# Orthopedic Applications of Platelet-Rich Plasma

**Policy #** 00476
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*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Note: Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Non–Orthopedic Conditions is addressed separately in medical policy 00262.*

**When Services Are Considered Investigational**
*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers the use of platelet-rich plasma (PRP) to be **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
  - Osteochondral lesions
  - Osteoarthritis
  - Plantar fasciitis

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

## Background/Overview

This policy addresses the use of PRP as a treatment of a variety of musculoskeletal conditions and as an adjunctive use in orthopedic surgical procedures. 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.

A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factors (PDGFs), epidermal growth factor, fibroblast growth factors, transforming growth factors, and

insulin-like growth factors. Autologous platelets are a rich source of PDGF, transforming growth factors that function as a mitogen for fibroblasts, smooth muscle cells, osteoblasts, and vascular endothelial growth factors. Recombinant PDGF has also been extensively investigated for clinical use in wound healing.

Autologous platelet concentrate suspended in plasma, also known as PRP, can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets, releasing the various growth factors. The polymerization of fibrin from fibrinogen creates a platelet gel, which can then be used as an adjunct to surgery with the intent of promoting hemostasis and accelerating healing. In the operating room setting, PRP has been investigated as an adjunct to a variety of 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. Platelet-rich plasma 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. However, prolotherapy differs in that it involves injection of chemical irritants that are intended to stimulate inflammatory responses and induce release of endogenous growth factors.

Platelet-rich plasma is distinguished from fibrin glues or sealants, which have been used for many years 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®‡ are examples of commercially available fibrin sealants. Autologous fibrin sealants can be created from platelet-poor plasma. This policy does not address the use of fibrin sealants.

## FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
The U.S. 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, FDA has not attempted to regulate activated PRP.

A number of PRP preparation systems are available, many of which were cleared for marketing by FDA through the 510(k) process for producing platelet-rich preparations intended to be mixed with bone graft materials to enhance the bone grafting properties in orthopedic practices. The use of PRP outside of this setting (eg, an office injection) would be considered off-label. The Aurix System™‡ (previously called AutoloGel™‡; Cytomedix) and SafeBlood®‡ (SafeBlood Technologies) are 2 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 (eg, Medtronic Electromedics, Elmd-500 Autotransfusion system, the Plasma Saver device, the SmartPReP®‡ [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 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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

## Rationale/Source

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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 PRP consists of several RCTs comparing PRP with conservative therapy (eg, rest, physical therapy) and medication (eg. corticosteroid injection), and systematic reviews of these trials. A number of systematic reviews of RCTs, with or without the addition of observational studies on PRP, 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 PRP or PRP 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.

**PRP AS A PRIMARY TREATMENT FOR TENDINOPATHY**

Several systematic reviews have evaluated PRP for treating mixed tendinopathies. They include trials on tendinopathies of the Achilles, rotator cuff, patella, and/or lateral epicondyle (tennis elbow). Recent (ie, 2014 to present) systematic reviews of RCTs and/or nonrandomized studies are described next.

Miller et al (2017) conducted a systematic review and meta-analysis on PRP 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 PRP differed across trials as did the number of injections, with most studies administering 1 injection and a few administering 2 injections. Eight of the 18 groups reported statistically significant lower pain scores using PRP compared with control and the other ten reported no differences in pain scores between trial arms. A meta-analysis reported a standard mean difference (SMD) in pain scores favoring PRP over control (0.47; 95% confidence interval [CI], 0.21 to 0.72; $I^2$=67%).

Tsikopoulos et al (2016) published a meta-analysis of RCTs that compared PRP 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, 2 rotator cuff tendinopathy, and 2 patellar tendinopathy. Three RCT studies had a saline control group, and 2 compared PRP 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 PRP and placebo/dry needling (SMD = -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 (SMD = -0.48; 95% CI, -0.86 to -0.10). While statistically significant, reviewers noted that the difference between groups in pain intensity at 6 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 PRP group (SMD = -0.47; 95% CI, -0.85 to -0.09). Functional disability 6 months postintervention was not addressed.

A systematic review by Balasubramaniam et al (2015) included RCTs on PRP for tendinopathy. Unlike the Tsikopoulos (2016) review, these reviewers did not limit inclusion criteria by type of control intervention or

postintervention length of follow-up. They included 4 of the 5 RCTs in the Tsikopoulos 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 1 trial on PRP 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 PRP 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 PRP in the treatment of painful tendinopathies. 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 7 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 PRP 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 PRP and control interventions was significant at -1.56. Due to heterogeneity between studies, these findings had low power and precision.

**Section Summary: PRP as a Primary Treatment of Tendinopathy**
Multiple RCTs and systematic reviews with meta-analyses have evaluated the efficacy of PRP injections in individuals who have tendinopathy. The more recently-published systematic reviews and meta-analyses that only included RCTs failed to show a statistically and/or clinically significant impact on symptoms (ie, pain) or functional outcomes.

**PRP AS A PRIMARY TREATMENT OF NON–TENDON SOFT TISSUE INJURY OR INFLAMMATION**
Franceschi et al (2014) published a qualitative systematic review of the literature on PRP 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 PRP. The 3 single-blinded RCTs (n=90 patients) compared PRP treatment with corticosteroids (n=60) or prolotherapy (n=30). Two trials reported statistically significant improvements with PRP and 1 trial reported no difference. The largest RCT (N=40) by Monto (2014) compared PRP with corticosteroid injection and had a follow-up to 24 months. There was an apparent difference in age and baseline scores between the PRP 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 PRP group, the 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 PRP in plantar fasciitis.

**Section Summary: PRP as a Primary Treatment of Non–Tendon Soft Tissue Injury or Inflammation**
Three small RCTs and multiple prospective observational studies have evaluated the efficacy of PRP injections in individuals with chronic plantar fasciitis. Preparation of PRP and outcome measures differed across studies. Results among the RCTs were inconsistent. The largest of the 3 RCTs showed that treatment using PRP compared with corticosteroid resulted in statistically significant but temporary improvements in AOFAS Ankle-Hindfoot Scale scores, indicating improved outcomes. Larger RCTs would be required to confirm these findings.

**PRP AS A PRIMARY TREATMENT OF OSTEOCHONDRAL LESIONS**
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 PRP. At 28-week follow-up, scores on the AOFAS Ankle-Hindfoot Scale score improved to a greater extent in the PRP 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 PRP group (from 58 to 91) than in the hyaluronic acid group (from 56 to 73). Interpretation of the composite measures of visual analog scale (VAS) scores for pain and function is limited by differences between the groups at baseline. Also, neither the patients nor the evaluators were blinded to treatment in this small study.

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

**PRP AS A PRIMARY TREATMENT OF KNEE OR HIP OSTEOARTHRITIS**
A number of RCTs and several systematic reviews of RCTs evaluating the use of PRP for knee osteoarthritis (OA) have been published. Protocols used in PRP interventions for knee OA varied widely. For example, in the studies identified in the Laudy et al (2015) systematic review, PRP was prepared using single, double, or triple spinning techniques and interventions included between 1 and 3 injections delivered 1 to 3 weeks apart.

**Systematic Reviews**
Xu et al (2017) conducted a systematic review and meta-analysis of RCTs comparing PRP with hyaluronic acid (8 trials), or placebo (2 trials), for the treatment of knee OA (see Table 1). 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 PRP with hyaluronic acid showed that PRP significantly improved Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or International Knee Documentation Committee (IKDC) scores compared with HA at 6-month follow-up; however, when meta-analyses included only the 2 high-quality RCTs, there was not a significant difference between PRP and hyaluronic acid (see Table 2). (Note that WOMAC 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 IKDC is a patient-reported, knee-specific outcome measure that measures pain and functional activity.) In the meta-analysis comparing PRP with placebo, a third trial was included, which had four treatment groups, two of which were PRP and placebo. This analysis showed that PRP significantly improved WOMAC or 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 ($I^2$≥90%).

Laudy et al (2015) conducted a systematic review of RCTs and nonrandomized clinical trials to evaluate the effect of PRP on patients with knee OA (see Table 1). 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 PRP was more effective than placebo or hyaluronic acid in reducing pain and improving function (see Table 2), 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 1). 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 PRP (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 PRP (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. PRP also had lower efficacy in patients with higher degrees of cartilage degeneration. Results were consistent when analyzing only RCTs, but asymmetry in funnel plots suggested significant publication bias.

**Table 1. Systematic Review Characteristics for Knee or Hip Osteoarthritis**

| Study | Search Date | Trials | Participants | Design |
|---|---|---|---|---|
| **Xu et al (2017)** | May 2016 | • 8 PRP vs HA<br>• 2 PRP vs placebo | Patients with knee OA | • 10 RCTs |
| **Laudy et al (2015)** | Jun 2014 | • 8 PRP vs HA<br>• 1 PRP vs placebo | Patients with knee OA | • 6 RCTs<br>• 4 nonrandomized |

| | | | | |
|---|---|---|---|---|
| | | • 1 PRP, different preparations | | |
| **Chang et al (2014)** | Sep 2013 | • 6 PRP vs HA<br>• 1 PRP vs placebo<br>• 1 PRP, different preparations<br>• 8 single-arm PRP | Patients with knee OA | • 5 RCTs<br>• 3 quasi-randomized<br>• 8 single-arm |

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

**Table 2. Systematic Review Results for Knee or Hip Osteoarthritis**

| Study | Change in Functional Scores (95% CI)[a] | |
|---|---|---|
| | **6 Months** | **12 Months** |
| **Xu et al (2017)** | PRP vs HA:<br>• All trials: -0.9 (-1.4 to -0.3)<br>• Low quality: -13.3 (-33.9 to 3.7)<br>• Moderate quality: -1.3 (-1.6 to -1.0)<br>• High quality: -0.1 (-0.3 to 0.1)<br>PRP vs placebo:<br>• All trials (3): -2.1 (-3.3 to -1.0) | NR |
| **Laudy et al (2015)** | PRP vs HA: -0.8 (-1.0 to -0.6) | PRP vs HA: -1.3 (-1.8 to -0.9) |
| **Chang et al (2014)** | PRP, baseline vs post-treatment:<br>• All studies: 2.5 (1.9 to 3.1)<br>• Single-arm: 3.1 (2.0 to 4.1)<br>• Quasi-randomized: 3.1 (1.4 to 3.8)<br>• RCT: 1.5 (1.0 to 2.1) | PRP, baseline vs posttreatment:<br>• All studies: 2.9 (1.0 to 4.8)<br>• Single-arm: 2.6 (-0.4 to 5.7)<br>• Quasi-randomized: 4.5 (4.1 to 5.0)<br>• RCT: 0.9 (0.5 to 1.3) |

CI: confidence interval; HA: hyaluronic acid; NR: not reported; PRP: platelet-rich plasma.
[a] Functional outcomes were measured by the International Knee Documentation Committee, Knee Injury and Osteoarthritis Outcome Score, or Western Ontario McMaster Osteoarthritis Index.

**Randomized Controlled Trials**

The systematic review by Chang et al (2014) identified a single placebo-controlled trial, Patel et al (2013). This RCT included 78 patients with bilateral knee OA. Patients were randomized to a single injection of PRP, 2 injections of PRP, or a single saline placebo injection. There was significantly greater improvement in the WOMAC scores at 1, 3, and 6 months in the active treatment groups combined, compared with the placebo group ($p<0.01$) as well as in VAS scores ($p<0.01$). WOMAC scores in the PRP arm decreased by approximately 50% of their baseline values at 6 months (from 50 to 27 in the group receiving 1 PRP

injection, from 53 to 31 in the group receiving 2 PRP injections). Based on a study by Tubach et al (2005), which determined minimal clinically important differences for WOMAC scores, the reductions experienced by the PRP groups met the clinically meaningful criteria. However, no responder analysis was reported. The difference in WOMAC scores between patients who received 1 or 2 PRP injections did not differ significantly. Multiple limitations of this trial were recognized. While powered to detect a difference of 1.5 points in VAS scores, the primary end point was deemed to be WOMAC scores. More importantly, methods to control for type I error for multiple comparisons were not described and possibly not used. Further, the process of randomization and randomized allocation was not described. Lastly, though the trial was described as double-blind, the number of injections between the active arm receiving 2 PRP injections differed from that for placebo and that for PRP patients who received only 1 injection; as such, maintenance of blinding through the trial period is questionable.

Smith et al (2016) conducted a double-blind, placebo-controlled trial (N=30) in patients with knee OA, which showed that treatment with PRP resulted in statistically and clinically significant improvements in WOMAC scores compared with placebo, beginning at week 2 ($p=0.016$) and continuing through the trial duration at 1 year. A similar trend was seen in all 3 domains of the WOMAC (pain, stiffness, physical function). Overall WOMAC mean scores in the PRP- and placebo-treated arms at baseline were 47 and 46, respectively. Post-1 year, the respective overall mean scores were 10 and 43 ($p<0.05$). Patients answered the questions and then received a cumulative score for each of the 3 domains.

Dallari et al (2016) reported on results of an RCT that compared PRP with hyaluronic acid alone or with a combination PRP plus hyaluronic acid in 111 patients with hip OA. Although this well-conducted RCT reported positive results, with statistically significant reductions in VAS scores (lower scores imply less pain) at 6 months in the PRP arm (21; 95% CI, 15 to 28) vs the hyaluronic acid arm (35; 95% CI, 26 to 45) or the PRP 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 WOMAC scores was not observed. Notably, there was no control for type I error for multiple group comparisons at different time points, and the trial design did not incorporate a sham-control arm.

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 PRP (n=10), or standard of care (n=10). All patients received the same rehabilitation protocol. At 18-month follow-up, total WOMAC scores improved most from baseline with Suprahyal/Adant (65% reduction). The next best improvement was seen with PRP (55% reduction), then Synvisc (50% reduction), and Orthovisc (30% reduction). The control group experienced a 15% increase in WOMAC scores.

**Section Summary: PRP as a Primary Treatment of Knee or Hip Osteoarthritis**
Multiple RCTs and systematic reviews with meta-analysis have evaluated the efficacy of PRP injections in individuals with knee or hip OA. Three RCTs have compared PRP with placebo while most trials have

compared PRP with hyaluronic acid for knee OA. A single RCT compared PRP with hyaluronic acid alone or combination PRP plus hyaluronic acid in hip OA. A meta-analysis of 3 trials comparing PRP with placebo showed a significant improvement in functional scores; however, only one of the trials was considered high quality. Comparisons between PRP and hyaluronic acid have found inconsistent results, with a meta-analysis including only low risk of bias studies showing no difference between the 2 treatments. Also, using HA as a comparator is questionable, because the evidence demonstrating the benefit of hyaluronic acid treatment for OA is not robust.-The single RCT evaluating hip OA reported statistically significant reductions in VAS scores, but no significant differences in Harris Hip Score and WOMAC scores. Additional larger controlled studies comparing PRP with placebo and alternatives other than hyaluronic acid are needed to determine the efficacy of PRP for knee and hip OA. Further studies are also needed to determine the optimal protocol for delivering PRP.

**PRP AS AN ADJUNCT TO SURGERY**

**Anterior Cruciate Ligament Reconstruction**

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 PRP used in conjunction with anterior cruciate ligament reconstruction. Pooled data found no significant difference in IKDC scores between the PRP and control groups.

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 PRP.

The largest RCT, reported by Nin et al (2009), randomized 100 patients to arthroscopic anterior cruciate ligament reconstruction with or without PRP. The use of PRP 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: PRP 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 PRP injections in individuals undergoing anterior cruciate ligament reconstruction. Only 1 of the 2 systematic reviews conducted a meta-analysis, which showed that adjunctive PRP treatment did not result in a significant effect on IKDC score. Individual studies have shown mixed results.

**Hip Fracture**

One RCT was identified for treatment of a hip fracture with PRP. Griffin et al (2013) reported on a single-blind randomized trial assessing the use of PRP 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 PRP 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% PRP; 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 PRP group. The length of stay was significantly reduced in the PRP-treated group (median difference, 8 days). For this measure, there is a potential for bias from the nonblinded treating physician.

***Subsection Summary: PRP as Adjunctive Treatment for Hip Fracture***
A single open-labeled RCT has evaluated the efficacy of PRP injections in individuals with hip fracture. This trial failed to show any statistically significant reductions in the need for revision surgery after PRP treatment.

**Long Bone Nonunion**
A Cochrane review by Griffin et al (2012) found only 1 small RCT (N=21) evaluating PRP for long bone healing. However, because only studies comparing PRP 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 PRP 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 PRP plus allogenic bone graft arm (8/9) compared with the allogenic bone graft alone arm (3/9; relative risk, 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; relative risk, 2.42; 95% CI, 0.88 to 6.68).

Calori et al (2008) compared application of PRP with recombinant human bone morphogenetic protein-7 (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 PRP 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 PRP patients). Clinical and radiologic evaluations by 1 radiologist and 2 surgeons trained in the study protocol revealed fewer unions in the PRP 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 PRP.

Samuel et al (2017) conducted a controlled trial in which patients with delayed unions (15-30 weeks old) were randomized to 2 PRP 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 three 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 PRP group vs 59% in the control group). Time to union also did not differ significantly (15.3 weeks for the PRP group vs 13.1 weeks for the control group).

***Subsection Summary: PRP as Adjunctive Treatment for Long Bone Nonunion***
Three RCTs have evaluated the efficacy of PRP 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 PRP 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 PRP in a modified intention-to-treat, the results did not differ in the intention-to-treat analysis. An RCT which compared PRP with rhBMP-7 also failed to show any clinical and radiologic benefits of PRP over rhBMP-7. The third RCT found no difference in a number of unions or time to union in patients receiving PRP injections or no treatment.

**Rotator Cuff Repair**
The literature on PRP for rotator cuff repair consists of RCTs that have evaluated the efficacy of PRP membrane or matrix combined with surgical repair of the rotator cuff. Also, several systematic reviews of the literature, which pooled analysis of data, generally did not show a statistically or clinically significant benefit of PRP.

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

Fu et al (2017) reported on the results of a meta-analysis that only included RCTs comparing the efficacy of PRP with platelet-rich fibrin matrix for improving healing of rotator cuff injuries. Eleven RCTs were included; they enrolled 320 patients with active treatment and 318 patients as controls. Results for the primary outcome (functional score change from pre- to posttreatment) were similar between patients administered PRP plus fibrin matrix and patients in the control group (SMD for functional scores, 0.029; 95% CI, -0.132 to

0.190; p=0.725). The SMD was also similar for patients administered PRP and the controls (SMD=0.142; 95% CI, -0.080 to 0.364; p=0.209). Reviewers concluded that meta-analytic results did not support the use of PRP plus platelet-rich fibrin matrix in patients with rotator cuff injuries.

Saltzman et al (2016) published a systematic review of meta-analyses on PRP at the time of surgery and clinical outcomes for patients undergoing rotator cuff repair. Reviewers identified 7 meta-analyses, all published after 2012, that pooled analyses of trial data. Systematic reviews varied in their outcomes of interest, but all pooled data on the overall re-tear rate and none reported a statistically significant difference in the re-tear rate among patients who received PRP compared with a control intervention; the relative risks ranged from 0.55 to 0.94 and the odds ratio reported in 1 study was 1.11. However, one of the meta-analyses included in the Saltzman review found a significantly lower risk of re-tear with PRP use when an outlier study was excluded from the analysis.

The 2013 Cochrane review by Moraes et al (2013), which pooled data for long-term function from 6 RCTs of PRP applied with rotator cuff repair, showed no statistically or clinically significant differences between the PRP groups and control groups. Moreover, a meta-analysis by Zhao et al (2015) included 8 RCTs with sample sizes ranging from 28 to 88 (total N=464 patients). Meta-analysis showed no significant differences between the PRP groups and control groups in re-tear rate (RR=0.94; 95% CI, 0.70 to 1.25; p=0.66), Constant score (mean difference, 1.12; 95% CI, -1.38 to 3.61; p=0.38), or University of California at Los Angeles Shoulder Score (mean difference, -0.68; 95% CI, -2.00 to 0.65; p=0.32). The strength of the evidence based on GRADE was considered to be low for re-tear, moderate for Constant score, and low for University of California at Los Angeles Shoulder Score.

***Randomized Controlled Trials***

Ebert et al (2017) published an RCT after the systematic reviews discussed above comparing rotator cuff repair alone with rotator cuff repair plus PRP treatment. Patients were randomized to 2 ultrasound-guided injections of PRP to the tendon repair site at 7 and 14 days after arthroscopic supraspinatus repair (n=27) or not (n=28). Outcomes of interest included Oxford Shoulder Score, Quick Disabilities of the Arm, Shoulder and Hand questionnaire, and VAS score for pain. At a mean follow-up of 3.5 years, there were no statistically significant differences in any of the outcomes of interest. There was also no difference in re-tear rates, with 2 patients in each trial group experiencing symptomatic re-tears.

***Subsection Summary: PRP as Adjunctive Treatment for Rotator Cuff Repair***

Multiple RCTs and systematic reviews with meta-analyses have evaluated the efficacy of PRP injections in individuals undergoing rotator cuff repair. The systematic reviews and meta-analyses failed to show a statistically and/or clinically significant impact on symptoms (ie, pain) or functional outcomes. The variability in PRP preparation techniques and PRP administration limit the generalizability of the studies.

**Spinal Fusion**
No RCTs on use of PRP for spinal fusion were identified. Two prospective observational studies found no differences in fusion rates with use of a platelet gel or platelet glue compared with historical controls.

**Subacromial Decompression Surgery**
One small RCT evaluated the use of PRP 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 (PLRP) 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 PLRP group across the 6 weeks of measurements. For example, at 2 weeks after surgery, VAS scores for pain were lower by about 50% in the PLRP group (close to 4 in the control group, close to 2 in the PLRP group), and only 1 (5%) patient in the PLRP group was taking pain medication compared with 10 (50%) control patients. Objective measures of range of motion showed clinically significant improvements in the PLRP group across the 6-week assessment period, with patients reporting improvements in activities of daily living, such as the ability to sleep on the operated shoulder at 4 weeks after surgery and earlier return to work.

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

**Total Knee Arthroplasty**
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 PRP (n=20) or no additional intraoperative treatment (n=20). There were no significant differences between the PRP 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: PRP as Adjunctive Treatment for Total Knee Arthroplasty***
A single small RCT has evaluated the efficacy of PRP injections in individuals undergoing total knee arthroplasty. There were no significant differences between the PRP and untreated control groups across several functional and pain outcomes.

**SUMMARY OF EVIDENCE**
**Primary Treatment for Tendinopathies**
For individuals with tendinopathy who receive PRP injections, the evidence includes multiple 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 PRP did not have a statistically and/or clinically significant impact on symptoms (ie, pain) or functional outcomes. 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 (eg, plantar fasciitis) who receive PRP injections, the evidence includes 3 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 PRP for plantar fasciitis, did not pool study findings. Results among the 3 RCTs were inconsistent. The largest RCT showed that treatment using PRP compared with corticosteroid injection resulted in statistically significant but temporary improvements in AOFAS Ankle-Hindfoot Scale scores, indicating improved outcomes. Confirmation of these results in larger double-blind RCTs would be needed to permit greater certainty on the efficacy of PRP in plantar fasciitis. 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 PRP 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 PRP group than in the hyaluronic acid group. Limitations of the evidence base include lack of adequately randomized studies, lack of blinding, lack of sham controls, and comparison only to an intervention of uncertain efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Primary Treatment for Knee or Hip Osteoarthritis**
For individuals with knee or hip OA who receive PRP 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. Three RCTs have compared PRP with placebo while most trials have compared PRP with hyaluronic acid for knee OA. A meta-analysis of 3 trials comparing PRP with placebo showed a significant improvement in functional scores. However, only one of the trials was considered at low risk of bias. Comparisons between PRP and hyaluronic acid have shown inconsistent results. A meta-analysis including only low risk of bias trials showed no difference between the 2 treatments in functional scores. Also, using hyaluronic acid as a comparator is questionable, because the evidence demonstrating the benefit of hyaluronic acid treatment for OA is not robust. The single RCT evaluating hip OA reported statistically significant reductions in visual analog scale scores for pain, with no difference in functional scores. Additional studies comparing PRP with placebo and with alternatives other than hyaluronic acid are needed to determine the efficacy of PRP for knee and hip OA. Studies are also needed

to determine the optimal protocol for delivering PRP. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Adjunct to Surgery**
For individuals with anterior cruciate ligament reconstruction who receive PRP 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 PRP treatment did not result in a significant effect on IKDC 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 PRP 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 PRP treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with long bone nonunion who receive PRP injections plus orthopedic surgery, the evidence includes 3 RCTs. Relevant outcomes are symptoms, functional outcomes, health status measures, 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 PRP 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 PRP in a modified intention-to-treat analysis, the results did not differ in the intention-to-treat analysis. The second RCT, which compared PRP with recombinant human bone morphogenetic protein-7, also failed to show any clinical or radiologic benefits of PRP over morphogenetic protein. The third RCT reported no difference in the number of unions or time to union in patients receiving PRP injections s no treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with rotator cuff repair who receive PRP injections plus orthopedic surgery, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The systematic reviews and meta-analyses failed to show a statistically and/or clinically significant impact on symptoms (ie, pain) or functional outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with spinal infusion who receive PRP injections plus orthopedic surgery, the evidence includes 2 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 PRP arm and the control arm. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with subacromial decompression surgery who receive PRP injections plus orthopedic surgery, the evidence includes a small RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, 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 PRP injections. However, subjective pain, use of pain medications, and objective measures of range of motion showed clinically significant improvements with PRP. Larger trials are required to confirm these benefits. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with total knee arthroplasty who receive PRP 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 PRP 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.

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## Policy History

Original Effective Date: 09/23/2015
Current Effective Date: 09/19/2018

| | |
|---|---|
| 09/03/2015 | Medical Policy Committee review |
| 09/23/2015 | Medical Policy Implementation Committee approval. New Policy. |
| 09/08/2016 | Medical Policy Committee review |
| 09/21/2016 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 09/07/2017 | Medical Policy Committee review |
| 09/20/2017 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |

Orthopedic Applications of Platelet-Rich Plasma

Policy # 00476
Original Effective Date: 09/23/2015
Current Effective Date: 09/19/2018

09/06/2018 Medical Policy Committee review
09/19/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 09/2019

## Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

| Code Type | Code |
|---|---|
| CPT | 0232T, 86999 |
| HCPCS | P9020 |
| ICD-10 Diagnosis | All related diagnoses |

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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