. Lansdale, PA: Hayes, Inc.; December 8, 2017. Updated March 30, 2021.

Hung CY, Hsiao MY, Chang KV, et al. Comparative effectiveness of dextrose prolotherapy versus control injections and exercise in the management of osteoarthritis pain: a systematic review and meta-analysis. J Pain Res. 2016;9:847-857.

Jahangiri A, Moghaddam FR, Najafi S. Hypertonic dextrose versus corticosteroid local injection for the treatment of osteoarthritis in the first carpometacarpal joint: a double-blind randomized clinical trial. J Orthop Sci. 2014 Sep;19(5):737-43.

Jain K, Murphy PN, Clough TM. Platelet rich plasma versus corticosteroid injection for plantar fasciitis: a comparative study. Foot (Edinb). 2015 Dec;25(4):235-7.

Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken). 2020 Feb;72(2):149-162.

Krstičević M, Jerić M, Došenović S, et al. Proliferative injection therapy for osteoarthritis: a systematic review. Int Orthop. 2017Apr;41(4):671-679.

Laudy AB, Bakker EW, Rekers et al. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. Br J Sports Med. 2015 May;49(10):657-72.

Lee DH, Kwack KS, Rah UW, et al. Prolotherapy for refractory rotator cuff disease: retrospective case-control study of 1-year follow-up. Arch Phys Med Rehabil. 2015;96(11):2027-2032.

Lin KY, Yang CC, Hsu CJ, et al. Intra-articular injection of platelet-rich plasma Is superior to hyaluronic acid or saline solution in the treatment of mild to moderate knee osteoarthritis: a randomized, double-blind, triple-parallel, placebo-controlled clinical trial. Arthroscopy. 2019 Jan;35(1):106-117.

López-Royo MP, Ortiz-Lucas M, Gomez-Trullen EM, et al. The effectiveness of minimally invasive techniques in the treatment of patellar tendinopathy: a systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med. 2020 Sep 5;2020:8706283.

Louw WF, K. Reeves D, Lam, SKH, et al. Treatment of temporomandibular dysfunction with hypertonic dextrose injection (prolotherapy): a randomized controlled trial with long-term partial crossover. Mayo Clinic Proceedings, 2019-05-01, Volume 94, Issue 5, Pages 820-832, Mayo Foundation for Medical Education and Research.

Marston W, Tang J, Kirsner R, et al. Wound healing society 2015 update on guidelines for venous ulcers. Wound Repair and Regeneration. 2016(24): 136–144.

Martinez-Zapata MJ, Martí-Carvajal AJ, Sola I, et al. Autologous platelet-rich plasma for treating chronic wounds. Cochrane Database Syst Rev. 2016;(5).

Mei-Dan O, Carmont MR, Laver L, et al. Platelet-rich plasma or hyaluronate in the management of osteochondral lesions of the talus. Am J Sports Med. 2012 Mar;40(3):534-41.

Merolla G, Dellabiancia F, Ricci A, et al. Arthroscopic debridement versus platelet-rich plasma injection: A prospective, randomized, comparative study of chronic lateral epicondylitis with a nearly 2-year follow-up. Arthroscopy. 2017 Jul;33(7):1320-1329.

Miron RJ, Fujioka-Kobayashi M, Bishara M et al. Platelet-rich fibrin and soft tissue wound healing: a systematic review. Tissue Eng Part B Rev. 2017 Feb;23(1):83-99.

Moneib HA, Youssef SS, Aly DG, et al. Autologous platelet-rich plasma versus conventional therapy for the treatment of chronic venous leg ulcers: a comparative study. J Cosmet Dermatol. 2018 Jun;17(3):495-501.Morath O, Kubosch EJ, Taeymans J, et al. The effect of sclerotherapy and prolotherapy on chronic painful achilles tendinopathy-a systematic review including meta-analysis. Scand J Med Sci Sports. 2018 Jan;28(1):4-15.

Nasiri A, Sadat L, Jahromi M, et al. Comparison of the effectiveness of ultrasound-guided prolotherapy in supraspinatus tendon with ultrasound-guided corticosteroid injection of subacromial subdeltoid bursa in rotator cuff-related shoulder pain: a clinical trial study. Adv Biomed Res. 2021 Mar 30;10:12.

Navani A, Manchikanti L, Albers SL, et al. Responsible, safe, and effective use of biologics in the management of low back pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. Pain Physician. 2019 Jan;22(1S):S1-S74.

National Institute for Health and Care Excellence (NICE). Autologous blood injection for tendinopathy. Interventional procedures guidance [IPG438]. January 2013.

National Institute for Health and Care Excellence (NICE). NG19 Diabetic foot problems: prevention and management NICE guideline. August 26, 2015. Updated October 11. 2019.

National Institute for Health and Care Excellence (NICE). Platelet-rich plasma injections for knee osteoarthritis. Interventional procedures guidance [IPG637]. January 2019.

Newberry SJ, FitzGerald J, SooHoo NF, et al. Treatment of osteoarthritis of the knee: an update review. Comparative Effectiveness Review No. 190. (Prepared by the RAND Southern California Evidence-based Practice Center under Contract No. 290-2015-00010-I.) AHRQ Publication No.17-EHC011-EF. Rockville, MD: Agency for Healthcare Research and Quality; May 2017.

Non-Surgical Management of Hip & Knee Osteoarthritis Work Group. VA/DoD clinical practice guideline for the non-surgical management of hip & knee osteoarthritis. Washington (DC): Department of Veterans Affairs, Department of Defense; 2020 Jul. 127 p.

Pandey V, Bandi A, Madi S, et al. Does application of moderately concentrated platelet-rich plasma improve clinical and structural outcome after arthroscopic repair of medium-sized to large rotator cuff tear? A randomized controlled trial. J Shoulder Elbow Surg. 2016 Aug;25(8):1312-22.

Qu W, Wang Z, Hunt C, et al. Platelet-rich plasma for wound care in the Medicare population. Technology Assessment Program Project ID 040-353-492. (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. HHSA290201500013I.) Rockville, MD: Agency for Healthcare Research and Quality. September 2020.

Rabago D, Kijowski R, Woods M, et al. Association between disease-specific quality of life and magnetic resonance imaging outcomes in a clinical trial of prolotherapy for knee osteoarthritis. Arch Phys Med Rehabil. 2013;94(11):2075-2082.

Rabago D, Lee KS, Ryan M, et al. Hypertonic dextrose and morrhuate sodium injections (prolotherapy) for lateral epicondylosis (tennis elbow): results of a single-blind, pilot-level, randomized controlled trial. Am J Phys Med Rehabil. 2013 Jan 3.

Rabago D, Mundt M, Zgierska A, et al. Hypertonic dextrose injection (prolotherapy) for knee osteoarthritis: long term outcomes. Complement Ther Med. 2015 Jun;23(3):388-95.

Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care practice. Prim Care. 2010 Mar;37(1):65-80.

Rahimzadeh P, Imani F, Faiz SHR, et al. The effects of injecting intra-articular platelet-rich plasma or prolotherapy on pain score and function in knee osteoarthritis. Clin Interv Aging. 2018 Jan 4;13:73-79.

Refai H, Altahhan O, Elsharkawy R. The efficacy of dextrose prolotherapy for temporomandibular joint hypermobility: a preliminary prospective, randomized, double-blind, placebo-controlled clinical trial. J Oral Maxillofac Surg. 2011 Dec;69(12):2962-70.

Ryu K, Ko D, Lim G, Kim E, Lee SH. Ultrasound-guided prolotherapy with polydeoxyribonucleotide for painful rotator cuff tendinopathy. Pain Res Manag. 2018;2018:8286190. Published 2018 Mar 25.

Sanderson LM, Bryant A. Effectiveness and safety of prolotherapy injections for management of lower limb tendinopathy and fasciopathy: a systematic review. J Foot Ankle Res. 2015 Oct 20;8:57.

Schöffl V, Willauschus W, Sauer F, et al. Autologous conditioned plasma versus placebo injection therapy in lateral epicondylitis of the elbow: a double blind, randomized study. Sportverletz Sportschaden. 2017 Jan;31(1):31-36.

Seven MM, Ersen O, Akpancar S, et al. Effectiveness of prolotherapy in the treatment of chronic rotator cuff lesions. Orthop Traumatol Surg Res. 2017 May;103(3):427-433.

Sims SE, Miller K, Elfar JC, et al. Non-surgical treatment of lateral epicondylitis: a systematic review of randomized controlled trials. Hand (N Y). 2014 Dec;9(4):419-46.

Singla V, Batra YK, Bharti N, et al. Steroid vs. platelet-rich plasma in ultrasound-guided sacroiliac joint injection for chronic low back pain. Pain Pract. 2017 Jul;17(6):782-791.

Sit RW, Chung VCh, Reeves KD, et al. Hypertonic dextrose injections (prolotherapy) in the treatment of symptomatic knee osteoarthritis: a systematic review and meta-analysis. Sci Rep. 2016;6:25247.

Sit RW, Reeves KD, Zhong CC, et al. Efficacy of hypertonic dextrose injection (prolotherapy) in temporomandibular joint dysfunction: a systematic review and meta-analysis. Sci Rep. 2021 Jul 19;11(1):14638.

Sit RWS, Wu RWK, Rabago D, et al. Efficacy of intra-articular hypertonic dextrose (prolotherapy) for knee osteoarthritis: a randomized controlled trial. Ann Fam Med. 2020 May;18(3):235-242.

Suthar M, Gupta S, Bukhari S, et al. Treatment of chronic non-healing ulcers using autologous platelet rich plasma: a case series. J Biomed Sci. 2017 Feb 27;24(1):16.

Topol GA, Reeves KD. Regenerative injection of elite athletes with career-altering chronic groin pain who fail conservative treatment: a consecutive case series. Am J Phys Med Rehabil. 2008 Nov;87(11):890-902.

Trams E, Kulinksi K, Kozar-Kaminska K, et al. The clinical use of platelet-rich plasma in knee disorders and surgery-a systematic review and meta-analysis. Life (Basel). 2020 Jun 25;10(6):94.

Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, et al. Lumbar intradiskal platelet-rich plasma (PRP) injections: a prospective, double-blind, randomized controlled study. PM R. 2016 Jan;8(1):1-10; quiz 10.

Usuelli FG, Grassi M, Maccario C, et al. Intratendinous adipose-derived stromal vascular fraction (SVF) injection provides a safe, efficacious treatment for Achilles tendinopathy: results of a randomized controlled clinical trial at a 6-month follow-up. Knee Surg Sports Traumatol Arthrosc. 2018 Jul;26(7):2000-2010.

Verhaegen F, Brys P, Debeer P. Rotator cuff healing after needling of a calcific deposit using platelet-rich plasma augmentation: a randomized, prospective clinical trial. J Shoulder Elbow Surg. 2016 Feb;25(2):169-73.

Washington State Health Care Authority. Health Technology Assessment. Autologous Blood or Platelet Rich Plasma Injections. April 2016.

Wu J, Zhou J, Liu C, et al. A prospective study comparing platelet-rich plasma and local anesthetic (LA)/corticosteroid in intra-articular injection for the treatment of lumbar facet joint syndrome. Pain Pract. 2017 Sep;17(7):914-924.

Zhou H, Hu K, Ding Y. Modified dextrose prolotherapy for recurrent temporomandibular joint dislocation. Br J Oral Maxillofac Surg. 2014 Jan;52(1):63-6.

Policy History/Revision Information

Date	Summary of Changes
06/01/2022	Application *Mississippi and North Carolina* • Updated language to indicate this Medical Policy applies to the states of Mississippi and North Carolina (retired state-specific policy versions) Supporting Information • Archived previous policy version CS103.P

Instructions for Use

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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