# 02.01.32 Platelet-Rich Plasma and Autologous Protein Solution for Orthopedic Applications

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### Related Policies:

- 02.01.18 Prolotherapy
- 02.01.21 Temporomandibular Joint (TMJ) Dysfunction: Diagnosis and Treatments
- 02.01.61 Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions
- 07.01.64 Autologous Chondrocyte Implant for Focal Articular Cartilage Lesions
- 07.01.65 Osteochondral Allografts and Autografts in the Treatment of Focal Articular Cartilage Lesions
- 08.01.22 Stem Cell Therapy for Orthopedic Indications (Including Allograft Bone Products used with Stem Cells)

### Summary

## Description

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.

The use of autologous protein solution (APS), 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 factor has been proposed in the treatment of osteoarthritis by blocking the effects of inflammation in chondrocytes, macrophages, and cartilage explants.

## Summary of Evidence

### Platelet-Rich Plasma

### Primary Treatment for Tendinopathies

For individuals with tendinopathy who receive platelet-rich plasma (PRP) injections, the evidence includes multiple randomized controlled trials (RCTs) and systematic reviews with meta-analyses. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life (QOL), and treatment-related morbidity. Findings from meta-analyses of RCTs have been mixed and have generally found that PRP did not have a statistically and/or clinically significant impact on symptoms (i.e., pain) or functional outcomes. Findings from a subsequently published RCT failed to find improvement compared with placebo. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### Primary Treatment for Non-Tendon Soft Tissue Injury or Inflammation

For individuals with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis) who receive PRP injections, the evidence includes several small RCTs, multiple prospective observational studies, and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity. The 2014 systematic review, which identified 3 RCTs on PRP for plantar fasciitis, did not pool study findings. Results among the remaining RCTs were inconsistent. The largest RCT showed that treatment using PRP compared with corticosteroid injection resulted in statistically significant improvement in pain and disability, but not QOL. A 2023 systematic review found improved visual analog scale (VAS) scores with PRP compared to corticosteroid injections out to 6 months duration, but numerical differences between groups were small. Larger RCTs completed over a sufficient duration of time (i.e., 2-years) are still needed to address important uncertainties in efficacy and safety. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### Primary Treatment for Osteochondral Lesions

For individuals with osteochondral lesions who receive PRP injections, the evidence includes an open-labeled quasi-randomized study. Relevant outcomes are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity. The quasi-randomized study found a statistically significant greater impact on outcomes in the PRP group than in the hyaluronic acid group. Limitations of the evidence base include lack of adequately randomized studies, lack of blinding, lack of sham controls, and comparison only to an intervention of uncertain efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### Primary Treatment for Knee or Hip Osteoarthritis

For individuals with knee or hip osteoarthritis (OA) who receive PRP, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity. Most trials have compared PRP with hyaluronic acid for knee OA. Systematic reviews have generally found that PRP was more effective than placebo or hyaluronic acid in reducing pain and improving function. However, systematic review authors have noted that their findings should be interpreted with caution due to important limitations including significant residual statistical heterogeneity, questionable clinical significance, and high risk of bias in study conduct. RCTs with a follow-up of at least 12-months published subsequent to the systematic reviews found statistically significantly greater 12-month reductions in pain and function outcomes, but these findings were also limited by important study conduct flaws including potential inadequate control for selection bias and limited or unclear blinding. Also, benefits were not maintained at 5-years. Using hyaluronic acid as a comparator is questionable because the evidence demonstrating the benefit of hyaluronic acid treatment for OA is not robust. Two systematic reviews evaluating hip OA did not report any statistically or clinically significant differences in pain or functional outcomes compared to hyaluronic acid, corticosteroids, or placebo. Additional studies comparing PRP with placebo and with alternatives other than hyaluronic acid 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 that the technology results in an improvement in the net health outcome.

### Adjunct to Surgery

For individuals with anterior cruciate ligament (ACL) reconstruction who receive PRP injections plus orthopedic surgery, the evidence includes several systematic reviews of multiple RCTs and prospective studies and a retrospective matched case-control study. Relevant outcomes are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. In 2 systematic reviews that conducted a meta-analysis, adjunctive PRP treatment did not result in a significant effect on International Knee Documentation Committee (IKDC) scores, a patient-reported, knee-specific outcome measure that assesses pain and functional activity. One systematic review found improvements with PRP compared to controls in outcomes at 6-months, but these differences were determined to be clinically irrelevant with the exception of pain at 6-months which was improved with PRP. Individual trials have shown mixed results. A retrospective matched case-control study found no differences in knee function scores or time to return of activity between PRP and matched-control groups at 2-years; however, the PRP group demonstrated a higher rate of postoperative knee motion loss compared with the control group. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with hip fracture who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes an open-labeled RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. The single open-label RCT failed to show a statistically significant reduction in the need for surgical revision with the addition of PRP treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with long bone nonunion who receive PRP injections plus orthopedic surgery, the evidence includes 3 RCTs. Relevant outcomes are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. One trial with a substantial risk of bias failed to show significant differences in patient-reported or clinician-assessed functional outcome scores between individuals who received PRP plus allogenic bone graft versus those who received only allogenic bone graft. While the trial showed statistically significant increases in the proportion of bones that healed in individuals receiving PRP in a modified intention-to-treat analysis, the results did not differ in the intention-to-treat analysis. An RCT that compared PRP with recombinant human bone morphogenetic protein-7 (rhBMP-7) also failed to show any clinical and radiologic benefits of PRP over rhBMP-7. The third RCT found no difference in the number of unions or time to union in individuals receiving PRP injections or no treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with rotator cuff repair who receive PRP injections plus orthopedic surgery, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. Although systematic reviews consistently found significant reductions in pain with PRP at 12 months, important study conduct and relevance weaknesses limit interpretation of these findings. While the systematic reviews and meta-analyses generally failed to show a statistically and/or clinically significant impact on other outcomes, 1 meta-analysis found a statistically significant reduction in retear rate in a subgroup analysis of 4 RCTs that were at least 24 months in duration. The findings of a subsequently published 10-year follow-up of a small RCT failed to demonstrate the superiority of PRP over control for clinical and radiologic outcomes. Two newer RCTs also found no difference in the addition of PRP over control in functional outcomes at either 6-months or 1-year follow-up. The variability in PRP preparation techniques and PRP administration limits the generalizability of the available evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals undergoing spinal fusion who receive PRP injections plus orthopedic surgery, the evidence includes a single small RCT and a few observational studies. Relevant outcomes include symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. Studies have generally failed to show a statistically and/or clinically significant impact on symptoms (i.e., pain). The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with subacromial decompression surgery who receive PRP injections plus orthopedic surgery, the evidence includes a small RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. A single small RCT failed to show a reduction in self-assessed or physician-assessed spinal instability scores with platelet-rich plasma injections. However, subjective pain, use of pain medications, and objective measures of range of motion showed clinically significant improvements with PRP. Larger trials are required to confirm these benefits. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with total knee arthroplasty who receive PRP injections plus orthopedic surgery, the evidence includes systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. The reviews showed no significant differences between the PRP and untreated control groups in range of motion, functional outcomes, and long-term pain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

## Autologous Protein Solution

For individuals who receive autologous protein solution (APS) (nSTRIDE) the evidence is currently limited to the treatment of osteoarthritis (OA) of the knee, the evidence includes systematic review,  RCTs, nonrandomized controlled trial, and single-arm comparative studies. Relevant outcomes are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity. The RCTs performed by Kon et. al 2018 and 2020 evaluated the safety and effectiveness of APS injection nSTRIDE (n=31) compared to saline injection (n=15) at 12-months and at 3-years. While study results may show improved efficacy measurements such as the WOMAC, KOOS, Global Impression, and OMERACT-OARSI responder rate in study participants in the APS group, the saline group (n=15) was allowed to cross over to the APS group at 12-months (n=15). While their final scores were better than baseline, they were 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. An additional small, (n=40) placebo-controlled RCT by Ross et al (2024) found no significant difference between nSTRIDE and saline group at all time points with respect to WOMAC and KOOS scores up to one-year follow-up and inferior effects on pain relief for nSTRIDE. Additional RCTs are needed comparing APS with placebo and other alternative treatments including but not limited to hyaluronic acid and corticosteroids to determine the safety and effectiveness of APS in the treatment of knee OA and for any other musculoskeletal indications. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who receive APS for the treatment of hip OA the evidence includes a systematic review. Relevant outcomes are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity. The systematic review performed by Gupta et al (2024) evaluated the efficacy of autologous peripheral blood-derived orthobiologics (APBOs) to include the use of APS for the management of hip OA. There were no published clinical studies identified in peer reviewed medical literature that utilized APS for the management of hip OA. As of September 21, 2024 there were no ongoing clinical trials listed on any of the searched registers (ClinicalTrials.gov, BRTI, or ChiCTR) to evaluate the safety and/or effectiveness of APS to manage hip OA. RCTs are needed comparing APS with placebo and other alternative treatments including but not limited to corticosteroids to determine the safety and effectiveness of APS in the treatment of hip OA . The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

## OBJECTIVE

The objective of this evidence review is to determine whether the use of platelet-rich plasma or autologous protein solution improves the net health outcome in individuals with musculoskeletal conditions and those undergoing orthopedic surgical procedures.

## PRIOR APPROVAL

Not applicable.

## POLICY

### Platelet-Rich Plasma

The use of platelet - rich plasma (PRP) injections is considered **investigational** for all orthopedic indications; this includes but is not limited to use in the following situations because the evidence is insufficient to determine the effects of the technology on net health outcomes:

- As a primary use (injection) for the following conditions:
  - Achilles tendinopathy
  - Acute joint injuries (sprains/strains)
  - Anterior cruciate ligament (ACL) injuries
  - Carpal tunnel syndrome
  - Lateral epicondylitis
  - Muscle injuries
  - Osteoarthritis (hip, knee, and shoulder)
  - Osteochondral lesions
  - Plantar fasciitis
  - Rotator cuff injuries
  - Soft tissue trauma (e.g., tendon and ligament rupture/tears)
  - Temporomandibular disorders to include the treatment of temporomandibular osteoarthritis.

- Adjunctive use in the following surgical procedures:
  - Achilles tendon repair surgery
  - Anterior cruciate ligament (ACL) reconstruction
  - As a post-surgery supplement
  - Fractures, including hip fracture
  - Hip arthroscopy
  - Long bone non-union
  - Musculoskeletal soft tissue injury repairs (e.g., tendon and ligament rupture/tears)
  - Patellar tendon repair
  - Rotator cuff repair
  - Spinal fusion
  - Subacromial decompression surgery
  - Total or partial knee arthroplasty.

### Autologous Protein Solution

The use of autologous protein solution (APS) (e.g., nSTRIDE) is considered **investigational** for all orthopedic indications, including but not limited to the treatment of osteoarthritis because the evidence is insufficient to determine the effects of the technology on net health outcomes.

## POLICY GUIDELINES

### Coding

See the Codes table for details.

## BACKGROUND

### Platelet-Rich Plasma

A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factors, epidermal growth factor, fibroblast growth factors, transforming growth factors, and insulin-like growth factors. Autologous platelets are a rich source of platelet-derived growth factor, transforming growth factors that function as a mitogen for fibroblasts, smooth muscle cells, osteoblasts, and vascular endothelial growth factors. Recombinant platelet-derived growth factor has also been extensively investigated for clinical use in wound healing (see evidence review 02.01.61).

Autologous platelet concentrate suspended in plasma, also known as 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. The polymerization of fibrin from fibrinogen creates a platelet gel, which can then be used as an adjunct to surgery with the intent of promoting hemostasis and accelerating healing. In the operating room setting, PRP has been investigated as an adjunct to various periodontal, reconstructive, and orthopedic procedures. For example, bone morphogenetic proteins are a type of transforming growth factor, and thus platelet-rich plasma has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries. Alternatively, PRP may be injected directly into various tissues. PRP injections have been proposed as a primary treatment of miscellaneous conditions, such as epicondylitis, plantar fasciitis, and Dupuytren contracture.

Injection of PRP for tendon and ligament pain is theoretically related to prolotherapy (see evidence review 02.01.18). However, prolotherapy differs in that it involves the injection of chemical irritants intended to stimulate inflammatory responses and induce the release of endogenous growth factors.

PRP is distinguished from fibrin glues or sealants, which have been used as a surgical adjunct to promote local hemostasis at incision sites. Fibrin glue is created from platelet-poor plasma and consists primarily of fibrinogen. Commercial fibrin glues are created from pooled homologous human donors; Tisseel® (Baxter) and VITASEAL™ (Johnson & Johnson Surgical Technologies) are examples of commercially available fibrin sealants. Autologous fibrin sealants can be created from platelet-poor plasma. This evidence review does not address the use of fibrin sealants.

### Autologous Protein Solution

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. WBCs 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 individual, 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 using centrifuge. The kit permits APS 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 individual. 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 partitioned into multiple injections or injecting at multiple locations. This is given to inhibit inflammation and reduce cartilage degradation.

### Regulatory Status

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1,270 and 1,271. Blood products such as platelet-rich plasma are included in these regulations. Under these regulations, certain products including blood products such as platelet-rich plasma are exempt and therefore do not follow the traditional FDA regulatory pathway. To date, the FDA has not attempted to regulate activated platelet-rich plasma.

A number of platelet-rich plasma 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 (previously called AutoloGel™ Nuo Therapeutics, Inc. Gaithersburg, MD)
- Autotransfusion System (Medtronic)
- GPS® II (Biomet Biologics, Inc., Warsaw, IN)
- GPS® III (Zimmer Biomet)
- Magellan®™ Autologous Platelet Separator System (Isto Biologics)
- Plasma Saver device (Harvest Technologies Corporation, Plymouth, MA)
- SafeBlood® (SafeBlood Technologies)
- SmartPRePO® 2 APC+ system (Harvest Technologies Corporation, Plymouth, MA)

Filtration or plasmapheresis may also be used to produce platelet-rich concentrates. 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.

August 2023 the FDA through the 510(k) process cleared marketing for the nSTRIDE PRP Concentration System (Biomet Biologics, Warsaw, IN). The nSTRIDE PRP concentration system is intended to "produce platelet-rich plasma (PRP) from a small sample of peripheral blood and this PRP is mixed with autograft and/or allograft bone prior to application to body defect for improving handling characteristics."

## RATIONALE

This evidence review was created in August 2007 with searches of the PubMed database. The most recent literature update was performed through June 2025.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

At present, there are many techniques available for the preparation of platelet-rich plasma or platelet-rich plasma gel. The amount and mixture of growth factors produced by different cell-separating systems vary, and it is also uncertain whether platelet activation before the injection is necessary.

## Platelet-Rich Plasma as a Primary Treatment for Tendinopathy

### *Clinical Context and Therapy Purpose*

The purpose of platelet-rich plasma (PRP) 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 individuals with tendinopathy.

The following PICO was used to select literature to inform this review.

### *Populations*

The relevant population of interest is individuals with tendinopathy.

### *Interventions*

The therapy being considered is PRP injections. The use of PRP 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.

### *Comparators*

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

### *Outcomes*

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity. The existing literature evaluating PRP 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.

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

## Systematic Reviews

Many systematic reviews have evaluated platelet-rich plasma for treating mixed tendinopathies. They include trials on tendinopathies of the Achilles, rotator cuff, patella, and/or lateral epicondyle (tennis elbow). Select, recent (i.e., 2019 to present) systematic reviews of RCTs and/or nonrandomized studies are described next. A crosswalk of RCTs included in these systematic reviews is found in the Appendix (Table A1). Characteristics and results of these systematic reviews are found in Tables 1 and 2.

Masiello et. al. (2022) conducted a systematic review and meta-analysis of 33 RCTs (N=2025) comparing ultrasound-guided platelet-rich plasma to control (injection of steroids, saline, autologous whole blood, mesenchymal stem cells, or local anesthetic; dry needling; prolotherapy; or other non-injection intervention) for the treatment of tendinopathy. Tendinopathies included latera epicondylitis (n=5), Achilles tendinopathy (n=5), rotator tendinopathy (n=7), patellar tendinopathy (n=3), and carpal tunnel syndrome (n=3). Most trials (n=20) administered platelet-rich plasma as a single injection; however, up to 4 injections were administered in some trials. Few differences in efficacy between control and platelet-rich plasma were found with the exception of patients with carpal tunnel where pain and severity scores were reduced in the short and medium term. The overall mean differences in pain scores were: -0.24 (95% confidence interval [CI], -0.73 to 0.25) for lateral epicondylitis, -3.62 (95% CI, -8.16 to 0.91) for Achilles tendinopathy, 0.16 (95% CI, -0.18 to 0.50) for rotator cuff tendinopathy, 0.17 (95% CI, -0.64 to 0.98) for patellar tendinopathy, and 0.24 (95% CI, -0.32 to -0.16) for carpal tunnel syndrome. The evidence is rated as low quality due to risk of bias, imprecision, and inconsistency.

In 2023, Dai et. al. conducted a systematic review and meta-analysis of RCTs evaluating platelet-rich plasma versus control (saline injection, dry needling, or no treatment) for the treatment of tendinopathy. A total of 13 trials met the eligibility criteria and included patients with lateral epicondylitis (5 RCTs), Achilles tendinopathy (4 RCTs), rotator cuff tendinopathy (2 RCTs), and patellar tendinopathy (2 RCTs). Among the 13 RCTs, 7 studies were judged to be at low risk of bias and 6 were found to have a high risk of bias. The meta-analysis demonstrated that platelet-rich plasma was not superior to control for the primary outcomes of change in pain intensity or function at 12-weeks; these trends also persisted at 24-weeks.

The authors noted that included trials displayed significant heterogeneity with respect to platelet-rich plasma preparation and patient characteristics and had important methodological limitations.

Muthu et. al. (2021) conducted a systematic review with meta-analysis of RCTs comparing platelet-rich plasma, autologous blood, corticosteroids, local anesthetics, laser therapy, and surgery for patients with lateral epicondylitis. A total of 25 trials met the eligibility criteria (N=2040). Results demonstrated that based on data from 22 trials, only leukocyte-rich platelet-rich plasma significantly improved visual analog scale (VAS) pain scores compared to saline control (weighted mean difference [MD], -14.8; 95% CI, -23.18 to -6.39); in a subgroup analysis of 14 studies with at least 12 months of follow up, the weighted MD did not reach statistical significance (-7.69; 95% CI, -27.28 to 11.90). Based on data from 11 trials, none of the interventions were superior to saline control for improvement in the Disabilities of the Arm, Shoulder and Hand (DASH) score. Treatment ranking based on the P-score approach demonstrated that leukocyte-rich platelet-rich plasma was most likely to be the best treatment amongst autologous blood, corticosteroids, laser therapy, local anesthetics, and leukocyte-poor platelet-rich plasma.

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.

**Table 1. Systematic Reviews and Meta-Analysis Characteristics**

| Study | Dates | Trials | Participants | N (Range) | Design | Duration |
|---|---|---|---|---|---|---|
| Masiello et al (2022) | Through 2021 | 33 | Patients with tendinopathy | 2025 (NR) | RCT | 3 to 36 mo |
| Dai et al (2023) | 2010-2020 | 13 | Patients with tendinopathy | 576 (23 to 79) | RCT | 4 to ≥24 wk |
| Muthu et al (2021) | 2010-2020 | 25 | Patients with lateral epicondylitis | 2040 (25 to 230) | RCT | 3 to 24 mo |
| Johal et al (2019) | 2010-2016 | 10 | Patients with lateral epicondylitis | 25 to 231 | RCT | 6 wk to 24 mo |

NR: not reported; RCT: randomized controlled trial.

**Table 2. Systematic Reviews and Meta-Analysis Results**

| Study | SMD in Pain for PRP | SMD in functional disability for PRP | WMD in pain reduction (between LR-PRP and control ) | WMD in functional disability (between LR-PRP and control ) | WMD in pain reduction at 3 months (between LR-PRP and control ) | WMD in pain reduction at 1 year (between LR-PRP and control ) |
|---|---|---|---|---|---|---|
| Dai et al (2023) | -0.14 | 0.18 | | | | |
| 95% CI | -0.55 to 0.26 | -0.13 to 0.49 | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Muthu et al (2021) | | | -14.8 | -8.77 | | -7.69 |
| 95% CI | | | -23.18 to -6.39 | -30.60 to 13.07 | | -27.28 to 11.90 |
| Johal et al (2019) | -0.69 | | | | | |
| 95% CI | -1.15 to - 0.23 | | | | | |

CI: confidence interval; LR: leukocyte-rich; PRP: platelet-rich plasma; SMD: standard mean difference; WMD: weighted mean difference;.

## Randomized Controlled Trials

One larger RCT not included in the above systematic reviews was published in 2021 (N=240) comparing platelet-rich plasma to sham control. Victorian Institute of Sport Assessment-Achilles (VISA-A) score was not significantly different between groups. Tables 3 and 4 summarize the RCT characteristics and results, respectively, and Tables 5 and 6 describe study design and conduct limitations.

### Table 3. Summary of Key RCT Characteristics

| Study | Countries | Sites | Dates | Participants | Interventions | Comparator | |
|---|---|---|---|---|---|---|---|
| | | | | | Active | Comparator 1 | Comparator 2 |
| Kearney (2021) | UK | 24 | 2016-2020 | Adults with painful midportion Achilles tendinopathy lasting longer than 3 months | PRP (n=121) | Sham (n=119) | |

PRP: platelet-rich plasma; RCT: randomized controlled trial; UK: United Kingdom.

### Table 4. Summary of Key RCT Results

| Study | | | Other pain / disability assessment |
|---|---|---|---|
| Kearney (2021) | | | 6 mo VISA-A score |
| PRP | | | 54.4 |
| Sham | | | 53.4 |
| Adjusted MD; 95% CI | | | -2.7 (-8.8 to 3.3) |

CI: confidence interval; MD: mean difference; PRP: platelet-rich plasma; RCT: randomized controlled trial; VISA-A: Victorian Institute of Sport Assessment-Achilles score..

### Table 5. Study Relevance Limitations

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow.Up[e] |
|---|---|---|---|---|---|
| Kearney (2021) | | 1. 37 participants received additional treatments during the 6-month follow up | 1. 40 participants received additional treatments during the 6-month follow up | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

### Table 6. Study Design and Conduct Limitations

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Follow Up[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| Kearney (2021) | | 1. Single blinded (participants only) | | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference. 4. Underpowered
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated

### Section Summary: Platelet-Rich Plasma as a Primary Treatment for Tendinopathy

Multiple RCTs and systematic reviews with meta-analyses have evaluated the efficacy of PRP injections in individuals who have tendinopathy. 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 (i.e., pain) or functional outcomes. Although 1 systematic review found statistically significantly lower pain scores at 12-months with PRP versus the comparators, its results should be interpreted with caution due to important study conduct limitations. Additionally, in a recent RCT compared to sham control, PRP did not significantly improve pain after 6 or 12-months.

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

### *Clinical Context and Therapy Purpose*

The purpose of PRP 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 individuals with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis).

The following PICO was used to select literature to inform this review.

### *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 PRP injections. The use of PRP 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.

### *Comparators*

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

### *Outcomes*

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity. The existing literature evaluating PRP 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.

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

In individuals with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis), there are no large double-blind RCTs of sufficient duration (i.e., 2-years) to demonstrate efficacy.

## Systematic Reviews

Seth et al (2023) published a systematic review comparing corticosteroid injections to either platelet-rich plasma or extracorporeal shock wave therapy in patients with plantar fasciitis.[12,] The studies were limited to RCTs up to April 2021. A total of 18 studies were included, 12 of which evaluated platelet-rich plasma compared to corticosteroid injections. VAS scores were higher in the corticosteroid group than the platelet-rich plasma group at both 3 (MD, 0.62; 95% CI, 0.13 to 1.12; p=.01) and 6 months (MD, 1.49; 95% CI, 0.22 to 2.76; p=.02). Notably, numerical differences between groups were small. Functional outcomes were similar with corticosteroids compared to platelet-rich plasma at 3 months but worse with corticosteroids at 6 months (American Orthopaedic Foot and Ankle Society [AOFAS] MD, -11.53; 95% CI, -16.62 to -6.43; p<.0001). The authors deemed the evidence very low quality, and most studies had either high or unclear risk of bias.

### Randomized Controlled Trials

There are several additional RCTs not included in the Seth et al (2023) review. None were large double-blind RCTs of sufficient duration (i.e., 2-years) to conclusively demonstrate efficacy. The RCTs compared platelet-rich plasma treatment with corticosteroid injection or saline injection. The platelet-rich plasma protocols differed across RCTs. The RCTs were small, ranging in size from 28 to 155 participants. Follow-up duration ranged from 6 months to 18 months. Two were conducted in single centers in either the United Kingdom, or India. The other was a multicenter RCT of 5 sites in the Netherlands., None prespecified any methods to assess potential harms. Results were mixed across RCTs. The largest RCT (N=115) by Peerbooms et al (2019) compared platelet-rich plasma with corticosteroid injection and had a follow-up to 12 months. In the RCT by Peerbooms et al (2019), the proportion of patients with at least a 25% improvement in Foot Function Index Pain Scores between baseline and 12 months was significantly greater in the platelet-rich plasma group (88.4% vs. 55.6%; p =.003). Additionally, mean Foot Function Index Disability Scores were significantly lower in the platelet-rich plasma group at 12 months (MD, 12.0; 95% CI, 2.3 to 21.6). But these improvements did not translate into significantly greater quality of life in the platelet-rich plasma group. Also, important study design and conduct gaps exist that seriously limit the interpretation of these findings, including that analysis excluded 29% of the randomized patients, which was less than the calculated sample size. Therefore, although evidence continues to develop, important uncertainties in efficacy and safety remain and larger double-blind RCTs are still needed.

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

Several small RCTs, multiple prospective observational studies, and systematic reviews of these studies have evaluated the efficacy of PRP injections in individuals with chronic plantar fasciitis. Preparation of PRP and outcome measures differed across studies. Results among the RCTs were inconsistent. The largest of the RCTs showed that treatment using PRP compared with corticosteroid resulted in statistically significant improvements in pain and disability, but not QOL. Larger RCTs completed over a sufficient duration of time (i.e., 2- years) are still needed to address important uncertainties in efficacy and safety.

## Platelet-Rich Plasma as a Primary Treatment of Osteochondral Lesions

### *Clinical Context and Therapy Purpose*

The purpose of PRP 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 individuals with osteochondral lesions.

The following PICO was used to select literature to inform this review.

### *Populations*

The relevant population of interest is individuals with osteochondral lesions.

### *Interventions*

The therapy being considered is PRP injections. The use of PRP 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.

### *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, QOL, and treatment-related morbidity. The existing literature evaluating PRP 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.

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

## Comparative Studies

No high-quality RCTs on the treatment of osteochondral lesions were identified. Mei-Dan et al (2012) reported on a quasi-randomized study of 29 patients with 30 osteochondral lesions of the talus assigned to 3 intra-articular injections of hyaluronic acid or platelet-rich plasma.[17,] At 28-week follow-up, scores on the AOFAS Ankle-Hindfoot Scale improved to a greater extent in the platelet-rich plasma group (from 68 to 92) than in the hyaluronic acid group (from 66 to 78) ($p<.05$). Subjective global function also improved to a greater extent in the platelet-rich plasma group (from 58 to 91) than in the hyaluronic acid group (from 56 to 73). Interpretation of the composite measures of 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.

### Section Summary: Platelet-Rich Plasma as a Primary Treatment of Osteochondral Lesions

A single quasi-randomized study has evaluated the efficacy of PRP injections in individuals who have osteochondral lesions. Compared with hyaluronic acid, treatment with PRP resulted in statistically significant improvements in AOFAS Ankle-Hindfoot Scale scores and global function, indicating improved outcomes. Adequately powered and blinded RCTs are required to confirm these findings.

## Platelet-Rich Plasma as a Primary Treatment of Knee and Hip Osteoarthritis

### *Clinical Context and Therapy Purpose*

The purpose of PRP 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 individuals with knee or hip osteoarthritis (OA).

The following PICO was used to select literature to inform this review.

### *Populations*

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

### *Interventions*

The therapy being considered is PRP injections. The use of PRP 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.

### *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, QOL, and treatment-related morbidity. The existing literature evaluating PRP injections as a treatment for knee or hip OA 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.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.

c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

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 the studies identified in the Laudey et al (2015) systematic review, PRP was prepared using single, double, or triple spinning techniques and interventions included between 1 and 3 injections delivered 1 to 3 weeks apart.

## Systematic Reviews

In individuals with knee osteoarthritis undergoing platelet-rich plasma injections, findings from 6 systematic reviews are reported. A crosswalk of RCTs included in these systematic reviews is found in the Appendix (Table A2); the systematic review by Anil et al (2021) did not delineate which of its included studies evaluated platelet-rich plasma, therefore, is not included in Table A2. The systematic reviews have varied in their outcomes of interest and their findings. Systematic reviews have generally found that platelet-rich plasma was more effective than placebo or hyaluronic acid in reducing pain and improving function. However, systematic review authors have noted that their findings should be interpreted with caution due to important limitations including significant residual statistical heterogeneity, questionable clinical significance, and high risk of bias in study conduct.

In 2021, Anil et. al. published a systematic review with network meta-analysis to compare the efficacy of nonoperative injectable treatments for knee osteoarthritis.  A total of 79 RCTs (N=8761) were included, and the follow-up ranged from 4 weeks to 24 months. Intra-articular injectable treatments included platelet-rich plasma, autologous conditioned serum, bone marrow aspirate concentrate, botulinum toxin, corticosteroids, hyaluronic acid, mesenchymal stem cells, ozone, saline placebo, plasma rich in growth factor, and stromal vascular fraction; the publication did not delineate the number of RCTs that specifically evaluated on platelet-rich plasma. At 12 months, the treatment with the highest P-Score for the MD in Western Ontario and McMaster Osteoarthritis Index (WOMAC) scale score and VAS score was stromal vascular fraction. However, the MD in WOMAC scale and VAS scores for leukocyte-poor platelet-rich plasma and leukocyte-rich platelet-rich plasma versus saline placebo at 12 months did not reach statistical significance.

Trams et al (2020) published a systematic review that included 38 RCTs (N=2962) evaluating the effects of platelet-rich plasma on patients with knee osteoarthritis (see Tables 7 and 8). The meta-analysis focused on the review of 33 blinded studies. Follow-up ranged from 6 months to 2 years. Comparators included hyaluronic acid in 23 studies, placebo (e.g., saline, no injection, physical therapy) in 10 studies, corticosteroids in 4 studies, and acetaminophen in 2 studies. Twenty-two studies reported VAS pain outcomes for placebo (n=5), hyaluronic acid (n=15), and corticosteroids (n=2). Placebo and hyaluronic acid subgroups showed significant VAS differences in favor of platelet-rich plasma ($p<.00001$). The corticosteroid subgroup was not significantly different from platelet-rich plasma ($p=.23$). Six studies comparing single versus multiple injections of platelet-rich plasma showed a significant difference in favor of 3 platelet-rich plasma injections ($p<.00001$). Functional outcomes were reported via the WOMAC scale for placebo (n=9), corticosteroids (n=1), and hyaluronic acid (n=15). Both pooled and subgroup analyses favored platelet-rich plasma ($p<.00001$). In 5 studies assessing multiple versus single platelet-rich plasma injections, significant differences in favor of multiple injections were found ($p<.00001$). Functional outcomes assessed via International Knee Documentation Committee (IKDC) scores were reported in 2 placebo studies and 5 hyaluronic acid studies. While a significant difference was found for hyaluronic acid (p=.004), no significant difference was found for placebo (p=.24). Pooled estimates for 6 studies comparing platelet-rich plasma to corticosteroids, hyaluronic acid, or mesenchymal stem cells found no significant differences in Knee injury and Osteoarthritis Outcome Score (KOOS) sport, quality of life, activities of daily living, symptoms, or pain subscales. The pooled estimates for adverse events showed non-significant differences in favor of the control groups (p=.15). The risk of bias was assessed using Cochrane criteria. One study was at high risk of bias for 3 domains, 2 studies were at high risk of bias for 2 domains, and 12 studies were at high risk of bias for 1 domain. The most impacted domains were performance bias and reporting bias.

Johal et al (2019) conducted a systematic review and meta-analysis of RCTs comparing platelet-rich plasma with hyaluronic acid (8 trials, n=927), placebo (2 trials, n=105), no platelet-rich plasma (2 trials, n=123), acetaminophen (1 trial, n=75), or a corticosteroid (1 trial, n=48). Meta-analysis of VAS pain scores showed that platelet-rich plasma was more effective than its comparators at 12 months (standard MD, –0.91; 95% CI, –1.41 to –0.41). However, the systematic review authors noted that important limitations of this finding included lack of a clinically significant difference (i.e., less than the effect size threshold of 0.5 for a clinically important difference), high residual statistical heterogeneity between studies ($I^2$=89%), and high risk of bias in study conduct.

In 2017, Xu et. al. conducted a systematic review and meta-analysis of RCTs comparing platelet-rich plasma with hyaluronic acid (8 trials), or placebo (2 trials), for the treatment of knee osteoarthritis (see Tables 7 and 8). Risk of bias was assessed using Cochrane criteria. Four studies were assessed as being of low-quality, 3 as moderate-quality, and 3 as high-quality. Meta-analyses including 7 of the trials comparing platelet-rich plasma with hyaluronic acid showed that platelet-rich plasma significantly improved the WOMAC or IKDC scores compared with hyaluronic acid at 6-month follow-up; however, when meta-analyses included only the 2 high-quality RCTs, there was not a significant difference between platelet-rich plasma and hyaluronic acid (see Table 8). Also, note that the WOMAC evaluates 3 domains: pain, scored from 0 to 20; stiffness, scored from 0 to 8; and physical function, scored from 0 to 68. Higher scores represent greater pain and stiffness as well as worsened physical capability. The IKDC is a patient-reported, knee-specific outcome measure that measures pain and functional activity. In the meta-analysis comparing platelet-rich plasma with placebo, a third trial was included, which had 4 treatment groups, 2 of which were platelet-rich plasma and placebo. This analysis showed that platelet-rich plasma significantly improved the WOMAC or IKDC scores compared with placebo; however, only 1 of the trials was considered high-quality and that trial only enrolled 30 patients. All meta-analyses showed high heterogeneity among trials ($I^2$≥90%).

Laudy et. al. (2015) conducted a systematic review of RCTs and nonrandomized clinical trials to evaluate the effect of platelet-rich plasma on patients with knee osteoarthritis (see Tables 7 and 8). Ten trials (N=1110) were selected. Cochrane criteria for risk of bias were used to assess study quality, with 1 trial rated as having a moderate-risk of bias and the remaining 9 trials as high-risk of bias. While meta-analyses showed that platelet-rich plasma was more effective than placebo or hyaluronic acid in reducing pain and improving function (see Table 8), larger randomized studies with a lower risk of bias are needed to confirm these results.

In 2014, Chang et. al. published a systematic review that included 5 RCTs, 3 quasi-randomized controlled studies, and 8 single-arm prospective series (N=1543) (see Tables 7 and 8). The Jadad scale was used to assess RCTs, and the Newcastle-Ottawa Scale was used to assess the other studies; however, results of the quality assessments were not reported. Meta-analysis of functional outcomes at 6 months found that the effectiveness of platelet-rich plasma (effect size, 1.5; 95% CI, 1.0 to 2.1) was greater than that of hyaluronic acid (effect size, 0.7; 95% CI, 0.6 to 0.9; when only RCTs were included). However, there was no significant difference at 12-month follow-up between platelet-rich plasma (effect size, 0.9; 95% CI, 0.5

to 1.3) and hyaluronic acid (effect size, 0.9; 95% CI, 0.5 to 1.2; when only RCTs were included). Fewer than 3 injections, single spinning, and lack of additional activators led to greater uncertainty in the treatment effects. Platelet-rich plasma also had lower efficacy in patients with higher degrees of cartilage degeneration. Results were consistent when analyzing only RCTs but asymmetry in funnel plots suggested significant publication bias.

**Table 7. Systematic Review Characteristics for Knee Osteoarthritis**

| Study | Search Date | Trials | Participants | Design |
|---|---|---|---|---|
| Anil et al (2021) | Through 2020 | RCTs of patients receiving PRP, autologous conditioned serum, bone marrow aspirate concentrate, botulinum toxin, corticosteroids, hyaluronic acid, mesenchymal stem cells, ozone, saline placebo, plasma rich in growth factor, or stromal vascular fraction | Patients with knee OA | 79 RCTs |
| Trams et al (2020) | 2005-2020 | -10 PRP vs. placebo<br>-23 PRP vs. HA<br>-4 PRP vs. corticosteroid<br>-2 PRP vs. acetaminophen<br>-6 PRP, single vs. multiple injections | Patients with knee OA | 38 RCTs |
| Johal et al (2019) | Through Feb 2017 | -8 PRP vs. HA<br>-2 PRP vs. placebo<br>-2 PRP vs. no PRP<br>-1 PRP vs. corticosteroid<br>-1 PRP vs. acetaminophen | Patients with knee OA | 14 RCTs |
| Xu et al (2017) | Through May 2016 | -8 PRP vs. HA<br>-2 PRP vs. placebo | Patients with knee OA | 10 RCTs |
| Laudy et al (2015) | Through Jun 2014 | - 8 PRP vs. HA<br>-1 PRP vs. placebo<br>- 1 PRP, different preparations | Patients with knee OA | 6 RCTs; 4 nonrandomized |
| Chang et al (2014) | Through Sep 2013 | -6 PRP vs. HA<br>-1 PRP vs. placebo<br>-1 PRP, different preparations<br>-8 single-arm PRP | Patients with knee OA | 5 RCTs; 3 quasi-randomized; 8 single-arm |

HA: hyaluronic acid; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial.

**Table 8. Systematic Review Functional Score Results for Knee Osteoarthritis**

| Study | Change in Functional Scores (95% CI)[a] |
|---|---|
| | 6 Months to 2 Years |

| Study | Change in Functional Scores (95% CI)[a] | |
|---|---|---|
| Anil et al (2021) | WOMAC at 1 year: Leukocyte-poor PRP vs. saline placebo, -7.65 (-27.18 to 11.88); Leukocyte-rich PRP vs. saline placebo, -13.28 (-28.74 to 2.18) | |
| Trams et al (2020) | WOMAC: All trials, -12.10 (-14.12 to -7.24); PRP vs. placebo, -14.56 (-21.17 to -7. 96); PRP vs. steroid, -16.10 (-19.61 to -12.59); PRP vs. HA, -10,68 (-14.12 to -7.24)<br>IKDC: All trials, 6.94 (2.53 to 11.34); PRP vs. placebo, 8.96 (-5.88 to 23.81); PRP vs. HA, 6.58 (2.12 to 11.05)<br>KOOS - ADL: All trials, 1.23 (-4.85 to 7.31) | |
| | 6 Months | 12 Months |
| Xu et al (2017) | PRP vs. HA: All trials: -0.9 (-1.4 to -0.3); Low quality: -13.3 (-33.9 to 3.7); Moderate quality: -1.3 (-1.6 to -1.0); High quality: -0.1 (-0.3 to 0.1)<br>PRP vs. placebo:· All trials (3): -2.1 (-3.3 to -1.0) | NR |
| Laudy et al (2015) | PRP vs. HA: -0.8 (-1.0 to -0.6) | PRP vs. HA: -1.3 (-1.8 to -0.9) |
| Chang et al (2014) | PRP, baseline vs. post-treatment:· All studies: 2.5 (1.9 to 3.1); Single-arm: 3.1 (2.0 to 4.1); Quasi-randomized: 3.1 (1.4 to 3.8); RCT: 1.5 (1.0 to 2.1) | PRP, baseline vs. posttreatment:· All studies: 2.9 (1.0 to 4.8); Single-arm: 2.6 (-0.4 to 5.7); Quasi-randomized: 4.5 (4.1 to 5.0); RCT: 0.9 (0.5 to 1.3) |

ADL: activities of daily living; CI: confidence interval; HA: hyaluronic acid; IKDC: International Knee Documentation Committee; KOOS: Knee Injury and Osteoarthritic Outcome Score; NR: not reported; PRP: platelet-rich plasma; RCT: randomized controlled trial; WOMAC: Western Ontario McMaster Osteoarthritis Index.
[a] Functional outcomes were measured by the IKDC, KOOS, or WOMAC.

In individuals with hip osteoarthritis undergoing platelet-rich plasma injections, findings from 2 systematic reviews are reported. Belk et al (2022) identified 6 RCTs comparing the efficacy of platelet-rich plasma (n=211) and hyaluronic acid injections (n=197). The mean follow-up was approximately 12 months. In an analysis of 4 RCTs, platelet-rich plasma and hyaluronic acid groups had similar improvements in VAS score (MD, 5.9; 95% CI, -0.741 to 1.92) and WOMAC score (MD, 0.27; 95% CI, -0.05 to 0.59). Gazendam et al (2020) identified 11 RCTs (N=1353) assessing the efficacy of platelet-rich plasma, corticosteroids, and saline injections. Pooled pain and functional outcomes were reported for 2 to 4 and 6 months follow-up. No intervention significantly outperformed saline intra-articular injection at any time point. Clinically significant improvements in pain from baseline were observed for all treatment groups, including placebo.

## Randomized Controlled Trials

In individuals with knee osteoarthritis undergoing platelet-rich plasma injections, 3 RCTs with a follow-up of at least 12 months have been published subsequent to several of the above-described systematic reviews (Tables 9 to 12). All trials were conducted outside of the United States. Sample sizes ranged from 40 to 200 patients. Comparator treatments included corticosteroids, celecoxib, or hyaluronic acid. Two RCTs found statistically significantly greater 1-year reductions in pain and function scores with platelet-rich plasma versus corticosteroids or celecoxib. Sdeek et al (2021) reported on the results of a 36-month RCT that compared 3 intraarticular injections of either platelet-rich plasma (n=95) or hyaluronic acid (n=94) in patients with knee osteoarthritis. Both platelet-rich plasma and hyaluronic acid were effective in improving pain and functional status. Statistical analyses were not performed, however, trends for pain and function scores showed greater improvement in the group that received platelet-rich plasma. The findings of these RCTs should be interpreted with caution due to important study conduct limitations, including potential inadequate control for selection bias and limited or unclear blinding. No significant differences in pain or function scores were observed within the first month of treatment in either study.

Dallari et al (2016) reported on results of an RCT that compared platelet-rich plasma with hyaluronic acid alone or with a combination platelet-rich plasma plus hyaluronic acid in 111 patients with hip osteoarthritis. Although this well-conducted RCT reported positive results, with statistically significant reductions in VAS score (lower scores imply less pain) at 6 months in the platelet-rich plasma arm (21; 95% CI, 15 to 28) versus the hyaluronic acid arm (35; 95% CI, 26 to 45) or the platelet-rich plasma plus hyaluronic acid arm (44; 95% CI, 36 to 52), the impact of treatment on other secondary outcome measures such as Harris Hip Score and the WOMAC scores was not observed. Notably, there was no control for type I error for multiple group comparisons at different time points, and the trial design did not incorporate a sham-control arm. Nouri et al (2022) also conducted an RCT comparing platelet-rich plasma with hyaluronic acid in patients with hip osteoarthritis. A total of 105 patients were randomized to platelet-rich plasma, hyaluronic acid, or the combination. There were no differences in VAS scores between groups at 6 months; however, functional outcomes were improved in the platelet-rich plasma groups compared with hyaluronic acid alone.

**Table 9. Summary of Key RCT Characteristics**

| Study | Countries | Sites | Dates | Participants | Interventions | Comparator | |
|---|---|---|---|---|---|---|---|
| | | | | | Active | Comparator 1 | Comparator 2 |
| Nouri et al (2022) | Iran | 1 | 2019-2020 | Patients with hip OA, grade II to III | PRP (n=35); 2 x 5 mL 14 days apart | HA (n=35); 2 x 2.5 mL 14 days apart | HA + PRP (n=35); 2 x 5 mL PRP + 2.5 mL HA 14 days apart |
| Sdeek et al (2021) | Egypt | NR | 2016-2020 | Patients with knee OA, grade II to III | PRP (n=95); 3 x 2.5 mL 14 days apart | HA (n=94); 3 x 2.5 mL 14 days apart | |
| Reyes-Sosa et al (2020) | Mexico | 1 | NR | Patients with knee OA, grade II to III, who were previously treated with acetaminophen without improvement | Activated PRP (n=30); 2 x 3 mL 15 days apart | NSAID: (n=30); 200 mg celecoxib every 24 hours for 1 year | |
| Elksnins-Finogejevs et al (2020) | Latvia | 1 | 2016 - 2017 | Patients with knee OA, grade II to III | PRP (n=20); 8 ml single-dose | CS (n=20); 1 mL 40 mg/mL triamcinolone + 5 mL 2% lidocaine | |
| Dallari et al (2016) | Italy | NR | 2010 - 2011 | Patients with hip OA | PRP (n=44) | PRP+HA (n=31) | HA (n=36) |

CS: corticosteroid; HA: hyaluronic acid; NR: not reported; NSAID: non-steroidal anti-inflammatory drug; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial.

**Table 10. Summary of Key Results**

| Study | Pain Outcomes | Functional Outcomes |
|---|---|---|
| **Knee OA** | | |
| Sdeek et al (2021) | Mean VAS Score | Mean IKDC and WOMAC Scores |
| PRP | Baseline: 57.8<br>12 months: 47.1<br>36 months: 40.9 | IKDC:<br>Baseline: 49.1<br>12 months: 67.9<br>36 months: 55.2<br><br>WOMAC:<br>Baseline: 66.5<br>12 months: 52.8<br>36 months: 60.6 |
| HA | Baseline: 59.3<br>12 months: 50.3<br>36 months: 60.3 | IKDC:<br>Baseline: 47.3<br>12 months: 61.6<br>36 months: 46.1<br><br>WOMAC:<br>Baseline: 66.9<br>12 months: 54.9<br>36 months: 64.2 |
| Reyes-Sosa et al (2020) | Change in VAS Score from Baseline at 12 mo, % | Change in WOMAC Score from Baseline at 12 mo |
| PRP | -68.69 (p<.001) | -11.5[a] |
| Celecoxib | -40.94 (p<.001) | -4[a] |
| *P*-value for Difference | p<.001 | p<.001 |
| Elksnins-Finogejevs et al (2020) | Mean VAS Score, 95% CI | Mean IKDC Score, 95% CI |
| PRP | Baseline: 6.1 (5.4 to 6.6)<br>30 weeks: 1.6 (0.7 to 2.6)<br>58 weeks: 2.9 (2.2 to 3.6) | Baseline: 36.3 (31.2 to 41.4)<br>30 weeks: 77.5 (70.6 to 84.3)<br>58 weeks: 62.0 (54.5 to 69.6) |
| CS | Baseline: 6.0 (5.2 to 6.8)<br>30 weeks: 4.0 (3.2 to 4.8)<br>58 weeks: 5.1 (4.1 to 6.0) | Baseline: 28.0 (24.6 to 33.1)<br>30 weeks: 56.3 (47.4 to 65.3)<br>58 weeks: 39.8 (32.8 to 46.8) |
| **Hip OA** | | |
| Nouri et al (2022) | VAS at 6 mo | WOMAC at 6 mo |
| PRP | 3.13 ± 1.29 | 21.53 ± 10.40 |
| HA | 3.90 ± 1.40 | 27.21 ± 9.25 |

| Study | Pain Outcomes | Functional Outcomes |
|---|---|---|
| PRP + HA | 3.13 ± 1.18 | 21.16 ± 8.00 |
| Dallari et al (2016) | VAS Score at 6 mo | NR |
| PRP | 21 | |
| HA | 35 | |
| PRP + HA | 44 | |

CI: confidence interval; CS: corticosteroids; HA: hyaluronic acid; IKDC: International Knee Documentation Score; NR: not reported; OA: osteoarthritis; PRP: platelet-rich plasma; RCT: randomized controlled trial; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
[a] Calculated estimate.

### Table 11. Study Relevance Limitations

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| Nouri et al (2022) | | | | | 1. Only 6 months follow-up |
| Sdeek et al (2021) | | | | | |
| Reyes-Sosa (2020) | | | 3. Unclear adherence to treatment. | 5. Clinically significant difference not defined. | |
| Elksnins-Finogejevs (2020) | | | | | |
| Dallari (2016) | | | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

### Table 12.Study Design and Conduct Limitations

| Study | Allocation[a] | Binding[b] | Selective Reporting[c] | Follow Up[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| Nouri et al (2022) | | 1. Patients not fully blind due to differences in | | | | |

| Study | Allocation[a] | Binding[b] | Selective Reporting[c] | Follow Up[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| | | administration procedures | | | | |
| Sdeek et al (2021) | | | | | 1. Power calculations not reported; 2. Power not calculated for primary outcome | 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated. |
| Reyes-Sosa (2020) | 2. Allocation not concealed from patients or health care providers.<br>4. Inadequate control for selection bias in celecoxib group. | 1-3. Blinding of outcome assessors not clear. | 1. Not registered. | | 1. Power not calculated. | 2. Confidence intervals not reported. |
| Elksnins-Finogejevs (2020) | 2. Allocation not concealed from patients or health care providers. | 1-3. Not double-blinded. | | | | |
| Dallari (2016) | 2. Allocation not concealed from patients or health care providers | 1. Only data collectors and outcome assessors blinded to treatment assignment | | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

## Section Summary: Platelet-Rich Plasma as a Primary Treatment of Knee and Hip Osteoarthritis

Multiple RCTs and systematic reviews and meta-analysis have evaluated the efficacy of PRP injections in individuals with knee or hip OA. Most trials have compared PRP with placebo and hyaluronic acid (HA) for the knee OA. A single RCT compared PRP with HA alone or combination PRP plus HA in hip OA. Systematic reviews have generally found that PRP was more effective than placebo or HA in reducing pain and improving function. However, systematic review authors have noted that their findings should be interpreted with caution due to important limitations including significant residual statistical heterogeneity, questionable clinical significance, and high risk of bias in study conduct. RCTs with follow-up durations of at least 12-months published subsequent to the systematic reviews found statistically significantly greater 12-month reductions in pain and function outcomes, but these findings were also limited by important study conduct flaws including potential inadequate control for selection bias and limited or unclear blinding. Also, benefits were not maintained at 5-years. Using HA as a comparator is questionable because the evidence demonstrating the benefit of HA treatment for OA is not robust. Two systematic reviews evaluating hip OA did not report any statistically or clinically significant differences in pain or functional outcomes compared to HA, corticosteroids, or placebo. Additional larger controlled studies comparing PRP with placebo and with alternatives other than HA are needed to determine the efficacy of PRP for knee and hip OA. Further studies are also needed to determine the optimal protocol for delivering PRP.

## Platelet-Rich Plasma as an Adjunct to Surgery

### Anterior Cruciate Ligament Reconstruction

#### *Clinical Context and Therapy Purpose*

The purpose of PRP 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 individuals with anterior cruciate ligament (ACL) reconstruction.

#### *Populations*

The relevant population of interest is individuals with ACL reconstruction.

#### *Interventions*

The therapy being considered is PRP injections plus orthopedic surgery. The use of PRP 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.

#### *Comparators*

Comparators of interest include orthopedic surgery alone.

#### *Outcomes*

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating PRP 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.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

## Systematic Reviews

A Cochrane review by Moraes et al (2014) on platelet-rich therapies for musculoskeletal soft tissue injuries identified 2 RCTs and 2 quasi-randomized studies (N=203) specifically on platelet-rich plasma used in conjunction with ACL reconstruction. Pooled data found no significant difference in IKDC scores between the platelet-rich plasma and control groups.

A systematic review and meta-analysis by Trams et al (2020) identified 16 RCTs (N=740). Five studies showed no significant overall difference with respect to pain (p=.43). In 4 studies reporting IKDC scores, no significant differences were noted (p=.83). In 4 studies, no significant differences in functional outcomes as measured by the Lysholm score were reported (p=.19). Pooled estimates for Tegner scale activity assessments in 5 studies showed no significant differences (p=.38) in favor of the control. Twelve studies were deemed to be at high risk of bias in at least 1 domain.

A systematic review and meta-analyses by Lv et. al. (2022) identified 17 RCTs (N=970) in patients undergoing ACL reconstruction. Compared to controls, platelet-rich plasma improved VAS score (MD, -1.12; 95% CI, -1.92 to -0.31; p=.007), Lysholm score (MD, 8.49; 95 CI, 1.63 to 15.36) and subjective IKDC score (MD, 6.08; 95% CI, 4.39 to 7.77; p<.00001) at 6 months. The authors only considered the difference in pain score to be clinically relevant, and they did not consider any differences between groups at 12 months to be clinically meaningful (VAS MD, -0.47 and subjective IKDC score MD, 3.99). Overall, the evidence was determined to be of moderate quality.

## Randomized Controlled Trials

An RCT, reported by Nin et al (2009), randomized 100 patients to arthroscopic ACL reconstruction with or without platelet-rich plasma. The use of platelet-rich plasma on the graft and inside the tibial tunnel in patients treated with bone-patellar tendon-bone allografts had no discernable clinical or biomechanical effect at 2-year follow-up.

Ye et al (2024) randomized 120 patients undergoing ACL reconstruction 1:1 to receive either postoperative platelet-rich plasma at monthly intervals for 3 months or no postoperative injection.[39,] At 12 months, there were no significant differences in function or symptoms based on KOOS score between groups.

## Retrospective Cohort Studies

Bailey et al (2021) reported on a retrospective matched case-control study evaluating the effects of intraoperative platelet-rich plasma on postoperative knee function and complications at 2 years after ACL reconstruction with meniscal repair. The study was conducted between 2013 and 2017 and included 162 patients who received platelet-rich plasma and 162 patients who did not. Results demonstrated that there were no differences in knee function scores between the platelet-rich plasma and matched-control groups at 2 years, as well as no differences in the timing of return to activity (mean, 7.8 vs. 8.0 months; p=.765). However, the platelet-rich plasma group demonstrated a higher rate of postoperative knee motion loss compared with the control group (13.6% vs. 4.6%; p<.001).

### Subsection Summary: Platelet-Rich Plasma and Adjunctive Treatment of Anterior Cruciate Ligament Reconstruction

Several systematic reviews that included multiple RCTs, quasi-randomized studies, and/or prospective studies have evaluated the efficacy of platelet-rich plasma injections in individuals undergoing ACL reconstruction.  Three systematic reviews conducted a meta-analysis. Two showed that that adjunctive platelet -rich plasma treatment did not result in a significant effect on function and activity outcomes, including IKDC score. One systematic review did find significant benefit with platelet-rich plasma compared with control in terms of VAS, Lysholm score and IKDC at 6 months, however, the authors only considered the different in pain scores to be clinically relevant. By 12 months, none of the differences between groups were clinically relevant. Individual studies have shown mixed results. A retrospective matched case-control study found no differences in knee function scores or time to return of activity between platelet-rich plasma and matched-control groups at 2 years; however, the platelet-rich plasma group demonstrated a higher rate of postoperative knee motion loss compared with the control group (13.6% vs 4.6%).

### Hip Fracture

#### *Clinical Context and Therapy Purpose*

The purpose of PRP 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 individuals with hip fracture.

#### *Populations*

The relevant population of interest is individuals with hip fracture.

#### *Interventions*

The therapy being considered is PRP injections plus orthopedic surgery. The use of PRP 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.

#### *Comparators*

Comparators of interest include orthopedic surgery alone.

#### *Outcomes*

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating PRP injections plus orthopedic surgery as a treatment for hip fracture 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.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

### Review of Evidence

### Randomized Controlled Trials

One RCT was identified for treatment of a hip fracture with platelet-rich plasma. Griffen et. al. (2013) reported on a single-blind randomized trial assessing the use of platelet-rich plasma for the treatment of hip fractures in patients aged 65 years and older. Patients underwent internal fixation of the fracture with cannulated screws and were randomized to standard-of-care fixation (n=99) or standard-of-care fixation plus injection of platelet-rich plasma into the fracture site (n=101). The primary outcome measure was the failure of fixation within 12 months, defined as any revision surgery. The overall risk of revision by 12 months was 36.9%, and the risk of death was 21.5%. There was no significant risk reduction (39.7% control vs. 34.1% platelet-rich plasma; absolute risk reduction, 5.6%; 95% CI, -10.6% to 21.8%) or significant difference between groups for most of the secondary outcome measures. For example, mortality was 23% in the control group and 20% in the platelet-rich plasma group. The length of stay was significantly reduced in the platelet-rich plasma-treated group (median difference, 8 days). For this measure, there is a potential for bias from the nonblinded treating physician.

### Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Hip Fracture

A single open-label RCT evaluated the efficacy of 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.

### Long Bone Nonunion

#### *Clinical Context and Therapy Purpose*

The purpose of PRP 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 individuals with hip fracture.

#### *Populations*

The relevant population of interest is individuals with long bone nonunion.

### *Interventions*

The therapy being considered is PRP injections plus orthopedic surgery. The use of PRP 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.

### *Comparators*

Comparators of interest include  rhBMP-7 plus orthopedic surgery.

### *Outcomes*

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for long bone nonunion 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.

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

## Systematic Reviews

A Cochrane review by Griffin et al (2012) found only 1 small RCT (N=21) evaluating platelet-rich plasma for long bone healing. However, because only studies comparing platelet-rich plasma with no additional treatment or placebo were eligible for inclusion, reviewers did not select a larger RCT by Calori et al (2008; discussed below).

## Randomized Controlled Trials

The trial by Dallari et al (2007), which was included in the Cochrane review, compared platelet-rich plasma plus allogenic bone graft with allogenic bone graft alone in patients undergoing corrective osteotomy for medial compartment osteoarthrosis of the knee. According to Cochrane reviewers, the risk of bias in this study was substantial. Results showed no significant differences in patient-reported or clinician-assessed functional outcome scores between groups at 1 year. However, the proportion of bones united at 1 year was statistically significantly higher in the platelet-rich plasma plus allogenic bone graft arm (8/9) compared with the allogenic bone graft alone arm (3/9; relative risk [RR], 2.67; 95% CI, 1.03 to 6.91). This benefit, however, was not statistically significant when assuming poor outcomes for participants who were lost to follow-up (8/11 vs. 3/10; RR, 2.42; 95% CI, 0.88 to 6.68). Tables 13 and 14 describe this RCT and the subsequent RCT's characteristics and results, respectively. Tables 15 and 16 describe study design and conduct limitations.

Calori et al (2008) compared the application of platelet-rich plasma with rhBMP-7 for the treatment of long bone nonunions in an RCT involving 120 patients and 10 surgeons. Inclusion criteria were posttraumatic atrophic nonunion for at least 9 months, with no signs of healing over the last 3 months, and considered as treatable only by means of fixation revision. Autologous bone graft had been used in a prior surgery in 23 cases in the rhBMP-7 group and 21 cases in the platelet-rich plasma group. Computer-generated randomization created 2 homogeneous groups; there were generally similar numbers of tibial, femoral, humeral, ulnar, and radial nonunions in the 2 groups. Following randomization, patients underwent surgery for nonunion, including bone grafts according to the surgeon’s choice (66.6% of rhBMP-7 patients, 80% of platelet-rich plasma patients). Clinical and radiologic evaluations by 1 radiologist and 2 surgeons trained in the study protocol revealed fewer unions in the platelet-rich plasma group (68%) than in the rhBMP-7 group (87%). Clinical and radiographic healing times were also found to be slower by 13% to 14% with platelet-rich plasma.

Samuel et. al. (2017) conducted a controlled trial in which patients with delayed unions (15 to 30 weeks old) were randomized to 2 platelet-rich plasma injections at the fracture site at baseline and 3 weeks (n=23) or no treatment (n=17). The delayed unions were in the tibia (n=29), femur (n=8), forearm (n=2), and the humerus (n=1). The main outcome was long bone union, defined as no pain or tenderness on weight bearing, no abnormal mobility, and bridging at 3 or more cortices in x-ray. Examinations were conducted every 6 weeks for 36 weeks or until union. Percent union did not differ significantly between the 2 groups (78% in the platelet-rich plasma group vs. 59% in the control group). Time to union also did not differ significantly (15.3 weeks for the platelet-rich plasma group vs. 13.1 weeks for the control group).

**Table 13. Summary of Key RCT Characteristics**

| **Study** | **Countries** | **Sites** | **Dates** | **Participants** | **Interventions** | **Comparator** | |
|---|---|---|---|---|---|---|---|
| | | | | | *Active* | *Comparator 1* | *Comparator 2* |
| Dallari (2007) | Italy | NR | NR | Patients undergoing high tibial osteotomy to treat genu varum | Implantation of lyophilized bone chips with platelet gel (n=11) | Implantation of lyophilized bone chips with platelet gel and bone marrow stromal cells (n=12) | Implantation of lyophilized bone chips without gel (n=10) |
| Calori (2008) | Italy | 1 | 2005-2007 | Patients undergoing treatment of long bone nonunions | PRP (n=60) | rhBMP-7 (n=60) | |
| Samuel (2017) | India | 1 | 2010-2014 | Patients with delayed unions | PRP (n=23) | No treatment (n=17) | |

NR: not reported; PRP: platelet-rich plasma; RCT: randomized controlled trial; rhBMP-7: recombinant human bone morphogenetic protein-7.

**Table 14. Summary of Key RCT Results**

| Study | Knee Society Score at 1 yr | Knee Society Functional Score at 1 yr | Union Rate | Median Healing Time |
|---|---|---|---|---|
| Dallari (2007) | | | | |
| PRP | 91.3 ± 2 | 99.0 ± 0.6 | | |
| PRP+bone marrow | 89.9 ± 4 | 99.2 ± 0.5 | | |
| Non-PRP | 90.3 ± 4 | 98.8 ± 0.6 | | |
| Calori (2008) | | | | |
| PRP | | | 41 (68.3%) | 4 ± 0.61 months |
| rhBMP-7 | | | 52 (86.7%) | 3.5 ± 0.48 |
| P-value | | | .016 | |
| Samuel (2017) | | | | |
| PRP | | | 18 (78%) | 15.3 weeks |
| Control | | | 10 (59%) | 13.1 weeks |
| P-value | | | .296 | .54 |

PRP: platelet-rich plasma; RCT: randomized controlled trial; rhBMP-7: recombinant human bone morphogenetic protein-7.

**Table 15. Study Relevance Limitations**

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow.Up[e] |
|---|---|---|---|---|---|
| Dallari (2007) | 3. Only 33 patients included | | | | |
| Calori (2008) | | | | | |
| Samuel (2017) | | | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

**Table 16. Study Design and Conduct Limitations**

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Follow Up[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| Dallari (2007) | 3. Allocation concealment unclear | 1,2,3. No blinding described | | | 1,2. Study was underpowered and nonparametric statistical tests were performed | |
| Calori (2008) | 2. Allocation not concealed | 1,2,3. No blinding described | | | | |
| Samuel (2017) | 1. Randomization procedure not described, 3. Allocation concealment unclear | 1,2,3. No blinding described | | | | |

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Long Bone Nonunion

Three RCTs have evaluated the efficacy of platelet-rich plasma injections in individual with long bone nonunion. One trial with a substantial risk of bias failed to show significant differences in patient-reported or clinician-assessed functional outcome scores between patients who received platelet-rich plasma plus allogenic bone graft versus those who received only allogenic bone graft. While the trial showed statistically significant increases in the proportion of bones that healed in patients receiving platelet-rich plasma in a modified intention-to-treat analysis, the results did not differ in the intention-to-treat analysis. An RCT that compared platelet-rich plasma with rhBMP-7 also failed to show any clinical and radiologic benefits of platelet-rich plasma over rhBMP-7. The third RCT found no difference in the number of unions or time to union in patients receiving platelet-rich plasma injections or no treatment.

### Rotator Cuff Repair

#### *Clinical Context and Therapy Purpose*

The purpose of PRP 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 individuals with hip fracture.

#### *Populations*

The relevant population of interest is individuals with rotator cuff repair.

### *Interventions*

The therapy being considered is PRP injections plus orthopedic surgery. The use of PRP 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.

### *Comparators*

Comparators of interest include orthopedic surgery alone.

### *Outcomes*

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating PRP injections plus orthopedic surgery as a treatment for rotator cuff repair has varying lengths of follow-up, ranging from 6-months to 3.5- years. While studies described below all reported at least 1 outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, 3.5- years of follow-up is considered necessary to demonstrate efficacy.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

### Review of Evidence

### Systematic Reviews

The literature on platelet-rich plasma for rotator cuff repair consists of several RCTs and systematic reviews that have evaluated the efficacy of platelet-rich plasma membrane or matrix combined with surgical repair of the rotator cuff. A crosswalk of RCTs included in these systematic reviews is found in the Appendix (Table A3). The systematic reviews have varied in their outcomes of interest and findings (Tables 17 and 18). For pain outcomes, systematic reviews generally found significant reductions with platelet-rich plasma at 12 months. However, systematic review authors noted that the pain findings should be interpreted with caution due to significant residual statistical heterogeneity, lack of a clinically significant difference (i.e., less than the effect size threshold of 0.5 for a clinically important difference), and high risk of bias in study conduct. Some systematic reviews generally did not show a statistically or clinically significant benefit of platelet-rich plasma on other outcomes, including function, retear rate, and Constant scores. One systematic review found a statistically significant reduction in retear rate in a subgroup analysis of 4 long-term RCTs that were at least 24 months in duration. No reviews have demonstrated a consistent statistically and clinically significant benefit of platelet-rich plasma across multiple outcomes of interest for the 3.5 years of follow-up that is considered necessary to conclusively demonstrate efficacy. The systematic review by Wang et al (2019) reported on adverse effects, and noted that complications were only reported in 1 of the included RCTs, occurring in 5.6% of participants in the platelet-rich plasma groups and none in the control groups. The complications included infection, hematoma, and an exanthematous itchy skin lesion in 1 patient each

**Table 17. Systematic Reviews and Meta-Analysis Characteristics**

| Study | Dates | Trials | Participants | N (Range) | Design | Duration |
|---|---|---|---|---|---|---|
| Li (2021) | Through Oct 2020 | 16 (PRP) | Patients undergoing surgery for rotator cuff repair | 1440 (28 to 120) | RCT | 1.5 to 60 mo |
| Chen (2020) | 2011-2017 | 17 | Patients with rotator cuff tears | 1116[a] (36 to 120) | RCT | NR |
| Johal (2019) | 2011-2016 | 13 | Patients undergoing surgery for rotator cuff repair | 858 (25 to 120) | RCT | 7w to 24mo |
| Chen (2018) | 2011-2016 | 37 | Patients with tendon and ligament injuries | 1031[a] (NR) | RCT | NR |
| Fu (2017) | 2011-2015 | 11 | Patients with rotator cuff injury or tendinopathy | 638 (NR) | RCT | NR |
| Zhao (2015) | 2011-2013 | 8 | Patients with rotator cuff injury | 464 (28 to 88) | RCT | NR |
| Moraes (2014 ) | 2008-2013 | 19 | Patients undergoing rotator cuff repair | 1088 (23 to 150 | RCT and quasi-randomized trials | NR |

NR: not reported; PRP: platelet-rich plasma; RCT: randomized controlled trial.
[a] Number of participants which could be included in the quantitative analysis.

**Table 18. Systematic Reviews and Meta-Analysis Results**

| Study | VAS Reduction | VAS Reduction at 1 Year | Difference in Retear Rate | Difference in Function | Difference in Function at 1 Year |
|---|---|---|---|---|---|
| Li (2021) | 10 RCTs; n=559 | | 12 RCTs; n=700<br>RCTs ≥24 months: 4 RCTs, n=255 | UCLA Score:<br>7 RCTs; n=437 | |
| Point estimate | 10 RCTs: MD -0.13 | | 12 RCTs: RR, 0.56<br>RCTs ≥24 months: RR, 0.40 | 7 RCTs: MD, 1.55 | |
| 95% CI | 10 RCTs: -0.56 to -0.06 | | 12 RCTs: RR, 0.56<br>RCTs ≥24 months: 0.22 to 0.73 | 7 RCTs: MD, 0.86 to 2.24 | |
| Chen (2020) | | 8 RCTs; N=469 | | | UCLA Score: 6 RCTs; N=386 |
| WMD | | -0.34 | | | 1.39 |

| Study | VAS Reduction | VAS Reduction at 1 Year | Difference in Retear Rate | Difference in Function | Difference in Function at 1 Year |
|---|---|---|---|---|---|
| 95% CI | | -0.76 to 0.09 | | | 0.35 to 2.43 |
| $I^2$ | | 87.5% | | | 37.8% |
| Johal (2019) | | 7 RCTs, N=324 | | | |
| SMD | | -0.261 | | | |
| 95% CI | | -0.46 to -0.05 | | | |
| $I^2$ | | 0% | | | |
| Chen (2018) | | | | | |
| WMD | | -0.84 | | | |
| 95% CI | | -1.23 to -0.44 | | | |
| P-value | | <.01 | | | |
| Fu (2017) | | | | | |
| SMD | | 0.142[a] | | | |
| 95% CI | | -0.08 to 0.364 | | | |
| P-value | | .209 | | | |
| Zhao (2015) | | | | | |
| RR | | | 0.94 | | |
| 95% CI | | | 0.70 to 1.25 | | |
| P-value | | | .66 | | |
| Moraes (2014 ) | | | | | |
| SMD | | | | | 0.25 |
| 95% CI | | | | | -0.07 to 0.57 |
| P-value | | | | | .12 |

[a] Change from baseline at final follow-up. Follow-up durations ranged from 6 weeks to 24 months.
CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio; SMD: standard mean difference; UCLA: University of California at Los Angeles (UCLA) activity score; VAS: visual analog scale; WMD: weighted mean difference.

## Randomized Controlled Trials

Data from a 2011 double-blind RCT by Randelli et al that included 53 patients randomized to receive arthroscopic rotator cuff repair with or without the addition of platelet-rich plasma is included in multiple meta-analyses summarized above. Randelli et al (2021) published results of a 10-year follow-up of this trial, which included data for 17 patients who received platelet-rich plasma and 21 control group patients. At the 10-year follow-up, both platelet-rich plasma and control groups experienced improvements in the median (interquartile range [IQR]) University of California at Los Angeles activity score (34 [29 to 35] and 33 [29 to 35] points, respectively) and VAS score (0.34 [0 to 1.85] and 0.70 [0 to 2.45] points, respectively); the between-group differences did not reach statistical significance. Furthermore, approximately 37% of the operated patients had a re-rupture in each group. Retears occurred in 6% of the patients who received platelet-rich plasma treatment and 14% of patients in the control group (p=.61).

Rossi et al (2024) examined if the use of platelet-rich plasma as an adjuvant to arthroscopic rotator cuff repair decreased the rate of retears compared with a control group at a single center. Patients with rotator cuff tears <3 cm were enrolled and randomly allocated to rotator cuff repair alone (n=48) or rotator cuff repair with a platelet-rich plasma injection during surgery (n=48). The rate of retears in the platelet-rich plasma group was 15.2% (95% CI, 6% to 28%), which was lower than the rate of retears in the control group (34.1%; 95% CI, 20% to 49%; p=.037). Overall, functional outcomes were improved after surgery across groups and there were no significant differences in functional scores, postoperative pain, and other patient-reported outcomes between groups.

Yao et al (2024) reported on an RCT comparing adjunctive platelet-rich plasma, either leukocyte-rich (LR) or leukocyte-poor (LP), to no injection in patients with rotator cuff tears undergoing arthroscopic repairs. Patients randomized to the platelet-rich plasma groups were administered an injection postoperatively into the tendon-to-bone interface. Functional outcomes were analyzed in 142 individuals (LR platelet-rich plasma n=46; LP-platelet-rich plasma n=47; control n=49). There was no difference in the primary outcome of the UCLA score among the 3 groups (p=.169). Additionally, there were no significant differences in other functional outcomes and range of motion between the groups at 12 months. At 12 months post-surgery, the retear rate was 8% and there were no significant differences in the rates of overall retear (p=.755). The only surgical complication reported was postoperative stiffness, which occurred in 3% of patients, and did not differ among groups (p=.790).

## Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment of Rotator Cuff Repair

Although systematic reviews consistently found significant reductions in pain with PRP at 12-months, important study conduct and relevance weaknesses limit interpretation of these findings. While the systematic reviews and meta-analyses generally failed to show a statistically and/or clinically significant impact on other outcomes, 1 meta-analysis found a statistically significant reduction in retear rate in a subgroup analysis of 4 RCTs that were at least 24-months in duration. Findings of a subsequently published 10-year follow-up of a small RCT failed to demonstrate the superiority of PRP over control for clinical and radiologic outcomes. Two newer RCTs also found no difference in the addition of platelet-rich plasma over control in functional outcomes at either 6 months or 1 year follow-up. The variability in PRP preparation techniques and PRP administration limits the generalizability of the available evidence

## Spinal Fusion

### *Clinical Context and Therapy Purpose*

The purpose of PRP 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 individuals with spinal fusion.

### *Populations*

The relevant population of interest is individuals with spinal fusion.

### *Interventions*

The therapy being considered is PRP plasma injections plus orthopedic surgery. The use of PRP 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.

### *Comparators*

Comparators of interest include orthopedic surgery alone.

### *Outcomes*

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for spinal fusion has varying lengths of follow-up.

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

## Randomized Controlled Trials

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., 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.

### Prospective Cohort Studies

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

### Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Spinal Fusion

For individuals undergoing spinal fusion who receive PRP injections, the evidence includes a single small RCT and a few observational studies. Relevant outcomes include symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. Studies have generally failed to show a statistically and/or clinically significant impact on symptoms (i.e., pain).

### Subacromial Decompression Surgery

#### *Clinical Context and Therapy Purpose*

The purpose of PRP 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 individuals with subacromial decompression surgery.

#### *Populations*

The relevant population of interest is individuals with subacromial decompression surgery.

#### *Interventions*

The therapy being considered is PRP injections plus orthopedic surgery. The use of PRP 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.

#### *Comparators*

Comparators of interest include orthopedic surgery alone.

#### *Outcomes*

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating PRP injections plus orthopedic surgery as a treatment for subacromial decompression surgery 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.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

### Review of Evidence

### Randomized Controlled Trials

One small RCT evaluated the use of platelet-rich plasma as an adjunct to subacromial decompression surgery. Everts et al (2008) reported on a rigorously conducted, small (N=40), double-blinded RCT of platelet and leukocyte-rich plasma gel following open subacromial decompression surgery in a carefully selected patient population. Neither self-assessed nor physician-assessed instability improved. Both subjective pain and use of pain medication were lower in the platelet and leukocyte-rich plasma group across the 6 weeks of measurements. For example, at 2 weeks after surgery, VAS scores for pain were lower by about 50% in the platelet and leukocyte-rich plasma group (close to 4 in the control group, close to 2 in the platelet and leukocyte-rich plasma group), and only 1 (5%) patient in the platelet and leukocyte-rich plasma group was taking pain medication compared with 10 (50%) control patients. Objective measures of range of motion showed clinically significant improvements in the platelet and leukocyte-rich plasma group across the 6-week assessment period, with patients reporting improvements in activities of daily living, such as the ability to sleep on the operated shoulder at 4 weeks after surgery and earlier return to work.

### Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment for Subacromial Decompression Surgery

A single small RCT has evaluated the efficacy of PRP injections in individuals undergoing subacromial decompression surgery. Compared with controls, PRP treatment did not improve self-assessed or physician-assessed instability. However, subjective pain, use of pain medication, and objective measures of range of motion showed clinically significant improvements with PRP. Larger RCTs would be required to confirm these benefits.

### Total Knee Arthroplasty

#### *Clinical Context and Therapy Purpose*

The purpose of PRP 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 individuals with total knee arthroplasty (TKA).

#### *Populations*

The relevant population of interest is individuals with TKA.

#### *Interventions*

The therapy being considered is PRP injections plus orthopedic surgery. The use of PRP 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.

### *Comparators*

Comparators of interest include orthopedic surgery alone.

### *Outcomes*

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating PRP injections plus orthopedic surgery as a treatment for subacromial decompression surgery 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.

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

## Systematic Reviews

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.

Shu et. al. (2022) evaluated platelet-rich plasma in patients undergoing total joint replacement including 8 studies in patients with total knee arthroplasty (1 study for total hip arthroplasty and 1 on total hip or knee arthroplasty). Of the 3 studies reporting VAS scores in patients undergoing total knee arthroplasty (n=161), pain scores were similar during the first 2 postoperative days, but 3 weeks and 2 months had improvement with platelet-rich plasma compared with control (MD, -0.92; 95% CI, -1.25 to -0.60 and -0.93; 955 CI, -1.24 to -0.63, respectively). There were no differences in range of motion, WOMAC scores, length of hospital stay, or wound healing within 4 weeks between platelet rich plasma or controls in patient undergoing total knee arthroplasty. The authors noted high heterogeneity and the need for more high-quality RTCs.

## Section Summary: Platelet-Rich Plasma as Adjunctive for Total Knee Arthroplasty

Two systematic reviews have evaluated the efficacy of intraoperative PRP in individuals undergoing TKA. In the review by Trams et al (2020) there were no significant differences between the PRP and untreated control groups across several functional and pain outcomes. The systematic review by Shu et al (2022) found improved VAS scores in individuals undergoing TKA; however, there were no differences in other outcomes and the authors noted high heterogeneity and the need for well-designed RCTs.

## Autologous Protein Solution

### *Clinical Context and Therapy Purpose*

The purpose of autologous protein solution (APS) therapy 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 individuals with OA of knee and various musculoskeletal conditions.

The following PICO was used to select literature to inform this review.

### *Populations*

The relevant population of interest is individuals with OA of the knee and various musculoskeletal conditions.

### *Interventions*

The therapy being considered is APS therapy. The use of APS has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of APS therapy 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, and anti-inflammatory agents.

### *Outcomes*

The general outcomes of interest are symptoms, functional outcomes, health status measures, QOL, and treatment-related morbidity. The existing literature has varying lengths of follow-up, Longer follow-up is necessary to fully observe outcomes.

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

a. To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
b. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
c. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
d. Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

### Systematic Review

Gupta et al (2024) conducted a systematic review to evaluate the efficacy of autologous peripheral blood-derived orthobiologics (APBOs) for the management of hip osteoarthritis (OA) in improving pain and function. The reviewers searched Scopus, Embase, PubMed, and Web of Science to September 21, 2024 and only two studies fit the scope of the study and both studies involved the use of ACS. There were no published clinical studies identified in the peer reviewed medical literature that utilized APS for the management of hip OA. As of September 21, 2024 there were no ongoing clinical trials listed on any of the searched registers (ClinicalTrials.gov, BRTI, or ChiCTR) to evaluate the safety and/or effectiveness to manage hip OA. The reviewers concluded “more adequately powered, prospective, multicenter, controlled, open-label or blinded, randomized, and non-randomized trials with extended follow-up are necessary to determine the efficacy of various APBOs for managing hip OA.”

### Randomized Controlled Trials

Ross et al (2024) conducted a multicenter, double-blinded, placebo-controlled, two-arm randomized controlled trial (RCT) that evaluated the effectiveness of autologous protein solution (APS) intra-articular injection (nSTRIDE) compared to saline (placebo) injection. A total of 40 patients (21 nSTRIDE [7 males/12 females]; 19 saline [9 males/12 females]) were analyzed with unilateral moderate knee OA (Kallgren-Lawrence 2-3). Additional inclusion criteria included: age criteria between 21 and 80 years, BMI < 40 kg/m$^2$, and previous trial of nonoperative management that included physiotherapy or analgesia. The intervention involved a single intra-articular injection of nSTRIDE into the affected knee for the intervention group under ultrasound guidance and for the control group a single intra-articular injection of normal saline into the affected knee. Both the surgeon and participant remained fully blinded of the contents of the injection throughout the procedure. Outcome measures were based on knee symptoms using validated questionnaires (patient reported outcome measures [PROMS]); the primary outcome measure was the mean difference between the APS group and the saline group using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total score at one year after the injection. Secondary outcome measures (pain, sports & recreation, activities of daily living, QOL) were additional PROMS using Knee injury and Osteoarthritis Outcome Score (KOOS), and visual analogue scale (VAS) score at multiple time points up to one year after injection (baseline, 3, 6, and 12-months), to include any adverse reactions. There were no significant differences between the two groups for WOMAC total score at 12 months (mean difference -10.4 (95% CI -24.4 to 3.6; p = 0.141)). There were no significant differences between the intervention and control groups across all WOMAC and KOOS sub-scores at all timepoints. Point estimates consistently favored the saline group at all timepoints and measures of knee symptoms. With respect to VAS scores, results revealed significant mean differences favoring the saline group for both the rest and worst pain scales at one year post-injection (mean difference (worst) 21.5 (95% CI 6.2 to 36.8; p =0.008); mean difference (rest) 17.8 (95% CI 2.2 to 33.4; p =0.026)). There were no adverse events reported. Limitations included due to COVID-19 this study did not reach target sample size due to recruitment disruptions and patient selection was considered strict in regards to participation eligibility criteria which may have caused this cohort of participants to not represent the “typical” patient presenting with knee OA. “This pilot RCT revealed no significant differences between nSTRIDE and saline groups at all time points with respect to the WOMAC and KOOS scores up to one year following intra-articular injection. VAS at one year showed that both the worst pain and rest pain subscales favored the saline group over the nSTRIDE group. The results of this study suggested a potential detriment with nSTRIDE use on knee OA pain symptoms at one-year post-injection compared to saline.”

In 2020, Kon et. al. reported 3-year results regarding the effects of a single intra-articular injection of autologous protein solution (APS) in patients affected by knee osteoarthritis (OA) previously documented in a one year multicenter double-blind randomized saline controlled trial (Kon et al 2018 below). 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.

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.

## Nonrandomized Controlled Trials

In 2017, Hix et al in a single-center, single-arm, nonrandomized prospective study evaluated the safety and treatment effects of a single intra-articular APS injection for the treatment of individuals with painful unilateral OA using the nSTRIDE APS kit (Zimmer, Biomet). A total of 11 patients were enrolled of which 10 patients received the APS injection, and all 10 patients completed the 12-month followed-up. The primary end point of this study was to characterize the safety profile of APS at 1, 3, 6 and 12-months following the injection, and the secondary end point included monitoring of the index knee at 15 minutes, 1 hour and 2 hours post injection and measures of clinical efficacy that included Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Numeric Rating Scale (NRS) pain, and global assessments. The Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) set of responder criteria was utilized to determine the number of treatment responders. The WOMAC pain scores improved significantly over time (ANOVA, $p < 0.0001$), ($12.0 \pm 1.2$) before injection and ($3.3 \pm 2.9$) 1 year postinjection. This corresponded to a 72.5% WOMAC pain improvement on average. WOMAC stiffness ( $p \leq 0.0371$), WOMAC function ( $p \leq 0.0064$), and WOMAC total score ( $p \leq 0.0064$) were also improved at all time intervals compared to baseline. The mean KOOS pain score before injection was $36.9 \pm 16.2$. One week after the injection, the mean KOOS pain score was $56.7 \pm 16.5$, and it was $79.7 \pm 16.2$ one year after the injection. Preinjection KOOS pain was significantly different from KOOS pain at all postinjection intervals ( $p \leq 0.0029$). Also, the KOOS symptom ( $p \leq 0.0269$), KOOS stiffness ( $p \leq 0.0420$), KOOS function ( $p \leq 0.0050$), and KOOS sport function ( $p \leq 0.0231$) were significantly improved at all postinjection intervals. NRS pain at baseline was $5.9 \pm 1.9$. The lowest level of mean pain was observed at 1 year post-procedure ($1.6 \pm 1.6$). For patient-reported Global Impression, the p-value associated with a repeated means ANOVA to determine whether a difference between intervals exists was $p = 0.0002$. At baseline, the most frequently reported score was severe (n = 4), followed by moderate (n = 3) and mild (n = 3). One week after the injection, mild, moderate, and marked were each scored in three cases, severe in one case. At 1 year following treatment, two cases were scored as normal, two were borderline, four were mild, and two were moderate. Minor adverse events (AEs) were experienced by seven subjects (63.6%). The authors concluded "The safety evaluation yielded a positive profile of the subject device. No device related AEs were reported through the clinical study. y. Furthermore, considering the small number of subjects in this study, the consistency of favorable results among diverse efficacy measurements such as the WOMAC, KOOS, Global Impression, and OMERACT-OARSI responder rate was remarkable. Improvement continued through 12 months post procedure, indicating the durability of a single APS injection. The results of this clinical investigation indicate that treatment with a single, intraarticular injection of APS in patients with knee OA can be considered safe and warrants further investigation of the nSTRIDE APS Kit."

### Single-Arm Noncomparative Observational Studies

In 2016, van Drumpt et al assessed the safety and treatment effectiveness of a single autologous protein solution injection nSTRIDE in 11 patients (7 males [64%], 4 females [36%]) with unilateral knee osteoarthritis in an open-label, prospective trial. Mean age of the subjects was 57.5 years. Clinical outcomes and adverse events (AEs) were assessed at 1 and 2 weeks postinjection and 1, 3, and 6 months postinjection. Assessments included the WOMAC and both the subject's and physician's assessment of global change in the index knee, and AEs. Ten of the eleven subjects completed per the study protocol as 1 subject withdrew after 1-month assessment due to persistent OA symptoms. There were no AEs reported related to the device. At the 3-6 month follow-up ratings for both the physician and the subjects, 80% of the subjects were either ''Very Much Improved'' or ''Much Improved.'' The mean WOMAC pain subscale scores were reduced from 12.0 before treatment to 8.2 at 1 week post-treatment ( $p = 0.05$). Significant reductions in mean pain scores continued through the 3 month post-treatment visit where the mean score was reduced by 75% to 3.0. This significant reduction was maintained at 6 months post-treatment where the score was 3.1, representing a 74.2% reduction from the baseline pain score. This study is limited by the lack of a control group and small sample size. The authors concluded "This study not only demonstrated robust improvements in mean outcome scores but also demonstrated good treatment effects in 73% of the subjects at 3 and 6-months postinjection. To demonstrate that APS is effective in treating OA and truly can modify the disease process, more robust study designs, including randomized clinical trials, with advanced imaging of the joint are necessary."

## Case Series

In 2023, Kuwasawa et. al. completed a retrospective study which assessed the 12-month clinical outcomes of 220 knees with osteoarthritis Kellgren-Lawrence (KL) grades 2-4 that underwent autologous protein solution (APS) using the Knee Injury and Osteoarthritis Outcome Score (KOOS). The APS utilized was nSTRIDE APS Kit (Zimmer Biomet). KOOS was collected before and 1, 3, 6 and 12-months after the APS injection to measure the change from baseline to each time point to evaluate clinical efficacy of APS. The Outcome Measures in Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria were utilized to determine the effect of the APS injection. KOOS and efficacy rates were separately compared by KL grade. During the 12-month follow-up period 72 or 220 knees dropped out and nine knees (2 in KL3 and 7 in KL4) underwent total knee arthroplasty during the following up period. Comparing the follow-up rates among the groups (n=220), 80% (64/80) in KL2, 73% (54/74) in KL3, and 45% (30/66) in KL4 were observed. The follow-up rate of KL4 was significantly lower than that of KL2 at 6 and 12-months (p<0.01) and that of KL3 at 12-months (p<0.01). One hundred forty-eight (n=148) knees completed the 12-month follow-up and comparing the KOOS among the groups post-APS injection found KOOS of KL4 significantly lower than that of KL2 in symptoms (p<0.0001, ADL (p<0.05), sport (p<0.01) subcategories. The responder rate according to OMERACT-OARSI criteria was calculated and showed the overall responder rate was 55.4% (82/148) at 12-months. No significant differences were found in the responder rate among the KL grades. The safety related to APS injection caused knee joint swelling and pain within 24 hours of the injection with no major adverse events reported. The authors reported the most important finding of this study was a single injection of APS for mild to moderate OA can produce pain improvement up to 12-months after the injection, however, the effect did not sustain for severe OS with KL4 and was inferior to mild to moderate OA with more patients dropping out in the 12-month follow-up period. The efficacy of KOOS peaked at 3-6 months for sever OA with KL4, and many patients dropped out because of lack of efficacy. This study revealed that APS is unlikely to improve symptoms of patients with severe OA with KL4. Limitations of this study included this retrospective study reviewed the results in clinical practice of APS therapy without controls and the follow-up rate for KL4 was lower than other groups.

## Section Summary: Autologous Protein Solution

The evidence regarding APS (nSTRIDE) is limited to the treatment of OA of the knee and includes RCTs, nonrandomized controlled trial, observation and case studies. The RCTs performed by Kon et. al 2018 and 2020 evaluated the safety and effectiveness of APS injection nSTRIDE (n=31) compared to saline injection (n=15) at 12-months and at 3-years. While study results may show improved efficacy measurements such as the WOMAC, KOOS, Global Impression, and OMERACT-OARSI responder rate in study participants in the APS group, the saline group (n=15) was allowed to cross over to the APS group at 12-months (n=15) and while their final scores were better than baseline, they were 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. An additional small, (n-40) placebo-controlled RCT by Ross et al (2024) found no significant differences between nSTRIDE and saline group at all time points with respect to WOMAC and KOOS scores up to one-year follow-up an inferior effects on pain relief for nSTRIDE. Additional RCTs are needed comparing APS with placebo and other alternative treatments including but not limited to hyaluronic acid and corticosteroids to determine the safety and effectiveness of APS in the treatment of knee OA and for any other musculoskeletal indications.

Gupta et al (2024) conducted a systematic review to evaluate the efficacy of autologous peripheral blood-derived orthobiologics (APBOs) to include the use of APS for the management of hip osteoarthritis (OA) in improving pain and function. There were no published clinical studies identified in the peer reviewed medical literature regarding APS for the management of hip OA. As of September 21, 2024 there were no ongoing clinical trials listed on any of the searched registers (ClinicalTrials.gov, BRTI, or ChiCTR) to evaluate the safety and/or effectiveness of APS to manage hip OA. RCTs with extended follow-up are necessary to determine the efficacy of APS for managing hip OA.

## SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### *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.”

#### *American Academy of Orthopaedic Surgeons (AAOS)*

In 2021, the American Academy of Orthopaedic Surgeons (AAOS) guideline for the management of osteoarthritis of the knee made the following recommendation:

- “Platelet-rich plasma (PRP) may reduce pain and improve function in patients with symptomatic osteoarthritis of the knee. (Strength of Recommendation: Limited).” The variability of study findings was noted to have contributed to the low strength of recommendation rating.

In 2023, the AAOS updated the 2017 evidence-based guideline on the management of osteoarthritis of the hip. In the section on intra-articular injectables, the guideline gave a moderate recommendation based on high-quality evidence supporting the use of intra-articular corticosteroids as an option to improve function and reduce pain in the short term for patients with osteoarthritis of the hip. There was a strong recommendation based on high-quality evidence against the use of intra-articular hyaluronic acid, as it does not perform better than placebo in improving function, stiffness, and pain in patients with hip osteoarthritis. The guidelines did not mention any evidence or make recommendations related to the use of platelet-rich plasma for the treatment of osteoarthritis of the hip.

In 2020, the AAOS adopted the management of glenohumeral joint osteoarthritis evidence-based clinical practice guideline which states the following:

- “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 AAOS issued evidence-based guidelines on the management of rotator cuff injuries. The guideline noted the following recommendations related to the use of platelet-rich plasma in this setting:

- "There is limited evidence supporting the routine use of platelet-rich plasma for the treatment of cuff tendinopathy or partial tears (Strength of Recommendation: Limited)." The variability of study findings was noted to have contributed to the low strength of recommendation rating.
- "Strong evidence does not support biological augmentation of rotator cuff repair with platelet-derived products on improving patient reported outcomes; however, limited evidence supports the use of liquid platelet-rich plasma in the context of decreasing re-tear rates (Strength of Recommendation: Strong)."
- "In the absence of reliable evidence, it is the consensus of the work group that we do not recommend the routine use of platelet-rich plasma in the non-operative management of full-thickness rotator cuff tears (Strength of Recommendation: Consensus)."

### *National Institute for Health and Care Excellence (NICE)*

In 2013, NICE issued guidance on the use of autologous blood injection for tendinopathy. NICE concluded the current evidence on safety and efficacy remains of autologous blood injection for tendinopathy was “inadequate” in quantity and quality.

In 2013, NICE also issued guidance on autologous blood injection (with or without techniques to producing platelet rich plasma) for plantar fasciitis. NICE concluded the evidence on autologous blood injection for plantar fasciitis raised no major safety concerns but that the evidence on efficacy was “inadequate in quantity and quality."

In 2019, NICE issued guidance on the use of platelet-rich plasma for osteoarthritis of the knee. NICE concluded that current evidence on platelet-rich plasma injections for osteoarthritis of the knee raised “no major safety concerns”; however, the “evidence on efficacy is limited in quality." Therefore, NICE recommended that "this procedure should only be used with special arrangements for clinical governance, consent, and audit or research."

## Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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## CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

| Codes | Number | Description |
|---|---|---|
| **CPT** | | |
| | 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 |
| **HCPCS** | | |
| | P9020 | Platelet rich plasma, each unit |
| **Type of Service** | Medical | |
| **Place of Service** | Inpatient/Outpatient | |

## POLICY HISTORY

| Date | Action | Action |
|---|---|---|
| June 2025 | Annual Review | Policy Renewed |
| June 2024 | Annual Review | Policy Renewed |
| June 2023 | Annual Review | Policy Revised |
| January 2023 | Annual Review | Policy Renewed |
| January 2022 | Annual Review | Policy Revised |

| Date | Action | Action |
| --- | --- | --- |
| 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 |

## APPENDIX

**Table A1. Comparison of RCTs Included in SRs and M-As for Treatment of Mixed Tendinopathies**

| **Study** | Masiello (2022) | Dai (2023 ) | Muthu (2021) | Johal (2019) | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ***Mixed tendinopathy RCTs*** | | | | | | | |
| Boesen (2020) | ● | | | | | | |
| Boesen (2017) | ● | ● | | | | | |
| Chen (2021) | ● | | | | | | |
| Dadgostar (2021) | ● | | | | | | |
| De Jonge (2011) | ● | | | | | | |
| De Vos (2010) | ● | ● | | | | | |
| Dragoo (2014) | | ● | | | | | |
| Fildaro (2012) | | | | | | | |
| Gogna (2016) | ● | | | | | | |
| Kesikburun (2013) | ● | ● | | | | | |
| Kim (2013) | ● | | | | | | |
| Kwong (2021) | ● | | | | | | |

| Study | Masiello (2022) | Dai (2023 ) | Muthu (2021) | Johal (2019) | | | |
|---|---|---|---|---|---|---|---|
| ***Mixed tendinopathy RCTs*** | | | | | | | |
| Malahias (2017) | ● | | | | | | |
| Malahias (2019) | ● | | | | | | |
| Monto (2014) | ● | | | | | | |
| Nejati (2017) | ● | | | | | | |
| Rha (2013) | ● | ● | | | | | |
| Rodas (2021) | ● | | | | | | |
| Sari (2020) | ● | | | | | | |
| Schwitzguebel (2019) | ● | | | | | | |
| Scott (2019) | | ● | | | | | |
| Senna (2019) | ● | | | | | | |
| Shen (2019) | ● | | | | | | |
| Shams (2016) | | | | | | | |
| Thermann (2020) | | ● | | | | | |
| Vetrano (2013) | | | | | | | |
| Wu (2017) | ● | | | | | | |
| ***Lateral epicondylitis RCTs only*** | | | | | | | |
| Behera (2015) | ● | | ● | ● | | | |
| Creaney (2011) | ● | | | | | | |
| Gautam (2015) | | | ● | ● | | | |
| Gosens (2011) | | | ● | ● | | | |
| Gupta (2020 ) | | | ● | | | | |
| Khaliq (2015) | | | ● | | | | |
| Krogh (2013) | ● | ● | ● | ● | | | |
| Krogh (2016) | ● | ● | | | | | |
| Lebiedzinski (2015) | | | ● | | | | |
| Lim (2018) | ● | | ● | | | | |
| Linnanmaki (2020) | | ● | ● | | | | |
| Martin (2019) | ● | | ● | | | | |
| Merolla (2017) | ● | | ● | | | | |
| Mishra (2013) | | | ● | ● | | | |
| Montalvan (2016) | ● | ● | ● | ● | | | |
| Omar (2012) | | | | ● | | | |
| Palacio (2015) | | | ● | | | | |

| Study | Masiello (2022) | Dai (2023 ) | Muthu (2021) | Johal (2019) | | | |
|---|---|---|---|---|---|---|---|
| ***Mixed tendinopathy RCTs*** | | | | | | | |
| Palakuri (2020) | | | ● | | | | |
| Peerbooms (2010) | | | ● | ● | | | |
| Raeissadat (2014) | | | ● | ● | | | |
| Schoffi (2017) | | ● | ● | | | | |
| Seetharamiaiah (2017) | | | ● | | | | |
| Stenhouse (2013) | | | | | | | |
| Tetschke (2015) | | | ● | | | | |
| Thanasas (2011) | ● | | ● | ● | | | |
| Tonk (2014) | | | ● | | | | |
| Watts (2018) | | | ● | | | | |
| Yadav (2015) | | | ● | | | | |
| Yerlikaya (2018) | | ● | ● | | | | |

M-A:meta-analysis; RCT: randomized controlled trials; SR: systematic review.

### Table A2. Comparison of RCTs Included in SRs and M-As for Treatment of Knee or Hip Osteoarthritis

| Study | Trams et al (2020) | Johal et al (2019) | Xu et al (2017) | Laudy et al (2015) | Chang et al (2014) |
|---|---|---|---|---|---|
| Ahmad (2018) | ● | | | | |
| Bastos (2018) | ● | | | | |
| Bastos (2019) | ● | | | | |
| Buendia-Lopez (2018) | ● | | | | |
| Buendia-Lopez (2019) | ● | | | | |
| Bui (2014) | | ● | | | |
| Cerza (2012) | ● | | ● | ● | ● |
| Cole (2017) | ● | | | | |
| Di Martino (2019) | ● | | | | |
| Duif (2015) | | ● | | | |
| Duymus (2017) | ● | ● | ● | | |
| Elik (2020) | ● | | | | |
| Filardo (2012) | ● | | | ● | ● |
| Fildaro-Kon (2011) | | | | ● | |
| Filardo (2015) | ● | ● | ● | | |

| **Study** | Trams et al (2020) | Johal et al (2019) | Xu et al (2017) | Laudy et al (2015) | Chang et al (2014) |
|---|---|---|---|---|---|
| Forogh (2016) | | ● | | | |
| Görmeli (2017) | ● | | ● | | |
| Huang (2018) | ● | | | | |
| Jubert (2017) | ● | | | | |
| Kavadar (2015) | ● | | | | |
| Kon (2011) | | | | ● | |
| Kon (2018) | ● | | | | |
| Lana (2016) | ● | | | | |
| Lee (2013) | | ● | | | |
| Li Ming (2011) | | | | ● | ● |
| Lin (2018) | ● | | | | |
| Lisi (2018) | ● | | | | |
| Louis (2018) | ● | | | | |
| Montañez-Heredia (2016) | ● | | | | |
| Ming (2011) | | | ● | | |
| Patel (2013) | ● | ● | ● | ● | ● |
| Paterson (2016) | ● | ● | | | |
| Raeissadat (2015) | ● | ● | ● | | |
| Raeissadat (2017) | ● | | | | |
| Rahimzadeh (2018) | ● | | | | |
| Rayegani (2014) | ● | ● | | | |
| Sari | | | | | |
| Say (2013) | | | | ● | |
| Sánchez (2012) | ● | ● | ● | ● | ● |
| Simental- Mendía (2016) | ● | ● | | | |
| Simental-Mendía (2019) | ● | | | | |
| Smith (2016) | ● | ● | ● | | |
| Spakova (2012) | ● | ● | | ● | |
| Su (2018) | ● | | | | |
| Tavassoli (2019) | ● | | | | |
| Uslu-Guvendi (2018) | ● | | | | |
| Vaquerizo (2013) | ● | ● | ● | ● | |
| Wu (2018) | ● | | | | |

| Study | Trams et al (2020) | Johal et al (2019) | Xu et al (2017) | Laudy et al (2015) | Chang et al (2014) |
|---|---|---|---|---|---|
| Yu (2018) | ● | | | | |
| Zedde (2015) | | ● | | | |

M-A:meta-analysis; RCT: randomized controlled trials; SR: systematic review.

### Table A3. Comparison of Trials/Studies Included in SRs and M-As for Rotator Cuff Repair

| Study | Li (2021) | Chen (2020) | Johal (2019) | Chen (2018) | Fu (2017) | Zhao (2015) | Moraes (2014 ) |
|---|---|---|---|---|---|---|---|
| Antuna (2013) | ● | | ● | | | | ● |
| Carr (2015) | | ● | | ● | | | |
| Castricini (2011) | ● | ● | ● | ● | ● | ● | ● |
| D'Ambrosi (2016) | ● | ● | | | | | |
| Ebert (2017) | ● | ● | | | | | |
| Flury (2016) | ● | ● | ● | | | | |
| Gumina (2012) | ● | ● | | ● | ● | ● | ● |
| Hak (2015) | ● | | ● | | ● | | |
| Holtby (2016) | ● | | ● | | | | |
| Jo (2013) | ● | ● | ● | ● | | ● | |
| Jo (2015) | ● | ● | ● | ● | ● | | |
| Kesikburun (2013) | | ● | ● | ● | ● | | |
| Malavolta (2014) | ● | ● | ● | ● | ● | | |
| Malavolta (2018) | ● | | | | | | |
| Marquez (2011) | | | | | ● | | |
| NCT01029574 | | | | | | | ● |
| Pandey (2016) | ● | ● | ● | ● | | | |
| Randelli (2011) | ● | ● | ● | ● | ● | ● | ● |
| Rha (2013) | | ● | ● | ● | | | |
| Rodeo (2012) | ● | | | | ● | ● | ● |
| Ruiz-Moneo (2013) | ● | ● | | ● | ● | ● | |
| Sanchez-Marquez (2011) | ● | | | | | ● | |

| **Study** | Li (2021) | Chen (2020) | Johal (2019) | Chen (2018) | Fu (2017) | Zhao (2015) | Moraes (2014 ) |
|---|---|---|---|---|---|---|---|
| Shams (2016) | | | ● | | | | |
| Snow (2019) | ● | | | | | | |
| Walsh 2018) | ● | | | | | | |
| Wang (2015) | ● | ● | ● | ● | ● | | |
| Weber (2013) | ● | ● | ● | ● | | ● | |
| Wesner (2016) | | | ● | | | | |
| Zhang (2016) | ● | ● | | | | | |
| Zumstein (2016) | ● | ● | ● | ● | | | |

M-A:meta-analysis; RCT: randomized controlled trials; SR: systematic review.

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

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