Policy Statement

Use of platelet-rich plasma is considered investigational for all orthopedic indications. This includes, but is not limited to, use in the following situations:

- Primary use (injection) for the following conditions:
  - Achilles tendinopathy
  - Lateral epicondylitis
  - Osteoarthritis
  - Osteochondral lesions
  - Plantar fasciitis

- Adjunctive use in the following surgical procedures:
  - Anterior cruciate ligament (ACL) reconstruction
  - Hip fracture
  - Long-bone nonunion
  - Patellar tendon repair
  - Rotator cuff repair
  - Spinal fusion
  - Subacromial decompression surgery
  - Total knee arthroplasty (TKA)

Policy Guidelines

Coding

There is a CPT category III code for injections of platelet-rich plasma (PRP):

- **0232T**: Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed

The instructions issued with the code state that it is not to be reported with codes 20550, 20551, 20600-20610, 20926, 76942, 77002, 77012, 77021, and 86965. Code 0232T includes the harvesting and preparation of the platelet-rich plasma.

For situations other than injection (when 0232T would be reported), no specific CPT codes describe the preparation of autologous blood-derived products, but the following CPT code can be used:

- **86999**: Unlisted transfusion medicine procedure

It is questionable whether platelet-rich plasma is appropriately considered a tissue graft, but it has been reported that providers have used the following CPT code to describe the overall procedure:

- **20926**: Tissue grafts, other (e.g., paratenon, fat, dermis)

The American Medical Association’s Department of Coding instructs that placement of platelet-rich plasma into an operative site is an inclusive component of the operative procedure performed and not reported separately.

Description

The use of platelet-rich plasma (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.
Related Policies

- Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions
- Bone Morphogenetic Protein
- Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used with Autologous Bone Marrow)
- Prolotherapy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 1270 and 1271. Blood products such as PRP are included in these regulations. Under these regulations, certain products including blood products such as PRP are exempt and therefore do not follow the traditional FDA regulatory pathway. To date, the FDA has not attempted to regulate activated PRP.

A number of PRP preparation systems are available, many of which were cleared for marketing by the 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. The Aurix System™ (previously called AutoloGel™; Cytomedix) and SafeBlood® (SafeBlood Technologies) are two related but distinct autologous blood-derived preparations that can be used at the bedside for immediate application. Both AutoloGel™ and SafeBlood® have been specifically marketed for wound healing. Other devices may be used during surgery (e.g., Medtronic Electromedics, Elmd-500 Autotransfusion system, the Plasma Saver device, the SmartPRePÒ [Harvest Technologies] device). The Magellan™ Autologous Platelet Separator System (Medtronic Sofamor Danek) includes a disposable kit for use with the Magellan™ Autologous Platelet Separator portable tabletop centrifuge. GPS®II (BioMet Biologics), a gravitational platelet separation system, was cleared for marketing by the FDA through the 510(k) process for use as disposable separation tube for centrifugation and a dual cannula tip to mix the platelets and thrombin at the surgical site. 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.

Rationale

Background
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 Blue Shield of California Medical Policy: Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions).

Autologous platelet concentrate suspended in plasma, also known as platelet-rich plasma (PRP), can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets, releasing the various growth factors. 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 factors, and thus PRP 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 Blue Shield of California Medical Policy: Prolotherapy). 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 Hemaseel® (Haemacure Corp) 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.

**Literature Review**

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 patients 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. The best evidence on the efficacy of platelet-rich plasma consists of several RCTs comparing platelet-rich plasma with conservative therapy (e.g., rest, physical therapy) and medication (e.g., corticosteroid injection), and systematic reviews of these trials. A number of systematic reviews of RCTs, with or without the addition of observational studies on platelet-rich plasma,
have been published; we focus on them in this evidence review. Individual RCTs are reviewed if no systematic reviews are available or if an individual RCT is likely to influence this evidence review but was not included in a systematic review.

At present, there are a large number of 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.\textsuperscript{1,2,3,4,5,6}

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

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

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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

**Patients**
The relevant population of interest is individuals with tendinopathy. Patients with tendinopathy are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

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

**Comparators**
Comparators of interest include nonpharmacologic therapy (eg., exercise, physical therapy) analgesics, and anti-inflammatory agents. These treatments are managed by primary care providers in an outpatient clinical setting.

**Outcomes**
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for tendinopathy has varying lengths of follow-up, ranging from six months to two years. While studies described below all reported at least one 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.
Several 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). Recent (i.e., 2014 to present) systematic reviews of RCTs and/or nonrandomized studies are described next.

Johal et al (2019) conducted a systematic review and meta-analysis of 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.

Miller et al (2017) conducted a systematic review and meta-analysis on platelet-rich plasma for symptomatic tendinopathy and included only RCTs with injection controls. The literature search, conducted through November 2016, identified 16 RCTs, with 18 groups (some studies included >1 tendinopathy site) for inclusion (total $n=1018$ patients). The Cochrane Collaboration tool was used to assess the risk of bias: 5 studies had an uncertain risk of bias, and 11 studies had a high-risk of bias. The median sample size was 35 patients. Tendinopathy sites were lateral epicondylar (12 groups), rotator cuff (3 groups), Achilles (2 groups), and patellar (1 group). Preparation of platelet-rich plasma differed across trials as did the number of injections, with most studies administering one injection and a few administering two injections. Eight of the 18 groups reported statistically significant lower pain scores using platelet-rich plasma compared with control and the other ten reported no differences in pain scores between trial arms. A meta-analysis reported a standard mean difference in pain scores favoring platelet-rich plasma over control ($0.47; 95\%$ confidence interval [CI], 0.21 to 0.72; $p=67\%$).

Tsikopoulos et al (2016) published a meta-analysis of RCTs that compared platelet-rich plasma with placebo or dry needling in patients who had tendinopathy lasting at least 6 weeks. Minimum length of follow-up was 6 months. The primary outcome was pain intensity; the secondary outcome was functional disability. Five RCTs met reviewers’ eligibility criteria. Two RCTs addressed lateral epicondylitis, two rotator cuff tendinopathy, and two patellar tendinopathy. Three RCTs had a saline control group, and two compared platelet-rich plasma with dry needling. In a pooled analysis of all 5 RCTs, there was no statistically significant difference in pain intensity at 2 to 3 months between platelet-rich plasma and placebo/dry needling (standard mean difference = -0.29; 95% CI, -0.60 to 0.02). The between-group difference in pain intensity was statistically significant at 6 months in a pooled analysis of 4 trials (standard mean difference = -0.48; 95% CI, -0.86 to -0.10). While statistically significant, reviewers noted that the difference between groups in pain intensity at six months was not clinically significant. Three trials reported on functional disability levels at 3 months, and meta-analysis of these trials found a significantly greater improvement in function disability in the platelet-rich plasma group (standard mean difference = -0.47; 95% CI, -0.85 to -0.09). Functional disability 6 months post intervention was not addressed.

A systematic review by Balasubramaniam et al (2015) included RCTs on platelet-rich plasma for tendinopathy. Unlike the Tsikopoulos et al (2016) review, these reviewers did not limit inclusion criteria by type of control intervention or post intervention length of follow-up. They included 4 of the 5 RCTs in the Tsikopoulos et al (2016) review and 5 other RCTs. Four RCTs evaluated epicondylitis, 2 rotator cuff tendinopathy, 2 patellar tendinopathy, and 1 Achilles tendinopathy. Comparison interventions included placebo ($n=3$), dry needling ($n=2$), autologous blood ($n=2$), extracorporeal shock wave therapy ($n=1$), and corticosteroid injections ($n=2$). One study included both placebo and corticosteroid control groups. Reviewers did not pool study findings due to a high level of heterogeneity among studies. In their qualitative analysis of the literature...
by anatomic site of tendinopathy, they concluded that one trial on platelet-rich plasma for Achilles tendinopathy was insufficient to draw conclusions about efficacy. Findings of trials of other anatomic sites were mixed. Some showed statistically significant greater benefits of platelet-rich plasma than controls on outcomes, and some did not, or some found statistically significant better outcomes at some time points but not others.

Andia et al (2014) published a systematic review on the use of platelet-rich plasma in the treatment of painful tendinopathies.11 They included 13 prospective controlled trials (12 RCTs, 1 controlled trial that was not randomized) with data from 636 patients included in the meta-analysis. The trials assessed various tendinopathies, including seven on chronic elbow, 2 on rotator cuff, 3 on patellar, and 1 study on Achilles. Control interventions included physical therapy (1 trial), extracorporeal shock wave therapy (1 trial), corticosteroid (3 trials), autologous blood (3 trials), saline (3 trials), and dry needling (2 trials). Risk of bias was considered to be low in 4 studies, unclear in 3, and high in 6. The meta-analysis found that platelet-rich plasma was no better than control interventions in reducing pain at 1 or 2 month follow-up. A small significant effect in pain reduction was found at 3 months (weighted mean difference, -0.61). At 1 year, the weighted mean difference between platelet-rich plasma and control interventions was significant at -1.56. Due to heterogeneity between studies, these findings had low power and precision.

### Table 1. Systematic Reviews & Meta-Analysis Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller (2017)</td>
<td>2006-2015</td>
<td>16</td>
<td>Patients with symptomatic tendinopathy</td>
<td>median 35 (NR)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Tsikopoulos (2016)</td>
<td>2013-2014</td>
<td>5</td>
<td>Patients with tendinopathy</td>
<td>170 (23-40)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Andia (2014)</td>
<td>2010-2014</td>
<td>13</td>
<td>Patients with tendinopathy</td>
<td>636</td>
<td>Prospective</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: not reported; RCT: randomized controlled trial.

### Table 2. Systematic Reviews & Meta-Analysis Results

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD in Pain for PRP</th>
<th>SMD in functional disability for PRP</th>
<th>WMD in Pain Reduction at 3 Months</th>
<th>Year (WMD between PRP and Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johal (2019)</td>
<td>-0.69</td>
<td>-1.15 to -0.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miller (2017)</td>
<td>0.47</td>
<td>0.22-0.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsikopoulos (2016)</td>
<td>-0.48</td>
<td>-0.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>P-value</td>
<td>0.01</td>
<td></td>
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<tr>
<td>Andia (2014)</td>
<td>-0.61</td>
<td>-0.97 to -0.25</td>
<td>-1.56</td>
<td>-2.29 to -0.83</td>
</tr>
</tbody>
</table>

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

Four small RCTs (N=297, range of 57 to 80) have been published subsequent to the above-described systematic reviews.12,13,14,15. Tendinopathy sites were lateral epicondylar (2 RCTs), patellar (1 RCT), and gluteal (1 RCT). Follow-up durations ranged from 6 months to 1 year. Platelet-rich plasma protocols varied across studies including a single 3mL injection using a peppering technique, or ultrasound guided injections ranging from 3.5 mL to 6-7 mL. Concurrent rehabilitation protocols also differed, ranging from 6 weeks of supervised rehabilitation to 12 weeks of unsupervised rehabilitation. Compared to a corticosteroid injection, 2 RCTs found platelet-rich plasma injection to result in significantly improved pain scores. However, important relevancy gaps and study conduct limitations exist that preclude reaching strong conclusions.
based on this evidence. Additionally, compared to placebo, platelet-rich plasma did not significantly improve pain after 12 months. Finally, in the RCT by Martin et al (2019), compared with lidocaine, in individuals receiving platelet-rich plasma as an adjunct to ultrasound-guided tenotomy for recalcitrant elbow tendinopathy there were no significant differences in the primary outcome of rate of patients with an improvement exceeding 25% in disability based on Disabilities of the Arm, Shoulder and Hand scores (DASH-E, Spanish version), or other pain outcomes.

Table 3. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Comparator</th>
<th>Comparator 1</th>
<th>Comparator 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Gupta (2019)</td>
<td>India</td>
<td>1</td>
<td>2016-2017</td>
<td>Lateral epicondylitis</td>
<td>PRP (N=40)</td>
<td>CS (N=40)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick</td>
<td>Australia</td>
<td>NR</td>
<td>2013-2015</td>
<td>Gluteus Tendinopathy</td>
<td>PRP (N=40)</td>
<td>CS (N=40)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; PRP: platelet-rich plasma; CS: corticosteroids; LR: leukocyte-rich; LP: leukocyte-poor; NR: Not reported; US: United States

Table 4. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>VAS Score</th>
<th>WOMAC</th>
<th>Other pain / disability assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin (2019)</td>
<td></td>
<td></td>
<td>1 y rate of patients with an improvement ≥ 25% in disability based on DASH-E scores</td>
</tr>
<tr>
<td>PRP</td>
<td></td>
<td></td>
<td>76%</td>
</tr>
<tr>
<td>Lidocaine</td>
<td></td>
<td></td>
<td>70.83%</td>
</tr>
<tr>
<td>Unadjusted odds ratio; 95% CI</td>
<td></td>
<td></td>
<td>0.71 95% CI, 0.13 to 3.84</td>
</tr>
<tr>
<td>Gupta (2019)</td>
<td>12 mo mean score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td>2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>13.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.024</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scott (2019)</td>
<td></td>
<td></td>
<td>1 y NPRS</td>
</tr>
<tr>
<td>LR-PRP</td>
<td>4.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LP-PRP</td>
<td>5.6</td>
<td></td>
<td></td>
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<tr>
<td>Saline</td>
<td>5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick</td>
<td>24 wk mHHS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td>77.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td>65.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.0003</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; CI: confidence interval; PRP: platelet-rich plasma; CS: corticosteroids; LR: leukocyte-rich; LP: leukocyte-poor; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; PRP: platelet-rich plasma; HA: hyaluronic acid; VAS: visual analog scale; NS: not significant; NR: not reported; NPRS: Numeric Pain Rating Scale; mHHS: Modified Harris Hip Score; DASH-E: Spanish version of the Disabilities of the Arm, Shoulder and Hand questionnaires

Table 5. Study Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow.Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin (2019)</td>
<td>4. Diagnosis was based on clinical signs and local pain alone. No imaging verification</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationª</th>
<th>Interventionª</th>
<th>Comparatorª</th>
<th>Outcomesª</th>
<th>Follow.Upª</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta (2019)</td>
<td>4. Study population may not be representative of intended use as it was focused on athletes, including some elite athletes</td>
<td>4. Not the intervention of interest as it included 6 weeks of supervised rehab</td>
<td>1. Key health outcomes not addressed</td>
<td>1. Not sufficient duration for benefit</td>
<td></td>
</tr>
<tr>
<td>Scott (2019)</td>
<td>1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.</td>
<td>1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.</td>
<td>1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.</td>
<td>1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Delivery not similar intensity as intervention.</td>
<td>1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Delivery not similar intensity as intervention.</td>
</tr>
</tbody>
</table>

Table 6. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationª</th>
<th>Blindingª</th>
<th>Selective Reportingª</th>
<th>Follow Upª</th>
<th>Powerª</th>
<th>Statisticalª</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin (2019)</td>
<td>1. High amount of excluded data (38% for DASH at 12 mo); 6. Not intention to treat</td>
<td>1. Not blinded</td>
<td>Not registered</td>
<td>1. High amount of excluded data (38% for DASH at 12 mo); 6. Not intention to treat</td>
<td>4. Underpowered</td>
<td></td>
</tr>
<tr>
<td>Gupta (2019)</td>
<td>1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.</td>
<td>1. Not blinded</td>
<td>1. Not registered</td>
<td>1. High loss to follow-up or missing data at 12 months (21%)</td>
<td>4. Underpowered</td>
<td></td>
</tr>
<tr>
<td>Scott (2019)</td>
<td>1. Not blinded</td>
<td>1. Not registered</td>
<td>1. High loss to follow-up or missing data at 12 months (21%)</td>
<td>4. Underpowered</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.


ª 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).

ª Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Underpowered

ª 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 Tendinopathy

Multiple RCTs and systematic reviews with meta-analyses have evaluated the efficacy of platelet-rich plasma 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 platelet-rich plasma versus the comparators, its results should be interpreted with caution due to important study conduct limitations. Likewise, in subsequently published RCTs, although compared to a corticosteroid injection, 2 RCTs found platelet-rich plasma injection to result in significantly improved pain scores, important relevancy gaps and study conduct limitations exist that preclude reaching strong conclusions based on this evidence. Additionally, compared to placebo, platelet-rich plasma did not significantly improve pain after 12 months. Finally, compared to lidocaine, in individuals receiving platelet-rich plasma as an adjunct to ultrasound-guided tenotomy for recalcitrant elbow tendinopathy there were no significant differences in pain or disability outcomes.

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

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as nonpharmacologic therapy (e.g., exercise, physical therapy) analgesics, and anti-inflammatory agents, in patients with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis).

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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

Patients

The relevant population of interest is individuals with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis). Patients with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis) are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

Interventions

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

Comparators

Comparators of interest include nonpharmacologic therapy (e.g., exercise, physical therapy) analgesics, and anti-inflammatory agents. These treatments are managed by orthopedic surgeons and primary care providers in an outpatient clinical setting.

Outcomes

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

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

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. Franceschi et al (2014) published a qualitative systematic review of the literature on platelet-rich plasma for chronic plantar fasciitis. The literature search, conducted through June 2014, identified 8 prospective studies (total n=256 patients), 3 of which were randomized. Most studies did not have a control group or report imaging evaluations as outcomes. Each study used a different device to prepare platelet-rich plasma. The 3 single-blinded RCTs (n=90 patients) compared platelet-rich plasma treatment with corticosteroids (n=60) or prolotherapy (n=30).

Two trials reported statistically significant improvements with platelet-rich plasma and one trial reported no difference. The largest RCT (n=40) by Monto (2014) compared platelet-rich plasma with corticosteroid injection and had a follow-up to 24 months. There was an apparent difference in age and baseline scores between the platelet-rich plasma and steroid groups. Blinded assessment using American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale scores at 3, 6, 12, and 24 months showed temporary improvements in the corticosteroid group, with a return to near-baseline levels (score, 58; scoring range, 0-100, with higher scores indicating less disability) by 12 months. In the platelet-rich plasma group, the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale score increased from 37 at baseline to 95 at 3 months and remained elevated through 24 months, with a final score of 92 (difference of 46 from controls, p=0.001). Confirmation of these results in a larger double-blind RCT would permit greater certainty on the efficacy of platelet-rich plasma in plantar fasciitis.

Subsequent to the systematic review by Franceschi et al (2014), 3 additional randomized controlled trials have been published. None were large double-blind RCTs of sufficient duration (i.e., 2 years) to conclusively demonstrate efficacy. The RCTs compared platelet-rich plasma treatment (total N=107) with corticosteroid injection (N=82) or saline injection (N=44). 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 UK or India, and the third 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% versus 55.6%; P=0.003). Additionally, mean Foot Function Index Disability Scores were significantly lower in the platelet-rich plasma group at 12 months (mean difference, 12.0; 95% CI, 2.3-21.6). 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
Six small RCTs and multiple prospective observational studies have evaluated the efficacy of platelet-rich plasma injections in individuals with chronic plantar fasciitis. Preparation of platelet-rich plasma and outcome measures differed across studies. Results among the RCTs were inconsistent. The largest of the RCTs showed that treatment using platelet-rich plasma compared with corticosteroid resulted in statistically significant improvements in pain and disability, but not quality of life. Larger RCTs are still needed to address important uncertainties in efficacy and safety; these findings.

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

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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

Patients
The relevant population of interest is individuals with osteochondral lesions. Patients with osteochondral lesions are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

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

Comparators
Comparators of interest include nonpharmacologic therapy (e.g., exercise, physical therapy) analgesics, anti-inflammatory agents, and surgery. These treatments are managed by orthopedic surgeons and primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for osteochondral lesions has varying lengths of follow-up. While studies described below all reported at least one 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.

No 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. At 28-week follow-up, scores on the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale score 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<0.05). 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 visual analog scale 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 platelet-rich plasma injections in individuals who have osteochondral lesions. Compared with hyaluronic acid, treatment with platelet-rich plasma 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 or Hip Osteoarthritis**

**Clinical Context and Therapy Purpose**

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

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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

**Patients**

The relevant population of interest is individuals with knee or hip osteoarthritis. Patients with knee or hip osteoarthritis are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

**Interventions**

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

**Comparators**

Comparators of interest include nonpharmacologic therapy (e.g., exercise, physical therapy) analgesics, anti-inflammatory agents, and surgery. These treatments are managed by orthopedic surgeons and primary care providers in an outpatient clinical setting.

**Outcomes**

The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections as a treatment for knee or hip osteoarthritis has varying lengths of follow-up, ranging from 6-12 months. While studies described below all reported at least one 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.

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 Laudy et al (2015) systematic review, platelet-rich plasma was prepared using single, double, or triple spinning techniques and interventions included between 1 and 3 injections delivered 1 to 3 weeks apart.

**Review of Evidence**

**Systematic Reviews**
In individuals with knee or hip osteoarthritis undergoing platelet-rich plasma injections, findings from 4 systematic reviews are reported. 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.

Johal et al (2019) conducted a systematic review and meta-analysis of RCTs comparing platelet-rich plasma with hyaluronic acid (8 trials, N=927), or placebo (2 trials, N=105), or no platelet-rich plasma (2 trials, N=123) or acetaminophen (1 trial, N=75), or a corticosteroid (1 trial, N=48). Meta-analysis showed that platelet-rich plasma was more effective than its comparators at 12 months (standard mean difference, –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 (I²=89%) and high risk of bias in study conduct.

Xu et al (2017) 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 Table 7). Risk of bias was assessed using Cochrane criteria. Four studies were assessed as having 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 Western Ontario and McMaster Universities Osteoarthritis Index or International Knee Documentation Committee (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 Western Ontario and McMaster Universities Osteoarthritis Index evaluates 3 domains: pain, scored from 0-20; stiffness, scored from 0-8; and physical function, scored from 0-68. Higher scores represent greater pain and stiffness as well as worsened physical capability. The International Knee Documentation Committee (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 four treatment groups, two of which were platelet-rich plasma and placebo. This analysis...
showed that platelet-rich plasma significantly improved the Western Ontario and McMaster Universities Osteoarthritis Index or International Knee Documentation Committee (IKDC) scores compared with placebo; however, only one of the trials was considered high-quality and that trial only enrolled 30 patients. All meta-analyses showed high heterogeneity among trials (I² ≥ 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 Table 7). Ten trials (total n=1110 patients) 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 lower risk of bias are needed to confirm these results.

Chang et al (2014) published a systematic review that included 5 RCTs, 3 quasi-randomized controlled studies, and 8 single-arm prospective series (total n=1543 patients) (see Table 4). 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 a symmetry in funnel plots suggested significant publication bias.

### Table 7. Systematic Review Characteristics for Knee or Hip Osteoarthritis

<table>
<thead>
<tr>
<th>Study</th>
<th>Search Date</th>
<th>Trials</th>
<th>Participants</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johal et al (2019)</td>
<td>Feb 2017</td>
<td>- 8 PRP vs HA - 2 PRP vs placebo - 2 PRP vs no PRP - 1 PRP vs corticosteroid - 1 PRP vs acetaminophen</td>
<td>Patients with knee OA</td>
<td>14 RCTs</td>
</tr>
<tr>
<td>Xu et al (2017)</td>
<td>May 2016</td>
<td>· 8 PRP vs HA · 2 PRP vs placebo</td>
<td>Patients with knee OA</td>
<td>· 10 RCTs</td>
</tr>
<tr>
<td>Laudy et al (2015)</td>
<td>Jun 2014</td>
<td>· 8 PRP vs HA · 1 PRP vs placebo · 1 PRP, different preparations</td>
<td>Patients with knee OA</td>
<td>· 6 RCTs: 4 nonrandomized</td>
</tr>
<tr>
<td>Chang et al (2014)</td>
<td>Sep 2013</td>
<td>· 6 PRP vs HA · 1 PRP vs placebo · 1 PRP, different preparations · 8 single-arm PRP</td>
<td>Patients with knee OA</td>
<td>· 5 RCTs: 3 quasi-randomized · 8 single-arm</td>
</tr>
</tbody>
</table>

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

### Table 8. Systematic Review Results for Knee or Hip Osteoarthritis

<table>
<thead>
<tr>
<th>Study</th>
<th>6 Months Change in Functional Scores (95% CI)</th>
<th>12 Months Change in Functional Scores (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xu et al (2017)</td>
<td>PRP vs HA: All trials: -0.9 (-1.4 to -0.3)· Low quality: -13.3 (-13.2 to 2.8)· Moderate quality: -1.3 (-1.0 to -1.0)· High quality: -0.1 (-0.3 to 0.1)PRP vs placebo: All trials (3): -2.1 (-3.3 to -0.1)</td>
<td>NR</td>
</tr>
<tr>
<td>Laudy et al (2015)</td>
<td>PRP vs HA: -0.8 (-1.0 to -0.6)</td>
<td>PRP vs HA: -1.3 (-1.8 to -0.9)</td>
</tr>
<tr>
<td>Chang et al (2014)</td>
<td>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)</td>
<td>PRP, baseline vs post-treatment: All studies: 2.9 (1.0 to 4.8)· Single-arm: 2.6 (-0.4 to 5.7)· Quasi-</td>
</tr>
</tbody>
</table>
### Change in Functional Scores (95% CI)\(^a\)

<table>
<thead>
<tr>
<th>Study</th>
<th>Change in Functional Scores (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>randomised: 4.5 (4.1 to 5.0)</td>
</tr>
<tr>
<td></td>
<td>RCT: 0.9 (0.5 to 1.3)</td>
</tr>
</tbody>
</table>

CI: confidence interval; HA: hyaluronic acid; NR: not reported; PRP: platelet-rich plasma; RCT: randomized controlled trial; OA: osteoarthritis.

\(^a\) Functional outcomes were measured by the International Knee Documentation Committee, Knee Injury and Osteoarthritis Outcome Score, or Western Ontario Mc Master Osteoarthritis Index.

### Randomized Controlled Trials

In individuals with knee osteoarthritis undergoing platelet-rich plasma injections, 3 RCTs with follow-up durations of at least 12 months have been published subsequent to the above-described systematic reviews (Tables 9-12 below).30,31,32 All were conducted outside of the United States. Sample sizes ranged from 87 to 192 participants. Comparator treatments included hyaluronic acid in all 3 RCTs, and corticosteroids or placebo in 2 RCTs. Two of the RCTs found statistically significantly greater 12-month reductions in the Western Ontario and McMaster Universities Osteoarthritis Index scores with platelet-rich plasma versus the comparator treatments.30,32 However, these findings should be interpreted with caution due to important study conduct limitations, including potential inadequate control for selection bias and unclear blinding. Additionally, no significant differences between platelet-rich plasma and hyaluronic acid were found in the International Knee Documentation Committee (IKDC) subjective score or EuroQol visual analog scale score in the longest-term trial with 5 years of follow-up.31 In the RCT by Di Martino et al (2019) reintervention rates were significantly lower with platelet-rich plasma compared with hyaluronic acid at the 24-month follow-up assessment (22.6% 37.1%; P=0.036), but the difference was not maintained at 5 years.

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.33 Although this well-conducted RCT reported positive results, with statistically significant reductions in visual analog scale score (lower scores imply less pain) at 6 months in the platelet-rich plasma arm (21; 95% CI, 15 to 28) vs 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 Western Ontario and Mc Master Universities Osteoarthritis Index 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.

Trueba Vasavilbaso et al (2017) conducted a controlled trial that randomized patients after knee arthroscopy to 5 injections of Suprahyal/Adant (n=10), 4 injections of Orthovisc (n=10), 3 injections of Synvisc (n=10), 1 injection of platelet-rich plasma (n=10), or standard of care (n=10).34 All patients received the same rehabilitation protocol. At 18-month follow-up, total Western Ontario and Mc Master Universities Osteoarthritis Index scores improved most from baseline with Suprahyal/Adant (65% reduction). The next best improvement was seen with platelet-rich plasma (55% reduction), then Synvisc (50% reduction), and Orthovisc (30% reduction). The control group experienced a 15% increase in the Western Ontario and McMaster Universities Osteoarthritis Index scores.

### Table 9. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Comparator 1</th>
<th>Comparator 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2016)(^33)</td>
<td>Italy</td>
<td>NR</td>
<td>2010-2011</td>
<td>Patients with hip OA</td>
<td>PRP (n=44)</td>
<td>PRP+HA (n=31)</td>
<td>HA (n=36)</td>
</tr>
<tr>
<td>Trueba Vasavilbaso (2017)(^34)</td>
<td>Mexico</td>
<td>1</td>
<td>2013-2014</td>
<td>Patients with meniscal pathology and knee OA, following knee arthroscopic debridement</td>
<td>PRP (n=10)</td>
<td>5 injections of Suprahyal/Adant (n=10)</td>
<td>4 injections of Orthovisc (n=10) OR Comparator 3=3 injections of Synvisc (n=10) OR</td>
</tr>
<tr>
<td>Study</td>
<td>Countries</td>
<td>Sites</td>
<td>Dates</td>
<td>Participants</td>
<td>Interventions</td>
<td>Comparator</td>
<td></td>
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</tr>
<tr>
<td>Huang (2019)</td>
<td>China</td>
<td>NR</td>
<td>2016 - 2017</td>
<td>Patients with knee OA</td>
<td>PRP (N=40), HA (N=40)</td>
<td>CS (N=40)</td>
<td></td>
</tr>
<tr>
<td>Di Martino (2019)</td>
<td>Italy</td>
<td>1</td>
<td>2009 - 2013</td>
<td>Patients with knee OA</td>
<td>PRP (N=96), HA (N=96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin (2019)</td>
<td>Taiwan</td>
<td>1</td>
<td>2014</td>
<td>Patients with knee OA</td>
<td>PRP (N=31), HA (N=29)</td>
<td>Placebo (N=27)</td>
<td></td>
</tr>
</tbody>
</table>

HA: hyaluronic acid; RCT: randomized controlled trial; OA: osteoarthritis; PRP: platelet-rich plasma; NR: not reported; CS: corticosteroid.

### Table 10. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Change in WOMAC Scores from Baseline</th>
<th>General Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2016)</td>
<td>33</td>
<td>PRP</td>
<td></td>
<td></td>
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<tr>
<td>PRP</td>
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<tr>
<td>PRP+HA</td>
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<tr>
<td>HA</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Trueba Vasavilbaso et al (2017)</td>
<td>34</td>
<td>PRP</td>
<td></td>
<td>% reduction at 18 mo</td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td></td>
<td></td>
<td></td>
<td>-55%</td>
<td></td>
</tr>
<tr>
<td>Suprahyal/Adant</td>
<td></td>
<td></td>
<td></td>
<td>-65%</td>
<td></td>
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<tr>
<td>Synvisc</td>
<td></td>
<td></td>
<td></td>
<td>-50%</td>
<td></td>
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<tr>
<td>Orthovisc</td>
<td></td>
<td></td>
<td></td>
<td>-30%</td>
<td></td>
</tr>
<tr>
<td>Standard care</td>
<td></td>
<td></td>
<td></td>
<td>+15%</td>
<td></td>
</tr>
<tr>
<td>Huang (2019)</td>
<td>30</td>
<td>PRP</td>
<td></td>
<td>12 mo</td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td></td>
<td></td>
<td></td>
<td>1.98</td>
<td></td>
</tr>
<tr>
<td>HA</td>
<td></td>
<td></td>
<td></td>
<td>2.14</td>
<td></td>
</tr>
<tr>
<td>CS</td>
<td></td>
<td></td>
<td></td>
<td>2.26</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Di Martino (2019)</td>
<td>31</td>
<td>PRP</td>
<td></td>
<td>5y EuroQol visual analog scale</td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td></td>
<td></td>
<td></td>
<td>71.9</td>
<td></td>
</tr>
<tr>
<td>HA</td>
<td></td>
<td></td>
<td></td>
<td>66.6</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Lin (2019)</td>
<td>32</td>
<td>PRP</td>
<td></td>
<td>Mean score, % improvement at 12 mo</td>
<td></td>
</tr>
<tr>
<td>PRP</td>
<td></td>
<td></td>
<td></td>
<td>63.71, +21%</td>
<td></td>
</tr>
<tr>
<td>HA</td>
<td></td>
<td></td>
<td></td>
<td>49.33, -6%</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
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<td></td>
<td></td>
<td>46.94, -3%</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.05 for PRP vs placebo</td>
<td></td>
</tr>
</tbody>
</table>

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; PRP: platelet-rich plasma; HA: hyaluronic acid; VAS: visual analog scale; RCT: randomized controlled trial; CS: corticosteroid; NS: not significant.


### Table 11. Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trueba Vasavilbaso et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang (2019)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Martino (2019)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin (2019)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence 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. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as
intervention; 4. Not delivered effectively.

d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 12. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation key</th>
<th>Binding key</th>
<th>Selective Reporting key</th>
<th>Follow-Up key</th>
<th>Power key</th>
<th>Statistical key</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trueba Vasavilbaso et al (2017)</td>
<td>3. Inadequate control for selection bias: Orthovisc® group older than Synvisc® group (71.1 y vs 56.9 y; P=0.007)</td>
<td>1. Patients not blinded to treatment assignment</td>
<td>1. Not registered</td>
<td>6. Not intent to treat</td>
<td>1. Power not calculated</td>
<td></td>
</tr>
<tr>
<td>Di Martino (2019)</td>
<td>4. Inadequate control for selection bias: PRP group younger (52.7y vs 57.5y; p=0.014)</td>
<td>1. Unblinded to treatment after first year</td>
<td>6. Not intent to treat (excluded 13%)</td>
<td>4. Comparative treatment effects not calculated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin (2019)</td>
<td>4. Inadequate control for selection bias: greater BMI in HA group (26.26 vs PRP (23.96), P=0.0127)</td>
<td>1. Not registered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

- **Allocation key:** 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
- **Blinding key:** 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
- **Selective Reporting key:** 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
- **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).
- **Power key:** 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
- **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 or Hip Osteoarthritis

Multiple RCTs and systematic reviews with meta-analysis have evaluated the efficacy of platelet-rich plasma injections in individuals with knee or hip osteoarthritis. Most trials have compared platelet-rich plasma with hyaluronic acid for knee osteoarthritis. A single RCT compared platelet-rich plasma with hyaluronic acid alone or combination platelet-rich plasma plus hyaluronic acid in hip osteoarthritis. 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. RCTs with follow-up durations of at least 12 months published subsequent to the systematic reviews found statistically significantly greater 12-month reductions in the Western Ontario and McMaster Universities Osteoarthritis Index scores, but these findings were also limited by important study conduct flaws including potential inadequate control for selection bias and unclear blinding.

Also, benefits were not maintained at 5 years. Also, using hyaluronic acid as a comparator is questionable, because the evidence demonstrating the benefit of hyaluronic acid treatment for osteoarthritis is not robust. The single RCT evaluating hip osteoarthritis reported statistically significant reductions in visual analog scale scores but no significant differences in Harris Hip Score and the Western Ontario and McMaster Universities Osteoarthritis Index scores. Additional larger controlled studies comparing platelet-rich plasma with placebo and alternatives other than hyaluronic acid are needed to determine the efficacy of platelet-rich plasma for knee and hip osteoarthritis. Further studies are also needed to determine the optimal protocol for delivering platelet-rich plasma.

Platelet-Rich Plasma as an Adjunct to Surgery

Anterior Cruciate Ligament Reconstruction

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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

Patients

The relevant population of interest is individuals with anterior cruciate ligament (ACL) reconstruction. Patients with anterior cruciate ligament (ACL) reconstruction are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

Interventions

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

Comparators

Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.
Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for ACL reconstruction has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes. Therefore, two 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.

A Cochrane review by Moraes et al (2013) on platelet-rich therapies for musculoskeletal soft tissue injuries identified 2 RCTs and 2 quasi-randomized studies (total n=203 patients) 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.

e. A qualitative, systematic review by Figueroa et al (2015) included 11 RCTs or prospective cohort studies (total n=516 patients). Four studies found significantly faster graft maturation while 3 found no significant difference. One study showed faster tunnel healing while 5 showed no benefit. One study showed better clinical outcomes while 5 showed no improvement in clinical outcomes when using platelet-rich plasma.

f. The largest 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.

Subsection Summary: Platelet-Rich Plasma as Adjunctive Treatment of Anterior Cruciate Ligament Reconstruction
Two systematic reviews that included multiple RCTs, quasi-randomized studies, and prospective studies have evaluated the efficacy of platelet-rich plasma injections in individuals undergoing ACL reconstruction. Only one of the two systematic reviews conducted a meta-analysis, which showed that adjunctive platelet-rich plasma treatment did not result in a significant effect on IKDC score. Individual studies have shown mixed results.

Hip Fracture
Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in patients with hip fracture.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

The following PICO was used to select literature to inform this review.
Patients
The relevant population of interest is individuals with hip fracture. Patients with hip fracture are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

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

Comparators
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for hip fracture has varying lengths of follow-up. While studies described below all reported at least one 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.

One RCT was identified for treatment of a hip fracture with platelet-rich plasma. Griffin 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 ages 65 years and older. Patients underwent internal fixation of a hip 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, eight 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-labeled RCT has evaluated the efficacy of platelet-rich plasma injections in individuals with hip fracture. This trial failed to show any statistically significant reductions in the need for revision surgery after platelet-rich plasma treatment.

Long Bone Nonunion
Clinical Context and Therapy Purpose
The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as Recombinant...
human bone morphogenetic protein-7 (rhBMP-7) plus orthopedic surgery, in patients with long bone nonunion.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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

**Patients**
The relevant population of interest is individuals with long bone nonunion. Patients with long bone nonunion are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

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

**Comparators**
Comparators of interest include rhBMP-7 plus orthopedic surgery. This is performed by an orthopedic surgeon in an outpatient clinical setting.

**Outcomes**
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for long bone nonunion has varying lengths of follow-up. While studies described below all reported at least one 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.

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).

The trial study 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).

Calori et al (2008) compared 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 (15-30 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

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

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

Table 14. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Knee Society Score at 1 yr</th>
<th>Knee Society Functional Score at 1 yr</th>
<th>Union Rate</th>
<th>Median Healing Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2007)</td>
<td>91.3 +/- 2</td>
<td>99.0 +/- 0.6</td>
<td>41 (68.3%)</td>
<td>4 +/- 0.61 months</td>
</tr>
<tr>
<td>PRP</td>
<td>89.9 +/- 4</td>
<td>99.2 +/- 0.5</td>
<td>52 (86.7%)</td>
<td>3.5 +/- 0.48</td>
</tr>
<tr>
<td>Calori (2008)</td>
<td>90.3 +/- 4</td>
<td>98.8 +/- 0.6</td>
<td>18 (78%)</td>
<td>15.3 weeks</td>
</tr>
</tbody>
</table>

P-value: 0.016
<table>
<thead>
<tr>
<th>Study</th>
<th>Knee Society Score at 1 yr</th>
<th>Knee Society Functional Score at 1 yr</th>
<th>Union Rate</th>
<th>Median Healing Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10 (59%)</td>
<td>13.1 weeks</td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>P-value</td>
<td>0.296</td>
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</tr>
</tbody>
</table>

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

**Table 15. Relevance Limitations**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2007)</td>
<td>4. Only 33 patients included</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calori (2008)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Samuel (2017)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

*Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.*

*Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.*

*Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.*

*Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.*

*Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.*

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Follow Up</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallari (2007)</td>
<td>3. Allocation concealment unclear</td>
<td>1,2,3. No blinding described</td>
<td>1,2. Study was underpowered and nonparametric statistical tests were performed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calori (2008)</td>
<td>2. Allocation not concealed</td>
<td>1,2,3. No blinding described</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Samuel (2017)</td>
<td>1. Randomization procedure not described, 3. Allocation concealment unclear</td>
<td>1,2,3. No blinding described</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.


*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).*

*Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.*

*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 individuals 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 vs those who received the 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, the results did not differ in the intention-to-treat analysis. An RCT which 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 a 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 platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in patients with rotator cuff repair.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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

**Patients**

The relevant population of interest is individuals with rotator cuff repair. Patients with rotator cuff repair are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

**Interventions**

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

**Comparators**

Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

**Outcomes**

The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for 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 one 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.
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. The systematic reviews have varied in their outcomes of interest and findings (Tables 17 and 18). For pain outcomes, systematic reviews consistently 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. Additionally, the 12-month pain reduction with platelet-rich plasma was not maintained in RCTs with longer-term follow-up of 24 months or longer. 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.

No reviews have demonstrated a consistent statistical and clinical 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. Wang et al (2019) reported 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 & Meta-Analysis Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen (2017)</td>
<td>2011-2016</td>
<td>37</td>
<td>Patients with tendon and ligament injuries</td>
<td>1031a (NR)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Fu (2017)</td>
<td>2011-2015</td>
<td>11</td>
<td>Patients with rotator cuff injury or tendinopathy</td>
<td>638 (NR)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Zhao (2015)</td>
<td>2011-2013</td>
<td>8</td>
<td>Patients with rotator cuff injury</td>
<td>464 (28-88)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Moraes (2013)</td>
<td>2008-2013</td>
<td>19</td>
<td>Patients undergoing rotator cuff repair</td>
<td>1088 (23-150)</td>
<td>RCT and quasi-randomized trials</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: not reported; RCT: randomized controlled trial.
aNumber of participants from the 21 articles which could be included in the quantitative analysis.

Table 18. Systematic Reviews & Meta-Analysis Results

<table>
<thead>
<tr>
<th>Study</th>
<th>VAS Reduction at 1 Year</th>
<th>VAS Change from Pre to Posttreatment</th>
<th>Difference in Retear Rate</th>
<th>Difference in function at 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johal (2019)</td>
<td>7 RCTs; N=324</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMD</td>
<td>-0.261</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.46, -0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I²</td>
<td>0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang (2019)</td>
<td>5 RCTs; N=338</td>
<td></td>
<td>1-year results: 5 RCTs, N=215</td>
<td>UCLA Score: 5 RCTs, N=322</td>
</tr>
<tr>
<td>SMD</td>
<td>-0.41</td>
<td></td>
<td>2-year results: 5 RCTs, N=315</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.62, -0.19</td>
<td></td>
<td>RR for 1-year: 0.29RR</td>
<td>0.38</td>
</tr>
<tr>
<td>I²</td>
<td>0%</td>
<td></td>
<td>2-year: 0.96</td>
<td></td>
</tr>
<tr>
<td>Chen (2017)</td>
<td>WMD</td>
<td>-0.84</td>
<td>1-year: 0.13, 0.65 ≥ 2-year: 0.52, 1.78</td>
<td>0.16, 0.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1-year: 0% ≥ 2-year: 0%</td>
<td></td>
</tr>
</tbody>
</table>

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### Randomized Controlled Trials

Three small, single-center RCTs have been published subsequent to the systematic reviews described above. 49, 50, 51. Walsh et al (2018) published a prospective, randomized, single-blinded study evaluating platelet-rich plasma in fibrin matrix as a means to augment rotator cuff repair. 49. Malavolta et al (2018) published 5-year clinical and structural evaluations in follow-up to their 2014 publication of their 24-month results. 50. In contrast to previous RCTs that have focused on administration of platelet-rich plasma at the time of rotator cuff repair surgery, the third RCT, published by Snow et al (2019), 51, was unique in publishing a randomized double-blind trial of delayed delivery of platelet-rich plasma at 10-15 days post-surgery. Sample sizes ranged from 51 patients to 97 patients. 51. Results of these 3 RCTs are consistent with the systematic reviews in finding no statistically or clinically significant benefit of platelet-rich plasma on multiple outcomes.

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

For individuals undergoing rotator cuff repair who receive platelet-rich plasma injections, the evidence includes multiple RCTs and systematic reviews with meta-analyses. Relevant outcomes include symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Although systematic reviews consistently found significant reductions in pain with platelet-rich plasma at 12 months, important study conduct and relevance weaknesses limit interpretation of these findings. Additionally, the pain reductions with platelet-rich plasma were not maintained in longer-term studies. Further, the systematic reviews and meta-analyses failed to show a statistically and/or clinically significant impact on other outcomes. Findings of subsequently published small, single-center RCTs were consistent with the systematic reviews. The variability in platelet-rich plasma preparation techniques and platelet-rich plasma administration limit the generalizability of the studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

### Spinal Fusion

#### Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in patients with spinal fusion.
The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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

**Patients**
The relevant population of interest is individuals with spinal fusion. Patients with spinal fusion are actively managed pre- and postoperatively by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

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

**Comparators**
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

**Outcomes**
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for spinal fusion has varying lengths of follow-up. While studies described below all reported at least one 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.

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 visual analog scale scores between the 2 groups. Major limitations of this RCT include that patients were unblinded to treatment and there was no placebo comparator.

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

**Subsection Summary: Spinal Fusion**
For individuals undergoing spinal fusion who receive platelet-rich plasma injections, the evidence includes a single small RCT and a few observational studies. Relevant outcomes include symptoms, functional outcomes, health status measures, quality of life, 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 the effects of the technology on health outcomes.
Subacromial Decompression Surgery

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

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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

Patients
The relevant population of interest is individuals with subacromial decompression surgery. Patients with subacromial decompression surgery are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

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

Comparators
Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for subacromial decompression surgery has varying lengths of follow-up. While studies described below all reported at least one 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.

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 six weeks of measurements. For example, at 2 weeks after surgery, visual analog scale 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 six-week assessment period, with patients reporting improvements in activities of daily living, such as the ability to sleep on the operated shoulder at four 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 platelet-rich plasma injections in individuals undergoing subacromial decompression surgery. Compared with controls, platelet-rich plasma 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 platelet-rich plasma. Larger RCTs would be required to confirm these benefits.

**Total Knee Arthroplasty**

**Clinical Context and Therapy Purpose**

The purpose of platelet-rich plasma injections plus orthopedic surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as orthopedic surgery alone, in patients with total knee arthroplasty.

The question addressed in this evidence review is: Does the use of platelet-rich plasma improve the net health outcome in patients with musculoskeletal conditions and those undergoing orthopedic surgical procedures?

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

**Patients**

The relevant population of interest is individuals with total knee arthroplasty. Patients with total knee arthroplasty are actively managed by orthopedic surgeons, physical therapists, and primary care providers in an outpatient clinical setting.

**Interventions**

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

**Comparators**

Comparators of interest include orthopedic surgery alone. This is performed by an orthopedic surgeon in an outpatient clinical setting.

**Outcomes**

The general outcomes of interest are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The existing literature evaluating platelet-rich plasma injections plus orthopedic surgery as a treatment for total knee arthroplasty has varying lengths of follow-up. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

**Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- 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.

g. Morishita et al (2014) reported on the results of a controlled trial of 40 patients, scheduled for unilateral total knee arthroplasty, who were randomized to intraoperative platelet-rich plasma (n=20) or no additional intraoperative treatment (n=20). There were no significant differences between the platelet-rich plasma and untreated control groups in bleeding, range of motion, swelling around the knee joint, muscle power recovery, pain, Knee Society Scores, or Knee Injury and Osteoarthritis Outcome Score.

Subsection Summary: platelet-rich plasma as Adjunctive Treatment for Total Knee Arthroplasty

h. A single small RCT has evaluated the efficacy of platelet-rich plasma injections in individuals undergoing total knee arthroplasty. There were no significant differences between the platelet-rich plasma and untreated control groups across several functional and pain outcomes.

Summary of Evidence

Primary Treatment for Tendinopathies

For individuals with tendinopathy who receive platelet-rich plasma 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, and treatment-related morbidity. Findings from meta-analyses of RCTs have been mixed and have generally found that platelet-rich plasma did not have a statistically and/or clinically significant impact on symptoms (i.e., pain) or functional outcomes. Findings from subsequently published RCTs have also been mixed. In RCTs that have found significantly improved pain outcomes for platelet-rich plasma injections, important relevancy gaps and study conduct limitations preclude reaching strong conclusions based on their findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

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 platelet-rich plasma injections, the evidence includes 6 small RCTs, multiple prospective observational studies, and a systematic review. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The systematic review, which identified 3 RCTs on platelet-rich plasma for plantar fasciitis, did not pool study findings. Results among the 6 RCTs were inconsistent. The largest RCT showed that treatment using platelet-rich plasma compared with corticosteroid injection resulted in statistically significant improvement in pain and disability, but not quality of life. Larger RCTs are still needed to address important uncertainties in efficacy and safety. The evidence is insufficient to determine the effects of the technology on health outcomes.

Primary Treatment for Osteochondral Lesions

For individuals with osteochondral lesions who receive platelet-rich plasma injections, the evidence includes an open-labeled quasi-randomized study. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The quasi-randomized study found a statistically significant greater impact on outcomes in the platelet-rich plasma 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 the effects of the technology on health outcomes.
Primary Treatment for Knee or Hip Osteoarthritis
For individuals with knee or hip osteoarthritis who receive platelet-rich plasma injections, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

Most trials have compared platelet-rich plasma with hyaluronic acid for knee osteoarthritis. 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. RCTs with follow-up durations of at least 12 months published subsequent to the systematic reviews found statistically significantly greater 12 month reductions in the Western Ontario and McMaster Universities Osteoarthritis Index scores, but these findings were also limited by important study conduct flaws including potential inadequate control for selection bias and unclear blinding. Also, benefits were not maintained at 5 years. Also, using hyaluronic acid as a comparator is questionable, because the evidence demonstrating the benefit of hyaluronic acid treatment for osteoarthritis is not robust. The single RCT evaluating hip osteoarthritis reported statistically significant reductions in visual analog scale scores for pain, with no difference in functional scores. Additional studies comparing platelet-rich plasma with placebo and with alternatives other than hyaluronic acid are needed to determine the efficacy of platelet-rich plasma for knee and hip osteoarthritis. Studies are also needed to determine the optimal protocol for delivering platelet-rich plasma. The evidence is insufficient to determine the effects of the technology on health outcomes.

Adjunct to Surgery
For individuals with anterior cruciate ligament reconstruction who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes 2 systematic reviews of multiple RCTs and prospective studies. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Only 1 of the 2 systematic reviews conducted a meta-analysis; it showed that adjunctive platelet-rich plasma treatment did not result in a significant effect on International Knee Documentation Committee scores, a patient-reported, knee-specific outcome measure that assesses pain and functional activity. Individual trials have shown mixed results. The evidence is insufficient to determine the effects of the technology on health outcomes.

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, quality of life, morbid events, resource utilization, and treatment-related morbidity. The single open-labeled RCT failed to show a statistically significant reduction in the need for surgical revision with the addition of platelet-rich plasma treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with long bone nonunion who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes three RCTs. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, 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 those who received platelet-rich plasma plus allogenic bone graft and those who received only allogenic bone graft. While the trial showed a statistically significant increase 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. The second RCT, which compared platelet-rich plasma with recombinant human bone morphogenetic protein-7, also failed to show any clinical or radiologic benefits of platelet-rich plasma over morphogenetic protein. The third RCT reported no difference in the number of unions or time to union in patients...
receiving platelet-rich plasma injections vs no treatment. The evidence is insufficient to
determine the effects of the technology on health outcomes.

For individuals with rotator cuff repair who receive platelet-rich plasma injections plus orthopedic
surgery, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are
symptoms, functional outcomes, health status measures, quality of life, morbid events, resource
utilization, and treatment-related morbidity. Although systematic reviews consistently found
significant reductions in pain with platelet-rich plasma at 12 months, important study conduct
and relevance weaknesses limit interpretation of these findings. Additionally, the pain reductions
with platelet-rich plasma were not maintained in longer-term studies. Further, the systematic
reviews and meta-analyses failed to show a statistically and/or clinically significant impact on
other outcomes. Findings of subsequently published small, single-center RCTs were consistent
with the systematic reviews. The evidence is insufficient to determine the effects of the
technology on health outcomes.

For individuals with spinal fusion who receive platelet-rich plasma injections plus orthopedic
surgery, the evidence includes two controlled prospective studies. Relevant outcomes are
symptoms, functional outcomes, health status measures, quality of life, morbid events, resource
utilization, and treatment-related morbidity. The 2 studies failed to show any statistically
significant differences in fusion rates between the platelet-rich plasma arm and the control arm.
The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals undergoing spinal fusion who receive platelet-rich plasma injections, the
evidence includes a single small RCT and a few observational studies. Relevant outcomes
include symptoms, functional outcomes, health status measures, quality of life, 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 the effects of the technology on health outcomes.

For individuals with subacromial decompression surgery who receive platelet-rich plasma
injections plus orthopedic surgery, the evidence includes a small RCT. Relevant outcomes are
symptoms, functional outcomes, health status measures, quality of life, 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 platelet-rich plasma. Larger trials are required to
confirm these benefits. The evidence is insufficient to determine the effects of the technology on
health outcomes.

For individuals with total knee arthroplasty who receive platelet-rich plasma injections plus
orthopedic surgery, the evidence includes a small RCT. Relevant outcomes are symptoms,
functional outcomes, health status measures, quality of life, morbid events, resource utilization,
and treatment-related morbidity. The RCT showed no significant differences between the
platelet-rich plasma and untreated control groups in bleeding, range of motion, swelling around
the knee joint, muscle power recovery, pain, or Knee Society Score and Knee Injury and
Osteoarthritis Outcome Score. The evidence is insufficient to determine the effects of the
technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

American Academy of Orthopaedic Surgeons
In 2013, the American Academy of Orthopaedic Surgeons (AAOS) guidelines did not
recommend for or against growth factor injections and/or platelet-rich plasma for patients with
symptomatic osteoarthritis of the knee.[57] A recommendation of inconclusive was based on a
single low-quality study and conflicting findings. The AAOS recommendation was based on 3 studies published before May 2012.

In 2017, the AAOS issued evidence-based guidelines on the management of osteoarthritis of the hip.\textsuperscript{58} In the section on intra-articular injectables, the guidelines stated there is strong evidence supporting the use of intra-articular corticosteroids to improve function and reduce pain in the short term for patients with osteoarthritis of the hip. There was also strong evidence that the use of intra-articular hyaluronic acid does not perform better than placebo in improving function, stiffness, and pain in patients with hip osteoarthritis. The guidelines also noted that there were no high-quality studies comparing platelet-rich plasma with placebo for the treatment of osteoarthritis of the hip.

**National Institute for Health and Care Excellence**

In 2013, the National Institute for Health and Care Excellence (NICE) issued guidance on the use of autologous blood injection for tendinopathy.\textsuperscript{59} The NICE concluded that the current evidence on the safety and efficacy of autologous blood injection for tendinopathy was “inadequate” in quantity and quality.

In 2013, the NICE also issued guidance on the use of autologus blood injection (with or without techniques for producing platelet-rich plasma) for plantar fasciitis.\textsuperscript{60} The NICE concluded that 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, the NICE issued guidance on the use of platelet-rich plasma for osteoarthritis of the knee.\textsuperscript{61} The 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.”

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 15.

### Table 15. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01843504</td>
<td>Platelet-Rich Plasma (PRP) Injection for the Treatment of Chronic Patellar Tendinopathy</td>
<td>44</td>
<td>December 2023</td>
</tr>
<tr>
<td>NCT03138317</td>
<td>Evaluation of Platelet Rich Plasma (PRP) for Knee Osteoarthritis</td>
<td>60</td>
<td>May 2018</td>
</tr>
<tr>
<td>NCT01668953*</td>
<td>Impact of Platelet Rich Plasma Over Alternative Therapies in Patients With Lateral Epicondylitis (IMPROVE)</td>
<td>100</td>
<td>March 2020</td>
</tr>
<tr>
<td>NCT03129971</td>
<td>Platelet-Rich Plasma Combined with Conventional Surgery in the Treatment of Atrophic Nonunion of Femoral Shaft Fractures</td>
<td>92</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT01833598</td>
<td>Percutaneous Needle Tenotomy (PNT) Versus Platelet Rich Plasma (PRP) with PNT in the Treatment of Chronic Tendinosis</td>
<td>40</td>
<td>Oct 2022</td>
</tr>
<tr>
<td>NCT02984228</td>
<td>Platelet-rich Plasma vs. Hyaluronic Acid for Glenohumeral Osteoarthritis</td>
<td>70</td>
<td>Nov 2020</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>NCT02923700</td>
<td>Leukocyte-rich platelet-rich plasma (PRP) vs Leukocyte-poor platelet-rich plasma (PRP) for the Treatment of Knee Cartilage Degeneration: a Randomized Controlled Trial</td>
<td>192</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT02872753</td>
<td>Intra-operative platelet-rich plasma (PRP) Injection Following Partial Meniscectomy</td>
<td>90</td>
<td>Mar 2021</td>
</tr>
<tr>
<td>NCT03300531</td>
<td>Autologous Pure Platelet-rich Plasma in the Treatment of Tendon Disease: A Randomized Controlled Trial</td>
<td>540</td>
<td>Dec 2021</td>
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<tr>
<td>NCT04241354</td>
<td>A Comparison of Platelet-rich Plasma Treatment to the Intra-articular vs. Intra- and Extra-articular Environments in Patients Diagnosed With Hip Osteoarthritis</td>
<td>84</td>
<td>Dec 2021</td>
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<tr>
<td>NCT03136965</td>
<td>Platelet-Rich Plasma Therapy for Patellar Tendinopathy platelet-rich plasma (PRP)</td>
<td>66</td>
<td>Aug 2022</td>
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<tr>
<td>NCT03984955</td>
<td>A Prospective, Double Blind, Single Centre, RCT, Comparing the Effectiveness of Physiotherapy in Addition to One of 3 Types of Image Guided Injection of the Common Extensor Tendon, on Pain and Function in Patients With Tennis Elbow</td>
<td>123</td>
<td>April 2023</td>
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<tr>
<td>NCT01915979</td>
<td>Role of Biological Therapy in Rotator Cuff Tendinopathy. Effectiveness of Plasma Rich in Growth Factors Regarding Functional Capacity and Pain Compared With the Conventional Treatment Using Steroids</td>
<td>84</td>
<td>Dec 2016(completed)</td>
</tr>
<tr>
<td>NCT02694146</td>
<td>Clinical Trial to Evaluate the Use of Platelet Rich Plasma in Front Hyaluronic Acid in Coxarthrosis</td>
<td>74</td>
<td>May 2018</td>
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<tr>
<td>NCT03133416</td>
<td>Platelet-Rich Plasma Injections and Physiotherapy in the Treatment of Chronic Rotator Cuff Tendinopathy Treatment of Acute and Chronic Ligament and Tendon Injuries with Platelet Rich Plasma</td>
<td>165</td>
<td>July 2018</td>
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<tr>
<td>NCT01406821</td>
<td></td>
<td>30</td>
<td>March 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

**References**


2.01.98  Orthopedic Applications of Platelet-Rich Plasma
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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE

The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>0232T</td>
<td>Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed</td>
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<td>20926</td>
<td>Tissue grafts, other (e.g., paratenon, fat, dermis)</td>
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<tr>
<td></td>
<td>86999</td>
<td>Unlisted transfusion medicine procedure</td>
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<tr>
<td>HCPCS</td>
<td>C1734</td>
<td>Orthopedic/device/drug matrix for opposing bone-to-bone or soft tissue-to bone (implantable) (Code effective 1/1/2020)</td>
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<td></td>
<td>P9020</td>
<td>Platelet rich plasma, each unit</td>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>12/04/2015</td>
<td>BCBSA medical policy adaptation</td>
</tr>
<tr>
<td>07/01/2016</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>06/01/2017</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>06/01/2018</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>07/01/2019</td>
<td>Policy revision without position change</td>
</tr>
<tr>
<td>03/01/2020</td>
<td>Coding update</td>
</tr>
<tr>
<td>07/01/2020</td>
<td>Annual review. No change to policy statement. Literature review updated.</td>
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</table>
Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state government is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.