Platelet-Rich Plasma and Autologous Protein Solution for Orthopedic Applications

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DESCRIPTION

Platelet - Rich Plasma (PRP)

The use of platelet-rich plasma (PRP), an autologous growth factor has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low cost, and minimally invasive method of applying growth factors.

Autologous platelet-derived growth factors (APDGF) also referred to as platelet-rich plasma (PRP), have been proposed for the treatment of multiple orthopedic indications including but not limited to the following: degenerative cartilage lesions; tendonitis; joint

capsular injuries; plantar fasciitis; soft tissue trauma (e.g. tendon and ligament ruptures); fractures; osteoarthritis of the knee, hip, shoulder and temporomandibular joint; carpal tunnel syndrome; and muscle injuries and disorders to enhance healing.

Autologous platelets are a rich source of platelet-derived growth factor that function as a transforming growth factor as a mitogen (agent) for fibroblasts, smooth muscle cells, osteoblasts, and vascular endothelial growth factors. Autologous platelet concentrate suspended in plasma, platelet-rich plasma (PRP), can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets, releasing the various growth factors. Each growth factor released has a specific role in the cellular process that promotes healing and tissue growth.

Platelet-rich plasma (PRP) is extracted from a small quantity of blood collected from the patient using a standard peripheral vein puncture procedure followed by simple centrifuge to remove most of the larger cells (white and red blood cells) and the majority of the fluid and concentrate the platelets in a small volume of plasma (the liquid component of the blood) that is platelet-rich. The concentration of platelets and, thereby, the concentration of growth factors can be 5 to 10 times greater or richer than usual. Although it is not exactly clear how PRP works, many experts have speculated that chronic, painful, degenerative conditions of the connective tissues, such as tendinopathies and osteoarthritis, are the result of failed or inadequate healing responses to repeated subacute injuries. Because connective tissues often have limited blood circulation, they have only a limited innate ability to repair the damages of daily wear and tear. Thus, if such damage regularly exceeds the daily repair capacity, the damage will slowly accumulate until the tissue function becomes impaired. Because the tissues do not suffer an acute insult, the acute healing pathways are not triggered to assist in healing the accumulated damage. Therefore, practitioners speculate that if the acute healing pathways can be activated, the body can be induced to repair the damage. Injection of PRP into the injury site is thought to stimulate an acute injury and may induce an acute healing process.

Platelet-Rich Plasma as a Primary Treatment for Tendinopathy

Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (e.g., exercise, physical therapy) analgesics, and anti-inflammatory agents, in patients with tendinopathy.

Populations
The relevant population of interest is individuals with tendinopathy.

Interventions
The therapy being considered is platelet-rich plasma injections. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an

adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include nonpharmacologic therapy (eg, exercise, physical therapy) analgesics and anti-inflammatory agents.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for tendinopathy has varying lengths of follow-up, ranging from 6 months to 2 years. While studies described below all reported at least 1 outcome of interest, longer follow-up is necessary to fully observe outcomes.

In 2020, Gupta et. al., performed a randomized controlled trial to evaluate and compare the 6-week, 3-month and 1-year outcomes with platelet-rich plasma (PRP) and corticosteroid injections in lateral epicondylitis (LE). The authors hypothesized that PRP would prove more effective in relieving pain and improving function. 80 patients with LE were randomized into either receiving PRP (group A) or corticosteroids (group B) injections. Pre-injection visual analogue scale (VAS), disabilities of the arm, shoulder, and hand (DASH) score, Mayo elbow performance score (MEPS) and grip strength score (GSS) were recorded. Common extensor origins were identified and infiltrated with 3 ml of either PRP or corticosteroid (triamcinolone in 2% xylocaine) using a peppering technique. Follow-up scores and extent of pain relief were recorded and compared. At 6 weeks, there were greater improvements in group B versus A in mean VAS (13.8 vs. 44.5; $p < 0.001$), DASH (64.2 vs. 53.3; $p < 0.001$), MEPS (88.0 vs. 74.5; $p = 0.004$) and GSS (89.3 vs. 73.4; $p = 0.039$). These scores showed a reversed pattern at 3 months when group A outcomes superseded group B (VAS $p = 0.002$; DASH $p < 0.001$; MEPS $p = 0.002$; GSS $p = 0.045$). At 1-year follow-up, group A continued to enjoy better pain relief and function (VAS $p = 0.024$; DASH $p < 0.001$; MEPS $p = 0.009$; GSS $p = 0.028$). Study retention was 93% at 12 weeks and 79% after 1 year. There was no significant difference in mean change in VISA-P score, pain, or global rating of change among the 3 treatment groups at 12 weeks or any other time point. After 1 year, the mean (SD) outcomes for the LR-PRP, LP-PRP, and saline groups were as follows, respectively: VISA-P-58 (29), 71 (20), and 80 (18); pain-4.0 (2.4), 2.4 (2.3), and 2.0 (1.9); global rating of change-4.7 (1.6), 5.6 (1.0), and 5.7 (1.2) ($P > .05$ for all outcomes). The authors concluded Combined with an exercise-based rehabilitation program, a single injection of LR-PRP or LP-PRP was no more effective than saline for the improvement of patellar tendinopathy symptoms.

In 2019, Liu et. al. evaluated the current evidence for the efficacy of platelet-rich plasma (PRP) as a treatment for chronic Achilles tendinopathy. The PubMed, Embase, Web of Science, and The Cochrane Library databases were searched for articles on randomized

controlled trials (RCTs) that compared the efficacy of PRP with that of with placebo injections plus eccentric training as treatment for AT. The articles were uploaded over the establishment of the databases to May 01, 2018. The Cochrane risk of bias (ROB) tool was used to assess methodological quality. Outcome measurements included the Victorian Institute of Sports Assessment-Achilles (VISA-A), visual analog scale (VAS) and Achilles tendon thickness. Statistical analysis was performed with RevMan 5.3.5 software. Five RCTs (n=189) were included in this meta-analysis. Significant differences in the VISA-A were not observed between the PRP and placebo groups after 12 weeks [standardized mean difference (SMD)=0.2, 95% confidence interval (95% CI): 0.36 to 0.76, I^2=71%], 24 weeks (SMD=0.77, 95% CI: −0.10–1.65, I^2=85%) and 1 year (SMD=0.83, 95% CI: −0.76–2.42, I^2=72%) of treatment. However, PRP exhibited better efficacy than the placebo treatment after 6 weeks (SMD=0.46, 95% CI: 0.15–0.77, I^2=34%). Two studies included VAS scores and tendon thickness. VAS scores after 6 weeks (SMD=1.35, 95% CI: −0.1.04–3.74, I^2=93%) and 24 weeks (SMD=1.48, 95% CI: −0.1.59–4.55, I^2=95%) were not significantly different. However, VAS scores at the 12th week (SMD=1.10, 95% CI: 0.53–1.68, I^2=83%) and tendon thickness (SMD=1.51, 95% CI: 0.39–2.63, I^2=53%) were significantly different. The authors concluded PRP injection around the Achilles tendon is an option for the treatment of chronic AT. Limited evidence supports the conclusion that PRP is not superior to placebo treatment. These results still require verification by a large number of well designed, heterogeneous RCT studies.

In 2019, Li et. al. completed a systematic review and meta-analysis to compare the effectiveness of platelet-rich plasma (PRP) versus corticosteroids for the treatment of patients with lateral elbow epicondylitis. A literature search was performed in EMBASE, Medline, the Cochrane Library and PubMed. Randomized controlled studies comparing PRP with corticosteroids for the treatment of epicondylitis were included. The Cochrane Collaboration's tool for assessing the risk of bias was used to evaluate the methodological quality of the included trials. The Cochrane Collaboration's Review Manager software was used to perform the meta-analyses. The overall effect size of each anesthetic was calculated as the weighted average of the inverse variance of the study-specific estimates. Seven randomized controlled trials were included in this review. The data from 2 studies were unavailable for meta-analysis, and the systematic review criteria were just achieved. Local corticosteroid injection yielded a significantly superior Disabilities of the Arm, Shoulder and Hand (DASH) score at 4 weeks (WMD, 11.90; 95% CI: 7.72 to 16.08; P < .00001; heterogeneity, $\chi = 0$, I = 0%, P = 1.00) and 8 weeks (WMD, 6.29; 95% CI: 2.98 to 9.60; P = .0002, $\chi = 0$, I = 0%, P = 1.00). Otherwise, it was noteworthy that a significantly lower VAS score (WMD, -2.61; 95% CI: -5.18 to -0.04; P = .05; heterogeneity, $\chi = 29.85$, I = 97%, P < .00001) and DASH score (WMD, -7.73; 95% CI: -9.99 to -5.46; P < .00001, $\chi = 0.20$, I = 0%, P = .66) existed in the PRP regimen than in the steroid regimen at the 24-week follow-up. More effective treatments were achieved in the PRP-treated patients than in the patients treated with corticosteroids (WMD, 3.33; 95% CI: 1.81 to 6.14; P = .000; heterogeneity, $\chi = 0.43$, I = 0%, P = .51). The authors concluded local corticosteroid injections demonstrated favorable outcomes compared with those of local PRP treatments for lateral elbow epicondylitis during the short-term follow-up period (4 weeks and 8 weeks post-treatment). Otherwise, at the long-term

follow-up (24 weeks post-treatment), PRP injections had improved pain and function more effectively than corticosteroid injections.

Johal et. al., (2019) conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) on platelet-rich plasma for various orthopedic indications, including 10 RCTs of lateral epicondylitis. The meta-analysis evaluated the standardized mean difference in pain at both 3 and 12 months. Systematic review authors used the Cochrane Collaboration risk of bias tool to assess study quality. At 12 months, pain scores were statistically significantly lower for platelet-rich plasma versus its comparators (i.e., steroids, whole blood, dry needling, local anesthetics). However, these results should be interpreted with caution due to important limitations including high statistical heterogeneity (I^2 =73%), lack of a clinically significant difference (i.e., < effect size threshold of 0.5 for a clinically important difference), and moderate to high risk of bias in study conduct.

In 2019, Scott et. al., performed a randomized controlled trial to determine if a single ultrasound-guided PRP injection, either leukocyte-rich PRP (LR-PRP) or leukocyte-poor PRP (LP-PRP), was superior to saline injection for the treatment of patellar tendinopathy. The null hypothesis was that no treatment would be superior to another for the treatment of patellar tendinopathy. Athletes with patellar tendinopathy for ≥6 months (Blazina stage IIIB) were assessed for eligibility in a multisite single-blind controlled trial. There were 3 injection arms: LR-PRP, LP-PRP, and saline. Patients received a single ultrasound-guided injection, followed by 6 weeks of supervised rehabilitation (heavy slow resistance training, concentric and eccentric, 3 times per week). Outcome measures-Victorian Institute of Sport Assessment (patellar; VISA-P), pain during activity, and global rating of change-were assessed at 6 and 12 weeks and 6 and 12 months. VISA-P score at 12 weeks was the primary outcome. Fifty-seven patients (19 in each group) were included in an intention-to-treat analysis. Secondary outcome measures included pain during activity and patients' global rating of change.

In 2017, Miller et. al. conducted a systematic review and meta-analysis on platelet-rich plasma (PRP) for symptomatic tendinopathy and included only randomized controlled trials (RCTs) with injection control. Randomized controlled trials with 3 months minimum follow-up that evaluated pain reduction with PRP versus control (saline, local anesthetic, corticosteroid) injections in patients with symptomatic tendinopathy. A total of 16 randomized controlled trials (18 groups) of PRP versus control were included. Median sample size was 35 patients, a study size that would require an effect size ≥ 1.0 to achieve statistical significance. PRP was more efficacious than control in reducing tendinopathy pain, with an effect size of 0.47 (95% CI 0.22 to 0.72, p<0.001), signifying a moderate treatment effect. Heterogeneity among studies was moderate (I^2=67%, p<0.001). In subgroup analysis and meta-regression, studies with a higher proportion of female patients were associated with greater treatment benefits with PRP. However, there were limitations inherent in the studies included in this review: 1) the duration of tendinopathy symptoms was variable, frequently in short duration, and, in many cases, inadequately described. Thus, the meta-analysis was unable to discern the efficacy of

PRP based on chronology of symptoms; 2) there was significant heterogeneity in efficacy outcomes among studies with PRP versus control injections and definitive conclusions could not be drawn given the post hoc nature of the analysis; 3) the duration of patient follow-up may be an important determinant of PRP efficacy, however, the analysis was under-powered to varying follow-up durations; 4) safety reporting was not made in this study, and generally safety reporting in PRP literature is inconsistent and inadequate.

Tsikopoulos et. al. (2016) published a meta-analysis of randomized controlled trials (RCTs) that compared platelet-rich plasma (PRP) with placebo or dry needling in patients who had tendinopathy lasting at least 6 weeks. The primary outcome was pain intensity at two or three and six months after intervention. The secondary outcome was functional disability at three months after treatment. Five trials were included. There was a statistically significant difference in favor of the platelet-rich plasma intervention at the second primary outcome time point (SMD -0.48, 95%CIs -0.86 to -0.10, I(2) = 0%, p = 0.01) and at the secondary outcome time point (SMD -0.47, 95%CIs -0.85 to -0.09, I(2) = 0%, p=0.01). The authors concluded, platelet-rich plasma did not provide significantly greater clinical benefit versus placebo or dry needling for the treatment of tendinopathy at a six-month follow-up. However, there was a marginal clinical difference in favor of platelet-rich plasma injections on rotator cuff tendinopathy.

Andia et.al. (2014) published a systematic review and meta-analysis on the use of platelet-rich plasma (PRP) in the management of painful tendinopathies. Thirteen prospective controlled studies, comprising 886 patients and diverse tendons were included; 53.8% of studies used identical PRP protocol. Sources of heterogeneity included different comparators, outcome scores, follow-up periods and diverse injection protocols, but not PRP formulation per se. Pooling pain outcomes over time and across different tendons showed that L-PRP injections ameliorated pain in the intermediate-long term compared with control interventions, weighted mean difference (95% CI): 3 months, -0.61 (-0.97, -0.25); 1 year, -1.56 (-2.27, -0.83). However, these findings cannot be applied to the management of individual patients given low power and precision. The authors concluded, further studies circumventing heterogeneity are needed to reach firm conclusions. Available evidence can help to overcome hurdles to future clinical research and bring forward PRP therapies.

In 2015, Balasubramaniam et. al. completed a systematic review on the efficacy of platelet-rich plasma (PRP) in pain associated with chronic tendinopathy. The databases used in our search include the Elton B. Stephens Co. (EBSCO) database, Medline, the Cochrane library, Ovid, and Embase (the Excerpta Medica database). A total of 389 articles were reviewed from Feb 2010 to April 2014, for possible inclusion. Of these articles, a total of 9 randomized controlled trials (RCTs) met our inclusion criteria. Only 1 RCT was excluded due to previous surgery in both the trial and control groups. Each article was reviewed independently by 2 authors. Each article was analyzed using the Cochrane Criteria checklist. Where any discrepancy occurred in results, a third independent reviewer was consulted. 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 rotator cuff tendinopathy. The authors concluded, although the results of this review show promise for the use of PRP in chronic tendinopathy, the analysis highlighted the need for more controlled clinical trials comparing PRP with placebo.

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Summary
For individuals with tendinopathy who receive platelet-rich plasma (PRP) injections, the evidence includes multiple randomized controlled trials (RCTs) and systematic reviews with meta-analysis. The majority of the more recently published systematic reviews and meta-analyses that only included RCTs failed to show a statistically and/or clinically significant impact on symptoms (ie, pain) or functional outcomes. Although 1 systematic review found statistically significantly lower pain scores at 12 months with platelet-rich plasma versus the comparators, its results should be interpreted with caution due to important study conduct limitations. Likewise, in subsequently published RCTs, although compared to a corticosteroid injection, 2 RCTs found platelet-rich plasma injection to result in significantly improved pain scores, important relevancy gaps and study conduct limitations exist that preclude reaching strong conclusions based on this evidence. Additionally, compared to placebo, platelet-rich plasma did not significantly improve pain after 12 months. Finally, compared with lidocaine, in individuals receiving platelet-rich plasma as an adjunct to ultrasound-guided tenotomy for recalcitrant elbow tendinopathy, there were no significant differences in pain or disability outcomes. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Platelet-Rich Plasma as a Primary Treatment of Non-Tendon Soft Tissue Injury or Inflammation

Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy

(e.g., exercise, physical therapy) analgesics, and anti-inflammatory agents, in patients with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis).

Populations
The relevant population of interest is individuals with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis).

Interventions
The therapy being considered is platelet-rich plasma injections. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include nonpharmacologic therapy (eg, exercise, physical therapy) analgesics, and anti-inflammatory agents.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis) has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 2 years of follow-up is considered necessary to demonstrate efficacy.

In 2019, Peerbooms et. al., performed a double-blind multicenter randomized controlled trial to determine the effectiveness of PRP as compared with corticosteroid injections for chronic plantar fasciitis. Patients with chronic plantar fasciitis were allocated to have steroid injection or PRP. The primary outcome measure was the Foot Function Index (FFI) Pain score. Secondary outcome measures were function, as scored by the FFI Activity, FFI Disability, and American Orthopaedic Foot & Ankle Society, and quality of life, as scored with the short version of the World Health Organization Quality of Life (WHOQOL-BREF). All outcomes were measured at baseline and at 4, 12, and 26 weeks and 1 year after the procedure. Of the 115 patients, 63 were allocated to the PRP group, of which 46 (73%) completed the study, and 52 were allocated to the control group (corticosteroid injection), of which 36 (69%) completed the study. In the control group, FFI Pain scores decreased quickly and then remained stable during follow-up. In the PRP group, FFI Pain reduction was more modest but reached a lower point after 12 months than the control group. After adjusting for baseline differences, the PRP group showed significantly lower pain scores at the 1-year follow-up than the control group (mean difference, 14.4; 95% CI, 3.2-25.6). The number of patients with at least 25% improvement (FFI Pain score) between baseline and 12-month follow-up differed significantly between the groups. Of the 46 patients in the PRP group, 39 (84.4%)

improved at least 25%, while only 20 (55.6%) of the 36 in the control group showed such an improvement (*P* = .003). The PRP group showed significantly lower FFI Disability scores than the control group (mean difference, 12.0; 95% CI, 2.3-21.6).

Shetty et.al. (2019) compared the pain and functional outcomes of platelet-rich plasma (PRP) with corticosteroids (CS) and placebo injections for chronic plantar fasciitis. A 3-arm randomized controlled trial of 90 patients: PRP (n = 30 patients), CS (n = 30 patients), and placebo (n = 30 patients). The patients were followed at regular intervals until 18 months post injection using validated instruments. The mean visual analog scale score showed significant improvement in all groups between baseline and 18-month follow-up (PRP: 8.2 vs 2.1; CS: 8.8 vs 3.6; placebo: 8.1 vs 5.4), with CS showing significantly better improvement than PRP in the short term, whereas longer-term PRP was significantly better than CS. The mean Roles and Maudley score showed significant improvement in all groups between baseline and 18-month follow-up (PRP: 1.7 vs 3.7; CS: 1.2 vs 3.1; placebo: 1.2 vs 2.0), with CS showing significantly better improvement than PRP in the short term, whereas longer-term PRP was significantly better than CS. The mean Short Form 12 score showed significant improvement in all groups between baseline and 18-month follow-up (PRP: 55.4 vs 80.2; CS: 56.2 vs 76.2; placebo: 54.1 vs 62.4). We found that all 3 groups showed significant improvement between baseline and end of the follow-up period with regard to pain, function, and general health. The CS arm showed better improvement in the short term, whereas the PRP arm showed better results in the long term. In contrast to previous studies, we found no significant drop-off effect of CS in the long term, which may be owing to background natural healing process of the disease.

In 2014, Franceschi et. al. performed a systematic review on the effects of platelet-rich plasma (PRP) injections for chronic plantar fasciitis. The literature search conducted through June 2014 identified 8 articles that met inclusions criteria, and 3 of them were randomized. Out of the 3 randomized controlled trials, none of these studies had a true control group treated with placebo and one of the three studies had a very short (6 week) follow-up. A non-randomized study evaluating PRP versus corticosteroids (CCS) injections, and a randomized controlled trial comparing PRP and dextrose prolotherapy reported no statistically significant differences at 6 months. Most studies did not have a control group and imaging evaluation. The authors concluded, evidence for the use of PRP in plantar fasciitis shows promising results, and this therapy appears safe. However, the number of studies available is limited and randomized placebo-controlled studies are required. Characterizing the details of the intervention and standardizing the outcome scores would help to better document the response and optimize the treatment.

Monto et. al. (2014) compared autologous platelet-rich plasma (PRP) with traditional cortisone injection in the treatment of chronic plantar fasciitis resistant to traditional nonoperative management. Forty patients (23 females and 17 males) with unilateral chronic plantar fasciitis that did not respond to a minimum of 4 months of standardized traditional nonoperative treatment modalities were prospectively randomized and treated with either a single ultrasound guided injection of 3 cc PRP or 40 mg DepoMedrol

cortisone. American Orthopedic Foot and Ankle Society (AOFAS) hindfoot scoring was completed for all patients immediately prior to PRP or cortisone injection (pretreatment = time 0) and at 3-, 6-, 12-, and 24-months following injection treatment. Baseline pretreatment radiographs and MRI studies were obtained in all cases to confirm the diagnosis of plantar fasciitis. The cortisone group had a pretreatment average AOFAS score of 52, which initially improved to 81 at 3 months post-treatment but decreased to 74 at 6 months, then dropped to near baseline levels of 58 at 12 months and continued to decline to a final score of 56 at 24 months. In contrast, the PRP group started with an average pretreatment AOFAS score of 37, which increased to 95 at 3 months, remained elevated at 94 at 6 and 12 months, and had a final score of 92 at 24 months. Confirmation of these results in a larger double-blind randomized controlled trial (RCT) would permit greater certainty on the efficacy of PRP in plantar fasciitis

Summary
For individuals with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis) who receive platelet-rich plasma (PRP) injections, the evidence includes several small randomized controlled trials (RCTs) and multiple prospective observational studies have evaluated the efficacy of platelet-rich plasma injections in individuals with chronic plantar fasciitis. Preparation of platelet-rich plasma and outcome measures differed across studies. Results among the RCTs were inconsistent. The largest of the RCTs showed that treatment using platelet-rich plasma compared with corticosteroid resulted in statistically significant improvements in pain and disability, but not quality of life. Larger RCTs are still needed to address important uncertainties in efficacy and safety. The evidence is insufficient to determine the effects of this technology on net health outcomes.

Platelet-Rich Plasma as a Primary Treatment of Osteochondral Lesions

Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (e.g., exercise, physical therapy) analgesics, anti-inflammatory agents, and surgery in patients with osteochondral lesions.

Populations
The relevant population of interest is individuals with osteochondral lesions.

Interventions
The therapy being considered is platelet-rich plasma injections. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators

Comparators of interest include nonpharmacologic therapy (eg, exercise, physical therapy) analgesics, anti-inflammatory agents, and surgery.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for osteochondral lesions has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 28 weeks of follow-up is considered necessary to demonstrate efficacy.

No RCTs on the treatment of osteochondral lesions were identified.

In 2012, Mei-Dan et. al. evaluated the short-term efficacy of platelet-rich plasma (PRP) compared with hyaluronic acid (HA) in reducing pain and disability caused by osteochondral lesions of the ankle. Thirty-two patients aged 18 to 60 years were allocated to a treatment by intra-articular injections of either HA (group 1) or PRP (plasma rich in growth factors [PRGF] technique, group 2) for OCLs of the talus. Thirty OCLs, 15 per arm, received 3 consecutive intra-articular therapeutic injections and were followed for 28 weeks. The efficacy of the injections in reducing pain and improving function was assessed at each visit using the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale (AHFS); a visual analog scale (VAS) for pain, stiffness, and function; and the subjective global function score. The majority of patients were men (n = 23; 79%). The AHFS score improved from 66 and 68 to 78 and 92 in groups 1 and 2, respectively, from baseline to week 28 ($P < .0001$), favoring PRP ($P < .05$). Mean VAS scores (1 = asymptomatic, 10 = severe symptoms) decreased for pain (group 1: 5.6 to 3.1; group 2: 4.1 to 0.9), stiffness (group 1: 5.1 to 2.9; group 2: 5.0 to 0.8), and function (group 1: 5.8 to 3.5; group 2: 4.7 to 0.8) from baseline to week 28 ($P < .0001$), favoring PRP ($P < .05$ for stiffness, $P < .01$ for function, $P > .05$ for pain). Subjective global function scores, reported on a scale from 0 to 100 (with 100 representing healthy, preinjury function) improved from 56 and 58 at baseline to 73 and 91 by week 28 for groups 1 and 2, respectively ($P < .01$ in favor of PRP). Interpretation of the composite measures of visual analog scale (VAS) scores for pain and function is limited by differences between the groups at baseline. Also, neither the patients nor the evaluators were blinded to treatment in this small study. Adequately powered and blinded RCTs are required to confirm these findings.

Summary
For individuals with osteochondral lesions who receive platelet-rich plasma (PRP) injections, the evidence includes an open-labeled quasi-randomized study (study in which participants are allocated to different arms of the trial using a method of allocation that is not truly random, there is a greater risk that the investigator will be aware of which participant is in which group). This quasi-randomized study found a statistically greater impact on outcomes in the PRP group than in the hyaluronic acid (HA) group. Limitations of the evidence include lack of adequately randomized studies, lacking

blinding, lacking sham controls, and comparison only to an intervention of uncertain efficacy. Adequately powered and blinded RCTs are required to confirm these findings. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Platelet-Rich Plasma as a Treatment for Carpal Tunnel Syndrome
Carpal tunnel syndrome is caused by pressure on the median nerve. The carpal tunnel is a narrow passageway surrounded by bones and ligaments on the palm side of your hand. When the median nerve is compressed, the symptoms can include numbness, tingling and weakness in the hand and arm. Treatment options include wrist splinting, medications (NSAIDs) and surgery.

Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (e.g., exercise, physical therapy) analgesics, anti-inflammatory agents, and surgery, in patients with carpal tunnel syndrome.

Populations
The relevant population of interest is individuals with carpal tunnel syndrome.

Interventions
The therapy being considered is platelet-rich plasma injections. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include nonpharmacologic therapy (e.g., exercise, physical therapy) analgesics, anti-inflammatory agents, and surgery.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for carpal tunnel syndrome has varying lengths of follow-up. To fully observe outcomes 12- months of follow-up is considered necessary to demonstrate efficacy.

In 2019, Malahias et. al. completed a systematic and comprehensive review on the use of platelet-rich plasma (PRP) for carpal tunnel syndrome (CTS). A series of clinical trials focused on the use of ultrasound-guided platelet-rich plasma (PRP) infusions for the treatment of patients with carpal tunnel syndrome (CTS) were published over the last few years. However, the role of PRP for CTS remains unclear. A systematic review was performed according to Preferred Reporting Items for Systematic reviews and Meta-

Analyses guidelines. Two reviewers independently conducted the search using multiple databases: MEDLINE/PubMed, SCOPUS, Cochrane Database, and Web of Science. These databases were searched using terms "platelet" AND "rich" AND "plasma" AND "carpal" AND "tunnel". To maximize the search, backward chaining of references from retrieved papers was also undertaken. From the initial 19 studies, only five met eligibility criteria. These articles included one randomized controlled double-blind study, one randomized controlled single-blind study, one randomized controlled non-blind study, one case-control study, and one case report. Most of the included studies supported that PRP infusion improved the clinical condition of the patients and that PRP infusion was beneficial for patients with mild-to-moderate CTS. Therefore, PRP seems to be an interesting alternative for the treatment of mild-to-moderate CTS which, still, has not been thoroughly investigated. However, despite the promising results of the present studies, PRP has to be further tested before a definitive conclusion regarding its therapeutic value can be reached.

Summary
For individuals with carpal tunnel syndrome based on a recent systematic and comprehensive review on the use of platelet-rich plasma (PRP) for carpal tunnel syndrome (CTS). A series of clinical trials focused on the use of ultrasound-guided platelet-rich plasma (PRP) infusions for the treatment of patients with carpal tunnel syndrome (CTS) were published over the last few years. However, the role of PRP for CTS remains unclear. Most of the included studies supported that PRP infusion improved the clinical condition of the patients and that PRP infusion was beneficial for patients with mild-to-moderate CTS. Therefore, PRP seems to be an interesting alternative for the treatment of mild-to-moderate CTS which, still, has not been thoroughly investigated. However, despite the promising results of the present studies, PRP has to be further tested before a definitive conclusion regarding its therapeutic value can be reached. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Platelet-Rich Plasma as a Primary Treatment of Knee or Hip Osteoarthritis
Systematic Reviews

Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (e.g., exercise, physical therapy) analgesics, anti-inflammatory agents, and surgery, in patients with knee or hip osteoarthritis.

Populations
The relevant population of interest is individuals with knee or hip osteoarthritis.

Interventions
The therapy being considered is platelet-rich plasma injections. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma

has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include nonpharmacologic therapy (eg, exercise, physical therapy) analgesics, anti-inflammatory agents, and surgery.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for knee or hip osteoarthritis has varying lengths of follow-up, ranging from 6-12 months. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 12 months of follow-up is considered necessary to demonstrate efficacy.

A number of RCTs and several systematic reviews of RCTs evaluating the use of platelet-rich plasma for knee osteoarthritis have been published. Protocols used in platelet-rich plasma interventions for knee osteoarthritis varied widely. For example, in systematic review, platelet-rich plasma was prepared using single, double, or triple spinning techniques and interventions included between 1 and 3 injections delivered 1 to 3 weeks apart.

In 2021, Dong et. al. conducted an updated meta-analysis of randomized controlled trials to evaluate the effects of platelet-rich plasma (PRP) in patients with knee or hip osteoarthritis (OA). PubMed, Embase, and Web of Science were searched to identify randomized controlled trials (RCTs) that compared the efficacy of PRP with other intra-articular injections. The outcomes of interest included Western Ontario and McMaster (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analog Scale (VAS), Harris Hip Score (HHS), and International Knee Documentation Committee (IKDC). Twenty-four RCTs with 21 at knee OA and three at hip OA were included in this meta-analysis. The PRP injections significantly improved the WOMAC score, VAS score, IKDC score, and HHS score as compared with comparators. The WOMAC pain, stiffness, and physical function scores were also significantly better in the PRP group than in the control group. Most of the evaluated parameters that favored PRP were observed in knee OA but not in hip OA, at short-term (at 1, 2, 3, 6, 12 months) but not long-term follow-up (at 18 months), in RCTs with low risk of bias. The authors concluded intra-articular PRP injection provided better effects than other injections for OA patients, especially in knee OA patients, in terms of pain reduction and function improvement at short-term follow-up. Key Points: This updated meta-analysis, based on great sample size and high-quality studies, evaluates the effects of PRP in patients with knee or hip OA; Intra-articular PRP injection provided better effects than other injections for OA patients; Most of the evaluated parameters that favored PRP were observed in knee OA at short term (at 1, 2, 3, 6, 12 months) but not long term follow up at 18 months.

In 2020, Hohmann et. al. performed a systematic review and meta-analysis comparing intra-articular knee injection of platelet-rich plasma (PRP) and hyaluronic acid and investigate clinical outcomes and pain at both 6 and 12 months. A systematic review of Medline, Embase, Scopus, and Google Scholar was performed in the English and German literature reporting on intra-articular knee injections for knee osteoarthritis. All level 1 and 2 studies with a minimum of 6-month follow-up in patients with knee osteoarthritis from 2010 to 2019 were included. Clinical outcome was assessed by WOMAC and IKDC scores and pain by VAS and WOMAC pain scores. Subgroup analysis for autologous platelet-rich plasma (ACP) was performed. Publication bias and risk of bias were assessed using the Cochrane Collaboration's tools. The GRADE system was used to assess the quality of the body of evidence. Heterogeneity was assessed using χ^2 and I_2 statistics. Twelve studies (1,248 cases; 636 PRP, 612 HA) met the eligibility criteria. The pooled estimate demonstrated non-significant differences between PRP and HA for clinical outcomes at 6 months ($p = 0.069$) and at 12 months ($p = 0.188$). However, the pooled estimate for pain did demonstrate significant differences in favor of PRP at 6 months ($p = 0.001$) and 12 months ($p = 0.001$). For the ACP subgroup (249 cases), the pooled estimate for these studies demonstrated significant differences in favor of PRP ($p < 0.0001$) at 6 months. The authors concluded this systematic review and meta-analysis suggest that PRP is superior to HA for symptomatic knee pain at 6 and 12 months. ACP appears to be clearly superior over HA for pain at both 6 and 12 months. There were no advantages of PRP over HA for clinical outcomes at both 6 and 12 months.

In 2019, Delanois et. al. completed a systematic review and analysis of reports evaluating 1) platelet-rich plasma injections (PRPs); (2) bone marrow-derived mesenchymal stem cells (BMSCs); (3) adipose-derived mesenchymal stem cells (ADSCs); and (4) amnion-derived mesenchymal stem cells (AMSCs). PubMed, Embase, and Cochrane Library databases were queried for studies evaluating PRP injections, BMSCs, ADSCs, and AMSCs in patients with knee osteoarthritis. Of 1009 studies identified within the last 5 years, 123 met inclusion criteria. A comprehensive analysis of all levels-of-evidence was performed, as well as separate analysis on level-of-evidence I studies. Level-of-evidence was determined by the American Academy of Orthopedic Surgeons classification system. Although the majority of PRP reports demonstrated improvements in pain and/or function, others revealed no substantial improvements. Similar findings were noted for BMSCs, ADSCs, and AMSCs. Assessments of BMSC studies yielded majority with positive clinical results, although short-lived. Studies on ADSCs revealed improved clinical outcomes, but equivocal radiographic outcomes. Studies evaluating AMSCs demonstrated improvements in pain and function and decreased radiographic evidence of osteoarthritis. Despite some promising early results for PRP, BMSC, ADSC, and AMSC therapies, the majority of level-of-evidence I studies have multiple problems: small sample sizes, potentially inappropriate control cohorts, short-term follow-up, and so on. Despite the limitations, there still appears to be evidence justifying their use for knee osteoarthritis management. More high-level, larger studies utilizing standardized protocols are needed.

In 2017, Xu et. al. conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess the efficacy of platelet-rich plasma (PRP) in pain and self-reported function of patients with knee osteoarthritis on the basis of comparisons with hyaluronic acid or placebo. Literature retrieval was limited to RCTs assessing the efficacy of PRP in knee osteoarthritis. Methodology evaluation and data extraction were based on Cochrane Collaboration guidelines. Meta-analyses were performed using mean difference or standardized mean difference as effect size. Ten RCTs were included and analyzed. Meta-analysis showed significant superiority of PRP in outcome scores when compared with hyaluronic acid (standardized mean difference = -0.85, P = 0.004, I = 93%), but no statistical difference was found in well-designed double-blind trials (standardized mean difference = -0.09, P = 0.38, I = 0%). Pooled standardized mean difference of trials comparing PRP with placebo directly was -2.13 (95% confidence interval = -3.29 to -0.98), and that of indirect comparison was -0.22 (95% confidence interval = -0.45 to -0.01). The authors concluded, in relieving pain and improving self-report function, PRP showed no superiority over hyaluronic acid in well-designed double-blind trials, and beneficial effects of PRP in most trials probably resulted from insufficient blinding methods.

Laudy et. al. (2015) conducted a systematic review investigating the effect of platelet-rich plasma (PRP) injections in patients with knee osteoarthritis (OA) based on decreasing pain, improving function, global assessment and changes regarding joint imaging. A comprehensive systematic literature search was completed until June 2014 for randomized or non-randomized controlled trials. These were graded for risk of bias and a level of evidence was provided. If possible, meta-analysis was performed. Ten trials (total N=1110 patients) were included. In these, intra-articular PRP injections were more effective for pain reduction (mean difference (MD) -2.45; 95% CI -2.92 to -1.98; p value <0.00001 and MD -2.07; 95% CI -2.59 to -1.55; p value <0.00001, single and double PRP injections, respectively) compared with placebo at 6 months post-injection. Intra-articular PRP injections were compared with hyaluronic acid and showed a statistically significant difference in favor of PRP on pain reduction based on the visual analogue scale and numeric rating scale (standardized mean difference -0.92; 95% CI -1.20 to -0.63; p value <0.00001) at 6 months post-injection. Almost all trials revealed a high risk of bias. While meta-analysis showed that PRP was more effective than placebo or hyaluronic acid in reducing pain and improving function (level of evidence limited due to a high risk of bias), more large, randomized studies of good quality and low risk of bias are needed to confirm these results and test whether PRP injections should be a routine part of management of patients with OA of the knee.

In 2014, Chang et. al. published a systematic review exploring the effectiveness of platelet-rich plasma (PRP) injections in treating cartilage degenerative pathology in knee joints. They included single-arm prospective studies, quasi-experimental studies, and randomized controlled trials that used PRP to treat knee chondral degenerative lesions. Eight single-arm studies, 3 quasi-experimental studies, and 5 randomized controlled trials were identified, comprising 1543 participants. They determined effect sizes for the selected studies by extracting changes in functional scales after the interventions and

compared the PRP group pooled values with the pretreatment baseline and the groups receiving placebo or hyaluronic acid (HA) injections. PRP injections in patients with knee degenerative pathology showed continual efficacy for 12 months compared with their pretreatment condition. The effectiveness of PRP was likely better and more prolonged than that of HA. Injection doses ≤ 2, the use of a single-spinning approach, and lack of additional activators led to an uncertainty in the treatment effects. Patients with lower degrees of cartilage degeneration achieved superior outcomes as opposed to those affected by advanced osteoarthritis.

Randomized Controlled Trials

In 2019, Di Martino et. al. in a randomized controlled trial (RCT) compared the long-term clinical outcomes provided by intra-articular injections of either PRP or hyaluronic acid (HA) to treat knee osteoarthritis. Platelet-rich plasma (PRP) injections have been proposed as a new conservative option for knee degeneration to provide symptomatic relief and delay surgical intervention. Although the current literature provides some evidence on the benefits of this technique compared with viscosupplementation, no studies have been performed to compare their long-term effects. Patients with a history of chronic symptomatic knee degenerative changes and osteoarthritis (Kellgren-Lawrence grade 0-3) were enrolled: 192 patients were randomized to undergo 3 blinded weekly intra-articular injections of either PRP or HA. Patients were prospectively evaluated before the injection and then at 2, 6, 12, and 24 months and a mean of 64.3 months (SD, 7.8 months) of follow-up. Evaluation was based on International Knee Documentation Committee (IKDC) subjective (main outcome), EuroQol visual analog scale, and Tegner scores; 167 patients reached the final evaluation. Both treatments were effective in improving knee functional status and symptoms over time: Mean ± SD IKDC subjective score improved significantly for both PRP and HA groups ($P < .0005$) and remained stable over time up to 24 months (from 53.3 ± 14.3 to 67.3 ± 18.1 and from 50.3 ± 13.2 to 62.1 ± 20.8 for PRP and HA groups, respectively). At final evaluation, a significant IKDC reduction was observed in both treatment groups, with the PRP group still presenting significantly higher values compared with baseline: PRP 60.5 ± 19.0 ($P < .001$ vs baseline), HA 55.7 ± 18.8 (not significant vs baseline). A comparative analysis showed no significant intergroup difference in any of the clinical scores at any follow-up point. The median duration of patient subjective perception of symptomatic relief was 9 months for HA and 12 months for PRP (not significant). The only significant difference was observed in the rate of reintervention at 24 months, which was significantly lower in the PRP group (22.6% vs 37.1%, $P = .036$). The authors concluded both treatments were effective in improving knee functional status and symptoms over time. PRP did not provide an overall superior clinical improvement compared with HA in terms of either symptomatic-functional improvement at different follow-up points or effect duration. Vasavilbaso et. al. (2017) conducted a prospective, randomized, evaluator-blind pilot study on the effectiveness of viscosupplementation or platelet-rich plasma (PRP) compared to standard of care or pain relief after knee arthroscopic debridement in patients with meniscal pathology and osteoarthritis (OA) of the knee. Patients were randomized to receive 1) five injections of HA1 (Suprahyal®/Adant®); 2) four injections of HA2 (Orthovisc®); 3) three injections of HA3 (Synvisc®); 4) a single injection of PRP

(GPS™ II); or 5) standard care (control). Patients were followed up for 18 months. Clinical outcomes were evaluated using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) at 3, 6, 12, and 18 months. Minimally Clinical Important Improvement (MCII), as relative improvement ≥ 20 for pain and function, were also calculated. Fifty patients were included. At early follow-up (3 months), total WOMAC scores improved in all groups compared to baseline with reductions of 44.79% (HA1), 24.02% (HA2), 40.38% (HA3), 39.77% (PRP), and 27.64% (control) (p=0.002 HA1 compared to HA2). At 18 months, the higher improvement in total WOMAC was in HA1 with a 65.20% reduction, followed by PRP (55.01%), HA3 (49.57%), and HA2 (29.82%), whereas the control group had a 14.55% increase over baseline (p=0.001 control compared to HA1 and HA3). The percentage of patients achieving the MCII for both pain and function at 18 months was 100% (HA1), 80% (HA3), 60% (HA2), and 60% (PRP), whereas, in the control group, all patients returned to pre-arthroscopy levels. There were no adverse events attributable to surgery or to intraarticular administration. The authors concluded, viscosupplementation following arthroscopy is more effective than PRP in adequately selected patients with meniscal lesions occurring concomitantly with OA. Further controlled studies with a larger sample size and/or alternative regimens would be of interest for the scientific community.

Smith et. al. (2016) conducted a randomized, double-blind, placebo-controlled trial to determine the safety and efficacy of leukocyte-poor platelet-rich plasma (PRP) autologous conditioned plasma (ACP) for osteoarthritis (OA) of the knee. This was a feasibility trial regulated by the U.S. Food and Drug Administration (FDA). In accordance with FDA protocol, patient selection was based on strict inclusion/exclusion criteria; 114 patients were screened, and 30 were ultimately included in the study. These patients were randomized to receive either ACP (n = 15) or saline placebo (n = 15) for a series of 3 weekly injections. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores served as the primary efficacy outcome measure. Patients were followed for 1 year. No adverse events were reported for ACP administration. Furthermore, the results demonstrated no statistically significant difference in baseline WOMAC scores between the 2 groups. However, in the ACP group, WOMAC scores at 1 week were significantly decreased compared with baseline scores, and the scores for this group remained significantly lower throughout the study duration. At the study conclusion (12 months), subjects in the ACP group had improved their overall WOMAC scores by 78% from their baseline score, compared with 7% for the placebo group.

There is little evidence of platelet-rich plasma injections in the treatment of osteoarthritis (OA) in the hip. In 2016, Dallari et. al. reported on results of a randomized controlled trial (RCT) to compare the therapeutic efficacy of autologous platelet-rich plasma (PRP), hyaluronic acid (HA), or a combination of both PRP + HA in the treatment of osteoarthritis (OA) of the hip. Patients aged between 18 and 65 years who were treated with outpatient surgery and who had hip OA and pain intensity at baseline of >20 on a 100-mm visual analog scale (VAS) were recruited for this study. Exclusion criteria were extensive surgery; presence of excessive deformities; or rheumatic, infective, cardiovascular, or immune system disorders. The primary outcome measure was a change

in pain intensity as assessed by the VAS at 2, 6, and 12 months after treatment. Secondary outcome measures were the Harris Hip Score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and concentration of growth factors in PRP and their correlation with clinical outcomes. Clinical outcomes were evaluated by assessors and collectors blinded to the type of treatment administered. A total of 111 patients were randomly assigned to 3 groups and received 3 weekly injections of either PRP (44 patients), PRP+HA (31 patients), or HA (36 patients). At all follow-ups, the PRP group had the lowest VAS scores. In particular, at 6-month follow-up, the mean VAS score was 21 (95% CI, 15-28) in the PRP group, 35 (95% CI, 26-45) in the PRP+HA group, and 44 (95% CI, 36-52) in the HA group ($P < .0005$ [PRP vs HA] and $P = .007$ [PRP vs PRP+HA]; $F = 0.663$). The WOMAC score of the PRP group was significantly better at 2-month follow-up (mean, 73; 95% CI, 68-78) and 6-month follow-up (mean, 72; 95% CI, 67-76) but not at 12-month follow-up. The impact of treatment on secondary outcome measures such as Harris Hip Score was not observed. A significant, "moderate" correlation was found between interleukin-10 and variations of the VAS score ($r = 0.392$; $P = .040$). Significant improvements were achieved in reducing pain and ameliorating quality of life and functional recovery. However, the addition of PRP+HA did not lead to a significant improvement in pain symptoms. The trial design did not incorporate a sham-control arm. Additional larger controlled studies comparing PRP with placebo and alternatives other than hyaluronic acid (HA) are needed to determine the efficacy of PRP for hip osteoarthritis.

Summary

For individuals with knee osteoarthritis who receive platelet-rich plasma (PRP) injections, the evidence includes multiple randomized controlled trials (RCTs) and systematic reviews and meta-analysis. The RCTs have compared PRP with placebo and hyaluronic acid (HA) for the knee osteoarthritis (OA). Comparisons between PRP and HA have shown inconsistent results, but PRP may lead to reduction in pain, however, evidence for clinically significant efficacy is limited. A meta-analysis showed no difference between the two treatments in functional scores. Also, using HA as a comparator is questionable because the evidence demonstrating the benefit of HA treatment of OA is not robust. The single RCT evaluating hip OA reported statistically significant reductions in visual analog scale scores for pain, with no difference in functional scores. Additional studies comparing PRP with placebo and with alternatives other than HA are needed to determine the efficacy of PRP for knee and hip OA. Studies are also needed to determine the optimal protocol for delivering PRP. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Platelet-Rich Plasma for the Treatment of Temporomandibular Osteoarthritis

Temporomandibular joint (TMJ) acts like a sliding hinge, connecting the jawbone to the skull. There is one joint on each side of the jaw. TMJ disorders a type of temporomandibular disorder or TMD can cause pain in the jaw joint and in the muscles that control jaw movement. The exact cause of TMJ disorders is often difficult to determine. The pain could be due to a combination of factors such as genetics, arthritis or jaw injury. Surgery is typically a last resort after conservative measures have failed.

Signs and symptoms of TMJ disorders may include:

- Pain or tenderness of the jaw
- Pain in one or both of the temporomandibular joints
- Aching pain in and around the ear
- Difficulty chewing or pain while chewing
- Aching facial pain
- Locking of the joint making it difficult to open or close the mouth

Conservative treatment includes:

- Medications (pain relivers and anti-inflammatories, tricyclic antidepressants, muscle relaxants
- Oral splints or mouth guards (occlusal appliances)
- Physical therapy
- Counseling

Surgical or Other Procedures: When conservative measures fail

- Arthrocentesis
- Injections (corticosteroids, botulinum toxin type A [Botox])
- TMJ arthroscopy
- Modified condylotomy
- Open joint surgery

Platelet-rich plasma concentrate treatments for temporomandibular disorders is being investigated as treatment in terms of pain and maximum mouth opening.

In 2020, Al-Hamed et. al. completed a systematic review and meta-analysis comparing platelet concentrates (PCs) versus hyaluronic acid (HA) or saline/Ringer's solution injections as treatments of temporomandibular disorders and disc displacement in terms of pain and maximum mouth opening (MMO). PubMed, Cochrane, and Scopus were searched up to March 6, 2020. Inclusion criteria were randomized clinical trials (RCTs). Exclusion criteria were case series, observational studies, animal studies, and reviews. The Effective Public Health Practice Project (EPHPP) quality assessment tool was used to assess the risk of bias in the included studies. The weighted mean difference was used to compare the results. Nine RCTs were included with a total of 407 patients. The numbers of joints treated were 262, 112, and 112 in the PC, HA, and saline groups, respectively. The quality of studies was rated as strong in 4 studies, moderate in 4 studies, and weak in 1 study. The meta-analysis revealed that PCs decreased pain visual analogue scale (VAS) scores compared to HA by an average of -1.11 (CI, -1.62 to -0.60; $P < 0.0001$) and -0.57 (CI, -1.55 to 0.41; $P = 0.26$) at 3- and 12-months follow-up respectively. Also, the average decrease in pain scores with PC compared to saline was -1.33 (CI, -2.61 to -0.06; $P = 0.04$), -2.07 (CI, -3.46 to -0.69; $P = 0.003$), and -2.71 (CI, -4.69 to -0.72; $P = 0.008$) at 3, 6, and 12 months, respectively. Regarding MMO measurements, PC was comparable to HA, but it was significantly better than saline after

3 and 6 months [2.9 mm (CI,1.47 to 4.3; P < 0.0001), and 1.69 mm (CI, 0.13 to 3.25; P = 0.03) respectively]. The authors concluded that PC reduces pain VAS scores compared to HA during the first 3 months after treatment, and when compared to saline, it reduces pain and increases MMO for longer durations. However, due to differences between groups regarding PC preparation protocols and study heterogeneity, further standardized randomized controlled trials (RCTs) are required.

Summary
For individuals with temporomandibular osteoarthritis in 2020, a systematic review and meta-analysis comparing platelet concentrates (PCs) versus hyaluronic acid (HA) or saline/Ringer's solution injections as treatments of temporomandibular disorders and disc displacement in terms of pain and maximum mouth opening (MMO) was completed and the authors concluded PC reduces pain VAS scores compared to HA during the first 3 m after treatment, and when compared to saline, it reduces pain and increases MMO for longer durations. However, due to differences between groups regarding PC preparation protocols and study heterogeneity, further standardized RCTs are required. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Platelet-Rich Plasma as an Adjunct to Surgery
Platelet-rich plasma (PRP) may also be used as an adjunct in certain types of surgery for some injuries including Achilles tendon rupture, rotator cuff repair, anterior cruciate ligament (ACL) reconstruction, articular cartilage repair, long bone healing and nonunion repair. Non orthopedic indications include wound care, plastic surgery, trauma surgery and general surgery. This is done by preparing the PRP in a special way, the polymerization of fibrin from fibrinogen creates a platelet gel (platelet rich fibrin matrix), which can then be used as an adjunct to surgery with the intent of promoting hemostasis and accelerating healing.

Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in patients with anterior cruciate ligament (ACL) reconstruction.

Populations
The relevant population of interest is individuals with ACL reconstruction.

Interventions
The therapy being considered is platelet-rich plasma injections plus orthopedic surgery. The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

Comparators
Comparators of interest include orthopedic surgery alone.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for ACL reconstruction has varying lengths of follow-up. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 2 years of follow-up is considered necessary to demonstrate efficacy.

In 2019, Chu et. al. published consensus recommendations from 2018 AAOS/NIH U-13 conference regarding optimizing the use of biologics in orthopaedic surgery which included the following:

Concern that misinformation from direct-to-consumer marketing of largely unproven "biologic" treatments such as platelet-rich plasma and cell-based therapies may erode the public trust and the responsible investment needed to bring legitimate biological therapies to patients have resulted in calls to action from professional organizations and governing bodies. In response to substantial patient demand for biologic treatment of orthopaedic conditions, the American Academy of Orthopaedic Surgeons convened a collaborative symposium and established a consensus framework for improving and accelerating the clinical evaluation, use, and optimization of biologic therapies for musculoskeletal diseases. The economic and disease burden of musculoskeletal conditions is high. Of the various conditions discussed, knee osteoarthritis was identified as a "serious condition" associated with substantial and progressive morbidity and emerged as the condition with the most urgent need for clinical trial development. It was also recognized that stem cells have unique characteristics that are not met by minimally manipulated mixed cell preparations. The work group recommended that minimally manipulated cell products be referred to as cell therapy and that the untested and uncharacterized nature of these treatments be clearly communicated within the profession, to patients, and to the public. Minimum standards for product characterization and clinical research should also be followed. A framework for developing clinical trials related to knee OA was agreed upon. In addition to recommendations for development of high-quality multicenter clinical trials, another important recommendation was that physicians and institutions offering biologic therapies commit to establishing high-quality patient registries and biorepository-linked registries that can be used for post market surveillance and quality assessments.

Anterior Cruciate Ligament Reconstruction
Figueroa et. al. (2015) performed a systematic review of the literature that compared the use of platelet-rich plasma (PRP) with a control group in patients with anterior cruciate ligament (ACL) ruptures/injuries assessing graft-to-bone healing, graft maturation, and/or clinical outcomes and were randomized controlled trials or prospective cohort studies.

Eleven studies fulfilled the inclusion criteria, comprising 516 patients (266 ACL reconstructions using PRP and 250 ACL reconstructions without PRP). Six studies reported a statistically significant difference (4 studies) or tendency toward faster graft maturation in the platelet group (2 studies). One study found no differences. Regarding tunnel healing/widening, 1 study showed faster healing in the PRP group and 5 studies showed no differences between the 2 groups. Considering clinical outcomes, 1 study showed better clinical outcomes with PRP use and 5 studies showed no benefits with the use of PRP. The authors concluded, there is no proof that clinical outcomes of ACL surgery are enhanced by the use of PRP.

In 2013, Moraes et. al. conducted a Cochrane review to assess the effects (benefits and harms) of platelet-rich therapies for treating musculoskeletal soft tissue injuries. They included randomized and quasi-randomized controlled trials that compared platelet-rich therapy (PRT) with either placebo, autologous whole blood, dry needling or no platelet-rich therapy for people with acute or chronic musculoskeletal soft tissue injuries. Primary outcomes were functional status, pain and adverse effects. This trial included eight clinical conditions which included anterior cruciate ligament (ACL) reconstruction (four trials 203 patients). Pooled data found no significant difference in the IKDC (International Knee Documentation Committee) scores between platelet-rich plasma (PRP) and control groups. The authors concluded overall, there is currently insufficient evidence to support the use of PRT for treating musculoskeletal soft tissue injuries i.e. ACL injuries with reconstruction. Researchers contemplating RCTs should consider the coverage of currently ongoing trials when assessing the need for future RCTs on specific conditions. There is need for standardization of PRP preparation methods.

Summary
For individuals with anterior cruciate ligament reconstruction who receive platelet-rich plasma (PRP) injection plus orthopedic surgery, the evidence includes 2 systematic reviews of multiple randomized controlled trials (RCTs) and prospective studies. One review showed that adjunctive PRP treatment did not result in a significant effect on IKDC (International Knee Documentation Committee) scores, a patient reported, knee specific outcome measure that assesses pain and functional activity. The other review concluded that there was no proof that clinical outcomes of ACL surgery are enhanced by the use of PRP. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Hip Fracture
One RCT was identified for treatment of a hip fracture with platelet-rich plasma.

Griffen et. al. (2013) reported on a single center, parallel group, participant-blinded, randomized controlled trial assessing the use of platelet-rich plasma (PRP) for the treatment of hip fractures in patients aged 65 years and older. Participants underwent internal fixation of the fracture with cannulated screws and were randomly allocated to receive an injection of platelet-rich plasma into the fracture site (n=101) or not (n=99). Primary outcome data were available for 82 of 101 and 78 of 99 participants allocated to

test and control groups, respectively; the remainder died prior to final follow-up. There was an absolute risk reduction of 5.6% (95% CI −10.6% to 21.8%) favoring treatment with platelet-rich therapy (χ^2 test, p=0.569). An adjusted effect estimate from a logistic regression model was similar (OR=0.71, 95% CI 0.36 to 1.40, z test; p=0.325). There were no significant differences in any of the secondary outcome measures excepting length of stay favoring treatment with platelet-rich therapy (median difference 8 days, Mann-Whitney U test; p=0.03). The number and distribution of adverse events were similar. Estimated cumulative incidence functions for the competing events of death and revision demonstrated no evidence of a significant treatment effect (HR 0.895, 95% CI 0.533 to 1.504; p=0.680 in favor of platelet-rich therapy). The authors concluded, no evidence of a difference in the risk of revision surgery within one year in participants treated with PRP therapy compared with those not treated.

Summary
A single randomized controlled trial (RCT) evaluated the efficacy of platelet-rich plasma (PRP) injections in individuals with hip fractures. This trial failed to show any statistically significant reductions in the need for revision surgery after PRP treatment. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Hip Arthroscopy
In 2020, Ali et. al evaluated the influence of platelet-rich plasma (PRP) injections combined with hip arthroscopic surgery. The authors hypothesized that patients treated with PRP would have improved postoperative outcome scores. A search of the National Institute for Health and Care Excellence (NICE) healthcare database advanced search (HDAS) via Athens (PubMed, MEDLINE, CINAHL, EMBASE, and AMED databases) was conducted from their years of inception to May 2018 with the keywords: "Hip Arthroscopy" and "Platelet-Rich Plasma". A quality assessment was performed based on the Cochrane risk of bias tool. Three studies were included for analysis; two of which had low risk of bias. The studies included 363 hips, of which 141 were randomized for PRP treatment. The mean age of all patients was 35 years and the follow-up ranged from 18.5 to 36 months. Authors used different PRP systems and preparations. Modified Harris hip score was reported in all three studies with two studies favoring the use of PRP. The use of PRP following hip arthroscopy did not lead to significantly improved postoperative pain or functional outcomes when compared to control groups in the studies included in this review.

Summary
The evidence is insufficient to determine the effects of the technology on net health outcomes.

Long Bone Nonunion
Samuel et. al. (2017) evaluated the efficacy of percutaneous platelet concentrate (PC) injection in increasing the chances of attaining union in delayed union of long bones and to know whether the time taken for union decreases with use of PC. Forty delayed unions

(15-30 weeks old) were randomized into a study group in which autologous PC prepared by blood bank centrifuge was percutaneously injected at the fracture site under image intensifier after activation with 10% calcium gluconate and a control group where patients were observed over time. Follow-up was every 6 weeks till fracture union. At each follow-up visit clinical and radiological parameters of union were assessed. Percentage union was 78% (18/23) in PC group and 59% (10/17) in control group, respectively ($p = 0.296$). The mean time to fracture union treated with PC (15.33 ± 9.91 weeks) was not different from the control group (13.10 ± 7.21 weeks; $p = 0.540$). In the PC group union is seen in 12 weeks after PC injection in 60 per cent of the cases. The authors concluded; isolated percutaneous PC injection increases union rates in delayed union of long bones. The results were, however, not statistically significant but show high positive association. Further studies are required to recommend routine use of PC injection.

In 2012, Griffen et. al. in a Cochrane review assessed the effects (benefits or harms) of platelet-rich therapies for treating long bone osteotomies, acute fractures, un-united fractures and defects in adults. Randomized and quasi-randomized controlled clinical trials evaluating any type of platelet-rich therapy compared with either no additional treatment or a placebo in the management of long bone osteotomies, acute fractures, un-united fractures and defects in adults. Studies including participants over 18 years of age; reporting functional outcomes, time to union, non-union, secondary procedures such as for fixation failure or delayed or non-union, adverse effects, pain or costs were included. Only one eligible study, involving 21 participants, was included. The study compared platelet-rich therapy and allogenic bone graft with allogenic bone graft alone in patients undergoing corrective osteotomy for medial compartment osteoarthrosis of the knee. The risk of bias associated with this study was substantial. There was no significant difference in patient-reported or clinician-assessed functional outcome scores between groups at one year. There was a statistically significant benefit from platelet-rich therapy in the proportion of bones that were united at one year (8/9 versus 3/9; RR 2.67; 95% CI 1.03 to 6.91). This benefit, however, was not maintained when assuming poor outcomes for participants who were lost to follow-up (8/11 versus 3/10; RR 2.42; 95% CI 0.88 to 6.68). One adverse event was reported in a participant receiving platelet-rich therapy. The authors concluded, while a potential benefit of platelet-rich therapies to augment long bone healing in adults cannot be ruled out, the currently available evidence from a single trial is insufficient to support the routine use of this intervention in clinical practice. Future trials should focus on reporting patient-reported functional outcomes from all trial participants for a minimum follow-up of one year.

Summary

Randomized controlled trials (RCTs) have evaluated the efficacy of platelet-rich plasma (PRP) injections in individual with long bone nonunion. While these trials may have shown a promise in a potential benefit of PRP to augment long bone healing, the current available evidence is insufficient to support the use of this intervention in clinical practice. Further studies are required to recommend the use of PRP injections to augment long bone healing to include a focus on reporting functional outcomes from all trial

participants for a minimum follow-up of one year. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Rotator Cuff Repair

In 2020, Chen et. al. conducted a systematic review and meta-analysis with bias assessment on the use of platelet-rich plasma for the improvement of pain and function in rotator cuff tears. A total of 18 level 1 studies were included in this review, 17 (1116 patients) of which could be included in quantitative analysis. The mean modified CMS was 79.4 ± 10.39. The Constant scores of patients who received PRP were significantly better short term (weighted mean difference [WMD], 2.89 [95% CI, 0.89-4.90]; $P < .01$) and long term (WMD, 2.66 [95% CI, 1.13-4.19]; $P < .01$). The VAS scores were significantly improved short term (WMD, -0.45 [95% CI, -0.75 to -0.15]; $P < .01$). Sugaya grade IV and V retears in PRP-treated patients were significantly reduced long term (odds ratio [OR], 0.34 [95% CI, 0.20-0.57]; $P < .01$). In PRP-treated patients with multiple tendons torn, there were reduced odds of retears (OR, 0.28 [95% CI, 0.13-0.60]; $P < .01$). Patients who received leukocyte-rich PRP had significantly better Constant scores compared with the leukocyte-poor PRP group, but there was no difference in VAS scores. Patients receiving PRP gel reported higher Constant scores compared with the controls, whereas those receiving nongel PRP treatments did not, although there was no difference in VAS scores. Long-term odds of retears were decreased, regardless of leukocyte content (leukocyte-poor PRP: OR, 0.36 [95% CI, 0.16-0.82]; leukocyte-rich PRP: OR, 0.32 [95% CI, 0.16-0.65]; all $P < .05$) or usage of gel (nongel: OR, 0.42 [95% CI, 0.23-0.76]; gel: OR, 0.17 [95% CI, 0.05-0.51]; all $P < .01$). The authors concluded long-term retear rates were significantly decreased in patients with rotator cuff-related abnormalities who received PRP. Significant improvements in PRP-treated patients were noted for multiple functional outcomes, but none reached their respective minimal clinically important differences. Overall, the results suggest that PRP may positively affect clinical outcomes, but limited data, study heterogeneity, and poor methodological quality hinder firm conclusions.

In 2017, Chen et. al. conducted a systematic review and meta-analysis on the efficacy of platelet-rich plasma (PRP) on tendon and ligament healing. The literature search was conducted through April 2017 which identified 37 articles for qualitative synthesis, 21 of which reported VAS outcomes and were used in a meta-analysis. Of the 21 studies, 8 enrolled patients undergoing rotator cuff repair. Patients in the PRP group experienced significant reductions in VAS pain compared with the control group at both short term (6 months) follow-up (-0.5; 95% CI, -0.7 to -0.1) and long term (≥ 1 year) follow-up (-0.5; 95% CI, -1.0 to -0.1). While findings were encouraging, reviewers warned that there was extensive variability in both the way PRP was prepared and how the PRP injections were administered.

Ebert et. al. (2017) published a randomized controlled trial (RCT) investigating whether the midterm clinical and radiographic outcomes of arthroscopic supraspinatus repair are enhanced after repeated postoperative applications of platelet-rich plasma (PRP). A total of 60 patients (30 control; 30 PRP) were initially randomized to receive 2 ultrasound-guided injections of PRP to the tendon repair site at 7 and 14 days after double-row

arthroscopic supraspinatus repair or not. A total of 55 patients (91.7%) underwent a clinical review and magnetic resonance imaging (MRI) at a mean of 3.5 years after surgery (range, 36-51 months). Patient-reported outcome measures (PROMs) included the Constant score, Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH) questionnaire, Oxford Shoulder Score (OSS), and visual analog scale (VAS) for pain. Global rating of change (GRC) scale and patient satisfaction scores were evaluated. Structural integrity of the surgical repair was assessed via MRI using the Sugaya classification system. At the midterm review, there was no difference between the groups for any of the PROMs. No differences between the groups were demonstrated for the subjective and range of motion subscales of the Constant score, although a significantly higher Constant strength subscale score was observed in the PRP group (3.3 points; 95% CI, 1.0-5.7; P = .006). There was no evidence for any group differences in MRI scores or retear rates, with 66.7% of PRP patients and 64.3% of control patients rated as Sugaya grade 1. Two control patients had symptomatic retears (both full thickness) within the first 16 weeks after surgery compared with 2 PRP patients, who suffered symptomatic retears (both partial thickness) between 16 weeks and a mean 3.5-year follow-up.

Fu et. al. (2017) conducted a systematic review and meta-analysis examining the effectiveness of platelet-rich plasma (PRP) or platelet-rich fibrin matrix (PRFM) versus no platelet-rich product for improving healing of rotator cuff injuries. The primary outcome was a functional score change from pre- to post-treatment ($Score_{post}$ $Score_{pre}$). The secondary outcome was a visual analogue scale (VAS) pain score change from pre- to post-treatment (VAS_{post} VAS_{pre}). A total of 11 studies were included in the meta-analysis. The total number of patients that received platelet-rich plasma or platelet-rich fibrin matrix was 320 and the number of control patients was 318. The standard difference in means of the functional scores was similar between patients administered platelet-rich plasma/fibrin matrix and patients in the control group (standard difference in means for functional scores = 0.029; 95% confidence interval (CI): -0.132 to 0.190; $p = 0.725$). The standard difference in means was similar between patients administered platelet-rich plasma and the controls (standard difference in means = 0.142; 95% CI: -0.080 to 0.364; $p = 0.209$). The authors concluded, the results of the meta-analysis does not support the use of platelet-rich plasma/platelet-rich fibrin matrix in patients with rotator cuff injuries.

In 2016, Saltzman et. al. performed a systematic review and meta-analysis examining arthroscopic rotator cuff repairs augmented with platelet-rich plasma (PRP) versus control (no PRP). Seven meta-analyses met inclusion and exclusion criteria. All were considered as being of similar quality with Quality of Reporting of Meta-analyses scores >15 and Oxman scores of 7. A total of 3,193 overlapping patients treated were included with mean follow-up from 12 to 31 months. When compared with control patients, use of PRP at the time of rotator cuff repair did not result in significantly lower overall retear rates or improved clinical outcome scores. The following postoperative functional scores comparing PRP versus control were reported: Constant (no significant difference demonstrated with PRP use in 5 of 6 reporting meta-analyses), University of California - Los Angeles (no difference, 6 of 6), American Shoulder and Elbow Society (no

difference, 4 of 4), and Simple Shoulder Test (no difference, 3 of 5). Subgroup analysis performed by 3 meta-analyses showed evidence of improved outcomes with solid PRP matrix versus liquid, small- and/or medium-sized versus large and/or massive tears, PRP application at the tendon-bone interface versus over tendon, and in the setting of double-row versus single-row rotator cuff. The authors concluded, the current highest level of evidence suggests that PRP use at the time of arthroscopic rotator cuff repair does not universally improve retear rates or affect clinical outcome scores. However, the effects of PRP use on retear rates trend toward beneficial outcomes if evaluated in the context of the following specific variables: use of a solid PRP matrix; application of PRP at the tendon-bone interface; in double-row repairs; and with small- and/or medium-sized rotator cuff tears.

Zhao et. al. (2015) conducted a meta-analysis of randomized controlled trials to appraise the retear rate and clinical outcomes of platelet-rich plasma (PRP) in patients undergoing arthroscopic full-thickness rotator cuff repair. Eight randomized controlled trials were included, with the sample size ranging from 28 to 88. Overall methodological quality was high. Fixed-effects analysis showed that differences were not significant between the 2 groups in retear rate (RR, 0.94; 95% CI, 0.70 to 1.25; P = .66), Constant score (mean difference, 1.12; 95% CI, -1.38 to 3.61; P = .38), and University of California at Los Angeles (UCLA) score (mean difference, -0.68; 95% CI, -2.00 to 0.65; P = .32). The strength of GRADE evidence was categorized respectively as low for retear, moderate for Constant score, and low for UCLA shoulder score. The authors concluded, this meta-analysis does not support the use of platelet-rich plasma (PRP) in the arthroscopic repair of full-thickness rotator cuff tears over repairs without platelet-rich plasma (PRP) because of similar retear rates and clinical outcomes.

In 2013, Moraes et. al. conducted a Cochrane review to assess the effects (benefits and harms) of platelet-rich therapies (PRT) for treating musculoskeletal soft tissue injuries. They included randomized and quasi-randomized controlled trials that compared platelet-rich therapy with either placebo, autologous whole blood, dry needling or no platelet-rich therapy for people with acute or chronic musculoskeletal soft tissue injuries. Primary outcomes were functional status, pain and adverse effects. These trials covered eight clinical conditions that included rotator cuff tears (arthroscopic repair) (six trials). The pooled data showed no statistically significant differences between the PRT groups and control groups. The authors concluded overall, there is currently insufficient evidence to support the use of PRT for treating musculoskeletal soft tissue injuries i.e. rotator cuff repair. Researchers contemplating RCTs should consider the coverage of currently ongoing trials when assessing the need for future RCTs on specific conditions. There is need for standardization of PRP preparation methods.

Summary

Randomized controlled trials (RCTs) and systematic reviews with meta-analysis have evaluated the efficacy of platelet-rich plasma (PRP) injections in individuals undergoing rotator cuff repair which failed to show a statistically and/or clinically significant impact

on symptoms (i.e., pain) or functional outcomes. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Total Knee Arthroplasty

Trams et. al., (2020) published a systematic review and meta-analysis that included 6 RCTs (N=621) evaluating the effects of intraoperative platelet-rich plasma as an adjunct to total knee arthroplasty. Two studies were deemed at high risk of bias. The primary aim of the studies was to assess blood loss during the procedure. While there were significant differences in favor of platelet-rich plasma in the overall effect on blood parameters in comparison to the control groups (standard mean difference, -0.29; 95% CI, -0.46 to -0.11), no significant differences in range of motion, functional outcomes, or long-term pain were observed.

In 2014, Morishita et. al. conducted a randomized controlled study to assess the effects of platelet-rich plasma (PRP) in total knee arthroplasty. Forty patients who underwent unilateral TKA (total knee arthroplasty) were evaluated prospectively; 20 received intraoperative PRP and 20 served as control subjects (no additional intraoperative treatment). The results showed no significant differences in reduction of bleeding, range of motion, swelling around the knee joint, muscle power recovery, pain, Knee Society Scores, and Knee Injury and Osteoarthritis Outcome Score between the 2 groups. Additionally, no distinct clinical characteristics were found in patients who received intraoperative PRP. The authors concluded, that intraoperative PRP does not improve outcomes of total knee arthroplasty (TKA).

Summary

A single small randomized controlled trial (RCT) and systematic review and meta-analysis evaluated the efficacy of intraoperative platelet-rich plasma (PRP) in individuals undergoing total knee arthroplasty. The results showed no significant differences in reduction of bleeding, range of motion, swelling around the knee joint, muscle power recovery, pain, Knee Society Scores, and Knee Injury and Osteoarthritis Outcome Score between the 2 groups (intraoperative PRP and no PRP intraoperatively). Intraoperative PRP does not improve outcomes of function or pain outcomes in total knee arthroplasty (TKA). The evidence is insufficient to determine the effects of the technology on net health outcomes.

Musculoskeletal Soft Tissue Injuries

In 2013, Moraes et. al. conducted a Cochrane review on platelet-rich therapies (PRT) for musculoskeletal soft injuries. Platelet-rich therapies are being used increasingly in the treatment of musculoskeletal soft tissue injuries such as ligament, muscle and tendon tears and tendinopathies. These therapies can be used as the principal treatment or as an augmentation procedure (application after surgical repair or reconstruction). Platelet-rich therapies are produced by centrifuging a quantity of the patient's own blood and extracting the active, platelet-rich, fraction. The platelet-rich fraction is applied to the injured tissue, for example, by injection. Platelets have the ability to produce several growth factors, so these therapies should enhance tissue healing. There is a need to assess

whether this translates into clinical benefit. They included randomized and quasi-randomized controlled trials that compared platelet-rich therapy with either placebo, autologous whole blood, dry needling or no platelet-rich therapy for people with acute or chronic musculoskeletal soft tissue injuries. Primary outcomes were functional status, pain and adverse effects. They included data from 19 small single center trials (17 randomized and two quasi-randomized; 1088 participants) that compared platelet-rich therapy (PRT) with placebo, autologous whole blood, dry needling, or no platelet-rich therapy. These trials covered eight clinical conditions: rotator cuff tears (arthroscopic repair) (six trials); shoulder impingement syndrome surgery (one trial); elbow epicondylitis (three trials); anterior cruciate ligament (ACL) reconstruction (four trials), ACL reconstruction (donor graft site application) (two trials), patellar tendinopathy (one trial), Achilles tendinopathy (one trial) and acute Achilles rupture surgical repair (one trial). We also grouped trials into 'tendinopathies' where platelet-rich therapy (PRT) injections were the main treatment (five trials), and surgical augmentation procedures where PRT was applied during surgery (14 trials). Trial participants were mainly male, except in trials including rotator cuff tears, and elbow and Achilles tendinopathies. Three trials were judged as being at low risk of bias; the other 16 were at high or unclear risk of bias relating to selection, detection, attrition or selective reporting, or combinations of these. The methods of preparing platelet-rich plasma (PRP) varied and lacked standardization and quantification of the PRP applied to the patient. They were able to pool data for primary outcomes (function, pain, adverse events) for a maximum of 11 trials and 45% of participants. The evidence for all primary outcomes was judged as being of very low quality. Data assessing function in the short term (up to three months) were pooled from five trials that assessed PRT in three clinical conditions and used four different measures. These showed no significant difference between PRT and control (SMD 0.24; 95% confidence interval (CI) -0.07 to 0.56; P value 0.13; I^2 = 35%; 273 participants; positive values favor PRT). Medium-term function data (at six months) were pooled from six trials that assessed PRT in five clinical conditions and used six different measures. These also showed no difference between groups (SMD 0.06; 95% CI -0.39 to 0.51; P value 0.79; I^2 = 64%; 262 participants). Long-term function data (at one year) were pooled from 10 trials that assessed PRT in five clinical conditions and used six different measures. These also showed no difference between groups (SMD 0.25, 95% CI -0.07 to 0.57; P value 0.12; I^2 = 66%; 484 participants). Although the 95% confidence intervals indicate the possibility of a slightly poorer outcome in the PRT group up to a moderate difference in favor of PRT at short- and long-term follow-up, these do not translate into clinically relevant differences. Data pooled from four trials that assessed PRT in three clinical conditions showed a small reduction in short-term pain in favor of PRT on a 10-point scale (MD -0.95, 95% CI -1.41 to -0.48; I^2 = 0%; 175 participants). The clinical significance of this result is marginal. Four trials reported adverse events; another seven trials reported an absence of adverse events. There was no difference between treatment groups in the numbers of participants with adverse effects (7/241 versus 5/245; RR 1.31, 95% CI 0.48 to 3.59; I^2 = 0%; 486 participants). In terms of individual conditions, they pooled heterogeneous data for long-term function from six trials of PRT application during rotator cuff tear surgery. This showed no statistically or clinically significant differences between the two groups (324 participants). Pooled data

for short-term function for three elbow epicondylitis trials (179 participants) showed a statistically significant difference in favor of PRT, but the clinical significance of this finding is uncertain. The available evidence is insufficient to indicate whether the effects of PRT will differ importantly in individual clinical conditions. Authors concluded, there is currently insufficient evidence to support the use of PRT (platelet-rich therapy) for treating musculoskeletal soft tissue injuries. There is a need for standardization of platelet-rich therapy methods.

Summary
A systematic review of randomized and quasi-randomized controlled trials that compared platelet-rich therapy with either placebo, autologous whole blood, dry needling, or no platelet-rich therapy for people with acute or chronic musculoskeletal soft tissue injuries. The primary outcomes were functional status, pain, and adverse effects. This review showed overall for the individual clinical conditions there is currently insufficient evidence to support the use of platelet-rich therapies (PRT) for treating musculoskeletal soft tissue injuries. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Spinal Fusion
One small (N=62), unblinded, single-center RCT for spinal fusion conducted in Japan and published by Kubota et al (2019) was identified that compared platelet-rich plasma to no platelet-rich plasma.[54,] Follow-up was 24 months. Although fusion rates were significantly improved with platelet-rich plasma, there were no significant differences in VAS scores between the 2 groups. Major limitations of this RCT include that patients were unblinded to treatment and there was no placebo comparator.

Two prospective observational studies found no differences in fusion rates with use of a platelet gel or platelet glue compared with historical control.

Summary
For individuals undergoing spinal fusion who receive platelet-rich plasma injections, the evidence includes a single small RCT and a few observational studies. Studies have generally failed to show a statistically and/or clinically significant impact on symptoms (i.e., pain). The evidence is insufficient to determine the effects of the technology on health outcomes.

Summary of Evidence
Platelet-rich therapies (PRT) i.e., platelet-rich plasma (PRP) injections are being used increasingly in the treatment of musculoskeletal soft tissue injuries such as ligament, muscle and tendon tears and tendinopathies and osteoarthritis. These therapies can be used as the principal treatment or as an augmentation procedure (application after surgical repair or reconstruction). Platelet-rich therapies/platelet-rich plasma (PRP) are produced by centrifuging a quantity of the patient's own blood and extracting the active, platelet-rich, fraction. The platelet-rich fraction is applied to the injured tissue, for example, by injection. Platelets have the ability to produce several growth factors, so these therapies are thought to enhance tissue healing. There is a need to assess whether

this translates into clinical benefit. Based on review of the peer reviewed medical literature regarding platelet-rich plasma (PRP) there have been a number of studies looking at whether platelet-rich plasma (PRP) is effective for conditions affecting bones, muscles, ligaments, and other tissues as the principal treatment or as an augmentation procedure. The potential benefit of PRP has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors. However, current results of PRP trials are mixed and studies are limited in both size and quality. Systematic reviews with meta-analysis found that a greater portion of the studies reported no benefit from PRP than studies that reported a benefit. It is unknown if the mixed results are due to variability in the conditions studied and outcomes measured, to differences in platelet separation technique, concentration, or activation, or to differences in the timing and frequency of administration. Further controlled studies with larger sample size and longer follow-up are needed regarding the use of PRP in the treatment of musculoskeletal injuries and as an adjunct to surgery. There is also a need for standardization of PRP methods. The evidence is insufficient to determine the effects of the technology on net health outcomes.

In 2019, Chu et. al. published consensus recommendations from 2018 AAOS/NIH U-13 conference regarding optimizing the use of biologics in orthopaedic surgery which included the following:

Concern that misinformation from direct-to-consumer marketing of largely unproven "biologic" treatments such as platelet-rich plasma (PRP) and cell-based therapies may erode the public trust and the responsible investment needed to bring legitimate biological therapies to patients have resulted in calls to action from professional organizations and governing bodies. In response to substantial patient demand for biologic treatment of orthopaedic conditions, the American Academy of Orthopaedic Surgeons convened a collaborative symposium and established a consensus framework for improving and accelerating the clinical evaluation, use, and optimization of biologic therapies for musculoskeletal diseases. The economic and disease burden of musculoskeletal conditions is high. Of the various conditions discussed, knee osteoarthritis was identified as a "serious condition" associated with substantial and progressive morbidity and emerged as the condition with the most urgent need for clinical trial development. It was also recognized that stem cells have unique characteristics that are not met by minimally manipulated mixed cell preparations. The work group recommended that minimally manipulated cell products be referred to as cell therapy and that the untested and uncharacterized nature of these treatments be clearly communicated within the profession, to patients, and to the public. Minimum standards for product characterization and clinical research should also be followed. A framework for developing clinical trials related to knee OA was agreed upon. In addition to recommendations for development of high-quality multicenter clinical trials, another important recommendation was that physicians and institutions offering biologic therapies commit to establishing high-quality patient registries and biorepository-linked registries that can be used for post-market surveillance and quality assessments.

Autologous Protein Solution

Osteoarthritis is a common degenerative disease characterized by chronic pain, joint stiffness, reduced function, cartilage degradation, loss of subchondral bone and synovial inflammation. Although symptoms may be alleviated with conservative therapies such as analgesic drugs, lifestyle modifications, and physical therapy, no disease modifying treatment is currently available. New approaches may allow for earlier intervention than joint replacement, autologous protein solution (APS) is a new therapy under investigation for the treatment of osteoarthritis of the knee.

One mechanism of osteoarthritis progression is a degenerative feed-forward cycle caused by pathological increases in inflammatory cytokines and catabolic factors within and adjacent to the synovial space. Inflammatory and catabolic proteins such as interleukin-1 beta, tumor necrosis factor, and matrix metalloproteinase, have been implicated in cartilage degradation and continued osteoarthritis progression. It has been proposed that approaches to block these deleterious proteins could improve patients' symptoms and perhaps the progression of the disease may be halted or even reversed.

Autologous protein solution (APS) is an autologous blood derived therapy composed of concentrated white blood cells (WBCs), platelets and plasma to contain high concentrations of anti-inflammatory cytokines and anabolic growth factors. White blood cells are the main source of interleukin-1 receptor antagonist in the body which competitively inhibits inflammatory interleukin-1B signaling. Platelets alpha granules contain anabolic growth factors which are important in cartilage repair pathways and synergistically act with anti-inflammatory cytokines on the nuclear factor kappa-light chain enhancer of activated B-cells pathway. Plasma contains anti-inflammatory cytokines including soluble interleukin-1 receptor antagonist-type II and soluble tumor necrosis factor receptor type 1 and type II. The ability of APS to block both interleukin-1B and tumor necrosis factor signaling pathways suggest it may have utility in the treatment of osteoarthritis by blocking the effects of inflammation in chondrocytes, macrophages and cartilage explants.

A small amount of blood is drawn from the patient, autologous protein solution (APS) kits have been developed to process the autologous blood to produce the high concentrations of anti-inflammatory cytokines (proteins) and anabolic growth factors. The APS kit aids separation and concentration of the patient's blood components through the use of centrifuge. The kit permits autologous protein solution to be prepared at the point of care. The kit includes blood processing devices, a cell separator, cell concentrator and a vial of anticoagulant citrate dextrose solution. The use of prepared APS should be used within 4 hours after drawing blood from the patient. The safety and effectiveness of frozen stored APS has not been established. Prior to injecting APS intra-articularly, the physician may remove any synovial fluid or effusion before the injection. APS should be injected into a single anatomical location not partition into multiple injections or injecting at multiple locations. This is given to inhibit inflammation and reduce cartilage degradation.

Patel et. al. (2013) reported on treatment with platelet-rich plasma (PRP) being more effective than placebo for knee osteoarthritis in a prospective, double-blind, randomized trial. A total of 78 patients (156 knees) with bilateral OA were divided randomly into 3 groups. Group A (52 knees) received a single injection of PRP, group B (50 knees) received 2 injections of PRP 3 weeks apart, and group C (46 knees) received a single injection of normal saline. White blood cell (WBC)-filtered PRP with a platelet count 3 times that of baseline (PRP type 4B) was administered in all. All the groups were homogeneous and comparable in baseline characteristics. Clinical outcome was evaluated using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire before treatment and at 6 weeks, 3 months, and 6 months after treatment. They were also evaluated for pain by a visual analog scale, and overall satisfaction with the procedure and complications were noted. Statistically significant improvement in all WOMAC parameters was noted in groups A and B within 2 to 3 weeks and lasting until the final follow-up at 6 months, with slight worsening at the 6-month follow-up. The mean WOMAC scores (pain, stiffness, physical function, and total score) for group A at baseline were 10.18, 3.12, 36.56, and 49.86, respectively, and at final follow-up were 5.00, 2.10, 20.08, and 27.18, respectively, showing significant improvement. Similar improvement was noted in group B (mean WOMAC scores at baseline: 10.62, 3.50, 39.10, and 53.20, respectively; mean WOMAC scores at final follow-up: 6.18, 1.88, 22.40, and 30.48, respectively). In group C, the mean WOMAC scores deteriorated from baseline (9.04, 2.70, 33.80, and 45.54, respectively) to final follow-up (10.87, 2.76, 39.46, and 53.09, respectively). The 3 groups were compared with each other, and no improvement was noted in group C as compared with groups A and B ($P < .001$). There was no difference between groups A and B, and there was no influence of age, sex, weight, or body mass index on the outcome. Knees with Ahlback grade 1 fared better than those with grade 2. Mild complications such as nausea and dizziness, which were of short duration, were observed in 6 patients (22.2%) in group A and 11 patients (44%) in group B. The authors concluded, a single dose of WBC-filtered PRP in concentrations of 10 times the normal amount is as effective as 2 injections to alleviate symptoms in early knee OA. The results, however, deteriorate after 6 months. Both groups treated with PRP had better results than did the group injected with saline only.

In 2018, Kon et. al. investigated the clinical outcomes of one intra-articular injection of autologous protein solution (APS) for the treatment of knee osteoarthritis in a multicenter randomized, double blind, saline controlled trial. Forty-six patients with unilateral knee OA (Kellgren-Lawrence 2 or 3) were randomized into the APS group (n = 31), which received a single ultrasound-guided injection of APS, and the saline (control) group (n = 15), which received a single saline injection. Patient- reported outcomes and adverse events were collected at 2 weeks and at 1, 3, 6, and 12 months through visual analog scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee injury and Osteoarthritis Outcome Score (KOOS), Short Form-36 (SF-36), Clinical Global Impression of Severity/Change (CGI-S/C), Patient Global Impression of Severity/Change (PGI-S/C), and Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responder rate. Imaging evaluation was also performed with radiograph and magnetic resonance imaging

(MRI) before and after treatment (12 months and 3 and 12 months, respectively). The safety profile was positive, with no significant differences in frequency and severity of adverse events between groups. The improvement from baseline to 2 weeks and to 1, 3, and 6 months was similar between treatments. At 12 months, improvement in WOMAC pain score was 65% in the APS group and 41% in the saline group (P = .02). There were no significant differences in VAS pain improvement between groups. At 12 months, APS group showed improved SF-36 Bodily Pain subscale (P = .0085) and Role Emotional Health subscale (P = .0410), as well as CGI-C values (P = .01) compared with saline control. Significant differences between groups were detected in change from baseline to 12 months in bone marrow lesion size as assessed on MRI and osteophytes in the central zone of the lateral femoral condyle, both in favor of the APS group (P = .041 and P = .032, respectively). There were no significant differences between APS and control groups in other measured secondary endpoints.

In 2020, Wasai et. al. investigated the difference in the humoral factors in two types of platelet-rich plasma using the Autologous Protein Solution (APS) kit (group Z leucocyte-rich PRP) or the Cellaid Serum Collection Set P type (group J; leucocyte-poor [LP]-PRP) in patients with osteoarthritis of the knee (OAK). OAK patients (n=12; group Z=6 and group J=6). Both anti-inflammatory and inflammatory cytokines were highly enriched in APS. The concentrations of tumor necrosis factor (TNF)-α, platelet-derived growth factor, fibroblast growth factor, soluble TNF-receptor 2, soluble Fas and transforming growth factor-β1 were higher in group Z, while the total amounts were higher in group J. Clinical outcome scores evaluated using KOOS (Knee injury and Osteoarthritis Outcome Score) revealed a significant difference between kits only for the preoperative symptoms sub-score; no differences were detected in other sub-scores or KOOS total scores. However, the extent to which clinical outcome scores improved for other sub-scores and KOOS total scores over time was greater for group Z than for group J; of note, the magnitude of change in symptoms and quality of life (QOL) sub-scores and the KOOS total score at 3 months were significantly greater in group Z, suggesting that APS injections every 3to 6 months may be effective. Further studies are needed with greater number of participants and longer follow-up to assess APS in the treatment of OA of the knee.

In 2020, Kon et. al. in a case series investigated the effects of a single intra-articular injection of autologous protein solution (APS) in patients affected by knee OA previously documented in a one year multicenter double-blind randomized saline controlled trial last up to 3 years (see above trial from 2018). A total of 46 patients with Kellgren-Lawrence 2 or 3 knee OA were randomized into 2 groups: 1 ultrasound-guided APS injection (n = 31) or 1 saline injection (n = 15). At 1 year, the saline group was allowed to cross over. Patients were re-evaluated at 24 and 36 months through the visual analog scale for pain (VAS), Western Ontario and McMaster Universities Osteoarthritis Index Likert 3.1 (WOMAC LK 3.1), Knee injury and Osteoarthritis Outcome Score (KOOS), 36-Item Short Form Health Survey (SF-36), and Outcome Measures in Rheumatology–Osteoarthritis Research Society International (OMERACT-OARSI) responder rate. Magnetic resonance imaging evaluation was performed with the MRI Osteoarthritis Knee

Score (MOAKS) before and at 24 months after treatment, and radiographs were assessed per Kellgren-Lawrence before and annually after treatment. In the APS cohort, WOMAC pain improved from 11.5 ± 2.4 (mean ± SD) to 4.3 ± 4.0 at 1 year and to 5.7 ± 5.0 at 3 years ($P < .0001$ vs baseline). The APS cohort also showed a statistically significant improvement in its KOOS pain score from 39.4 ± 13.1 to 70.6 ± 21.5 at 1 year and to 64.1 ± 24.6 at 3 years ($P < .0001$ vs baseline) and VAS pain scores from 5.5 ± 2.2 to 2.6 ± 2.5 at 1 year and to 3.4 ± 2.9 at 3 years ($P = .0184$ vs baseline). VAS pain score significantly worsened from 12 to 36 months ($P = .0411$). All patients in the saline group decided to cross over to APS, and their final scores were better than baseline, although not significantly better than at the crossover point. Overall, 7 of 26 (26.9%) APS cases and 4 of 14 (28.6%) crossover cases were considered failures as patients underwent further injective treatments or surgical procedures between the 12- and 36-month follow-up. MOAKS findings showed no statistically significant differences. Patients with better cartilage had greater WOMAC pain improvement when their baseline scores were worse, whereas the trend was reversed for patients with cartilage loss at baseline.

Summary of Evidence
Based on review of the peer reviewed medical literature, the literature is limited regarding autologous protein solution (APS) for the treatment of osteoarthritis. Study results may show promise that symptoms were improved, however, based on study results authors concluded that well controlled, randomized multicenter clinical studies to establish safety and clinical effectiveness is warranted. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence (NICE)
In 2013, NICE issued guidance on the use of autologous blood injection for tendinopathy (with or without techniques to produce platelet-rich plasma). NICE concluded the evidence on efficacy remains inadequate, with few studies available that use appropriate comparators. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

NICE encourages further research comparing autologous blood injections (with or without techniques to produce platelet-rich plasma) 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, quality of life and function, and whether subsequent surgical intervention is needed.

In 2013, NICE issued guidance on autologous blood injection for plantar fasciitis (with or without techniques to produce platelet rich plasma). NICE concluded the evidence on efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

NICE encourages further research comparing autologous blood injection (with or without techniques to produce platelet-rich plasma) against established treatments for managing plantar fasciitis. Trials should clearly describe patient selection, including duration of symptoms and any prior treatments. Outcomes should include specific measures of pain and function.

In 2014, NICE issued guidance on the use of platelet rich plasma injections for osteoarthritis of the knee. NICE concluded that the current evidence on platelet-rich plasma injections for osteoarthritis of the knee raises no major safety concerns; however, the evidence on efficacy is inadequate in quality. NICE recommends this procedure should only be used with special arrangements for clinical governance, consent and audit or research.

Further research into platelet-rich plasma injections for treating osteoarthritis of the knee should clearly describe patient selection and should take the form of well-designed, controlled studies that compare the procedure against other methods of management. Outcomes should include measures of knee function, patient reported outcome measures and the timing of subsequent interventions. Studies aimed at assessing possible cartilage repair after platelet-rich plasma injections should include detailed radiographic or MRI imaging before and after the procedure.

American Academy of Orthopaedic Surgeons (AAOS)
In 2021, the American Academy of Orthopaedic Surgeons (AAOS) updated their guideline on the management of osteoarthritis of the knee (non-arthroplasty), evidence-based guideline, which states the following:

Platelet-rich Plasma
Platelet-rich plasma (PRP) may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee.

Strength of Recommendation: Limited (downgrade) Description: 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. Also, higher strength evidence can be downgraded to limited due to major concerns.

Future research in this area should embrace detailed osteoarthritis characterization including sub-group analyses and osteoarthrosis severity stratification. Furthermore, using clinically relevant outcomes and controls for bias are warranted along with cost-effectiveness analysis. Specifically, to platelet rich plasma it will be of outmost importance to include comprehensive platelet rich plasma characterization and description of platelet rich plasma preparation protocol.

In 2020, the American Academy of Orthopaedic Surgeons (AAOS) adopted the management of glenohumeral joint osteoarthritis evidence-based clinical practice guideline which states the following:

Injectable Biologics
In the absence of reliable evidence, it is the opinion of the work group that injectable biologics, such as stem cells or platelet-rich plasma, cannot be recommended in the treatment of glenohumeral osteoarthritis.

In 2019, the American Academy of Orthopaedic Surgeons (AAOS) adopted the management of rotator cuff injuries evidence-based clinical practice guideline which states the following:

Platelet Rich Plasma (PRP) Injection in Partial – Thickness Tears
Limited evidence does not support the routine use of platelet rich plasma for the treatment of rotator cuff tendinopathy or partial tears.

In 2017, the American Academy of Orthopaedic Surgeons (AAOS) issued guidance on the management of osteoarthritis of the hip. In the section on intra-articular injectables, the guideline states that there is strong evidence supporting the use of intra-articular corticosteroids to improve function and reduce pain in the short term for patients with osteoarthritis of the hip. There was also strong evidence that the use of intra-articular hyaluronic acid does not perform better than placebo in improving function, stiffness, and pain in patients with hip osteoarthritis. The guidelines also noted that there were no high-quality studies comparing platelet-rich plasma (PRP) with placebo for the treatment of osteoarthritis of the hip.

American Association of Hip and Knee Surgeons
In 2019, the American Association of Hip and Knee Surgeons issued a position statement regarding biologics for advanced hip and knee arthritis which states the following:

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.

Regulatory Status
Blood products such as platelet rich plasma (PRP) are regulated by the Center for Biologics Evaluation and Research (CBER). CBER is responsible for regulating human cells, tissues, and cellular and tissue-based products. The regulation process for these products is described in the U.S. Food and Drug Administration (FDA) 21 CFR 1271 of the Code of Federal Regulations. Under these regulations, certain products including blood products such as PRP are exempt and therefore do not follow the traditional FDA regulatory pathway. To date, FDA has not attempted to regulate activated PRP.

Several PRP preparation systems are available, many of which were cleared for marketing by FDA through the 510(k) process for producing platelet-rich preparations

intended to be mixed with bone graft materials to enhance the bone grafting properties in orthopedic practices. The use of PRP outside of this setting (e.g., an office injection) would be considered off-label. Examples of approved devices include:

- Aurix™ System (Nuo Therapeutics, Inc. Gaithersburg, MD)
- AutoloGel (Cytomedix, Inc., Rockville, MD)
- Autologous Platelet Grafting™ (SafeBlood® Technologies, Inc., Little Rock, AR)
- Cascade® Autologous Platelet System (Musculoskeletal Transplant Foundation [MTF], Edison, NJ)
- Fibrinet® Autologous PRP System (Cascade Medical Enterprises, Wayne, NJ)
- Gravitational Platelet Separation System (GPS®II) (Biomet Biologics, Inc., Warsaw, IN)
- Mini GPSII (Biomet Biologics, Inc., Warsaw, IN)
- Elmd-500 Autotransfusion System (Medtronic Electomedics)
- SmartPReP® 2 APC+ system (Harvest Technologies Corporation, Plymouth, MA)

The use of different devices and procedures can lead to variable concentrations of activated platelets and associated proteins, increasing variability between studies of clinical efficacy.

The nSTRIDE Autologous Protein Solution (APS) Kit (Biomet Biologics, Warsaw, IN) to treat knee osteoarthritis (OA) is not commercially available in the U.S.

PRIOR APPROVAL

Not applicable.

POLICY

See also medical policies

- 08.01.22 Stem Cell Therapy for Orthopedic Indications (Including Allograft Bone Products used with Stem Cells
- 02.01.18 Prolotherapy

Platelet - Rich Plasma

The use of platelet - rich plasma (PRP) injections as a primary treatment or as an adjunct to a surgical repair or reconstruction is considered **investigational** for all orthopedic indications, including but not limited to the following:

- Plantar fasciitis
- Achilles tendinopathy/Achilles tendon rupture
- Acute joint injuries (sprains/strains)
- Anterior cruciate ligament (ACL) injuries/ACL reconstruction

- As a post-surgery supplement
- Carpal tunnel syndrome
- Epicondylitis
- Fractures, including long bone non-union
- Muscle injuries
- Osteoarthritis (knee, hip and shoulder)
- Osteochondral lesions
- Plantar fasciitis
- Rotator cuff injuries/rotator cuff repair
- Shoulder impingement syndrome surgery
- Soft tissue trauma (e.g., tendon and ligament rupture/tears)
- Spinal fusion
- Tendinopathies (e.g., elbow, heel, knee, shoulder)
- Temporomandibular disorders to include the treatment of temporomandibular osteoarthritis
- Tendinopathies (e.g., elbow, heel, knee, shoulder)
- Total or partial knee or hip arthroplasty

Based on review of the peer reviewed medical literature regarding platelet-rich plasma (PRP) injections for the treatment of orthopedic indications the current results of platelet-rich plasma (PRP) trials are mixed, and studies are limited in both size and quality. Systematic reviews with meta-analysis found that a greater portion of the studies reported no benefit from platelet-rich plasma (PRP) than studies that reported a benefit. It is unknown if the mixed results are due to variability in the conditions studied and outcomes measured, to differences in platelet separation technique, concentration or activation, or to differences in the timing and frequency of administration. Further controlled studies with larger sample size and longer follow-up are needed regarding the use of platelet-rich plasma (PRP) in the treatment of orthopedic indications. There is also a need for standardization of PRP methods. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Autologous Protein Solution
The use of autologous protein solution (APS) is considered **investigational** for all orthopedic indications, including but not limited to the treatment of osteoarthritis.

Based on review of the peer reviewed medical literature, the literature is limited regarding autologous protein solution (APS) for the treatment of osteoarthritis. Study results may show promise that symptoms were improved, however, based on study results authors have concluded that well controlled, randomized multicenter clinical studies to establish safety and clinical effectiveness is warranted. The evidence is insufficient to determine the effects of the technology on net health outcomes.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 0232T Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed.
- 0481T Injection(s) autologous white blood cell concentrate (autologous protein solution), any site, including image guidance, harvesting and preparation when performed

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POLICY HISTORY

Date	Reason	Action
January 2022	Annual Review	Policy Revision
January 2021	Annual Review	Policy Revised
January 2020	Annual Review	Policy Renewed
January 2019	Annual Review	Policy Revised
January 2018	Annual Review	Policy Revised
January 2017	Annual Review	Policy Revised
January 2016	Annual Review	Policy Revised
February 2015	Annual Review	Policy Revised
April 2014	Annual Review	Policy Revised

May 2013	Annual Review	Policy Revised
May 2012	Annual Review	Policy Renewed
August 2011	Annual Review	Policy Revised

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
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