Medical Coverage Policy

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Autologous Platelet-Derived Growth Factors (Platelet-Rich Plasma [PRP])

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Overview

This Coverage Policy addresses proposed uses of autologous platelet-derived growth factors (APDGF), also referred to as platelet-rich plasma (PRP), for multiple conditions and indications.

Coverage Policy

The use of autologous platelet-derived growth factors (CPT® Code 0232T; HCPCS Codes G0460) for ANY condition or indication, including the following, is considered experimental, investigational, or unproven:

- anterior cruciate ligament (ACL) repair
- bone graft supplementation, regeneration, substitution and/or healing (e.g., lumbar fusion, iliac crest bone graft to maxilla)
- degenerative joint disease
- epicondylitis
- epithelial defects of the cornea, persistent
- fractures, including long-bone nonunion
- joint capsular injuries
- muscle injuries and disorders
- osteoarthritis of the knee
- periodontal disease, gingival recession and dental surgery
- plantar fasciitis
- sinus augmentation procedures
- soft tissue trauma (e.g., tendon and ligament ruptures)
- total knee arthroplasty
- tendonitis
- wound healing (e.g., surgical wounds; chronic wounds; lower extremity ulcers)

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

General Background

Autologous platelet-derived growth factors (APDGF) also referred to as platelet-rich plasma (PRP), platelet gel, platelet-rich concentrate, autogenous platelet gel, plasma rich in growth factors (PRGF) or platelet releasate, have been proposed for the treatment of multiple conditions to enhance healing. PRP is derived from autologous blood, with platelets being the main constituent. A collection and preparation system is used to collect a small sample of the patient's blood to be used to produce PRP. The plasma is combined with other substances to form a platelet-rich gel that can be applied to the wound. The mechanism of action is not well-understood but is proposed to provide a high concentration of growth factors including tissue growth factor and platelet-derived growth factors, which can mediate the proliferation of mesenchymal stem cells and increase matrix synthesis and collagen formation. APDGF has been proposed for numerous indications including wound care, orthopedic conditions, abdominal surgery, and oral/dental procedures. PRP is also being proposed as an additive to other injectables such as mesenchymal stem cells (e.g., Regenexx®). There is insufficient evidence to support the use of PRP for any indication including in combination with other substances. (For orthopedic indications see Coverage Policy Bone Graft Substitutes).

U.S. Food and Drug Administration (FDA)
Platelet rich plasma itself falls into the category of minimally manipulated tissue as an autologous blood product. The systems used for preparing autologous platelet-derived growth factors are FDA approved under the 510(k) process. In general, the systems are approved to be used at the patient's point of care and/or in a clinical laboratory to prepare autologous platelet-rich plasma/platelet concentrate from the patient's own blood. Examples of approved devices include:

- 3C Patch® System (Reapplix A/S, Birkerød, Denmark)
- Aeon CPKit (Aeon Biotherapeutics Corp., Taipei City, Taiwan)
- Arthrex Double Syringe (ACP) Kit (Arthrex, Inc., Naples, FL)
- Aurix™ System (Nuo Therapeutics, Inc., Gaithersburg, MD)
- Autologous Platelet Grafting™ (SafeBlood® Technologies, Inc., Little Rock, AR)
- Cascade® Autologous Platelet System (Musculoskeletal Transplant Foundation [MTF], Edison, NJ)
- Fibrinet® Autologous PRP System (Cascade Medical Enterprises, Wayne, NJ)
- Gravitational Platelet Separation System (GPS®III) (Zimmer Biomet [previously Biomet Biologics],
- PurePRP® SupraPhysiologic Concentrating System (EmCyte Corporation. Fort Myers, FL)
- SmartPReP® 2 APC+ system (Terumo Corporation, Lakewood, CO [previously Harvest Technologies Corporation, Plymouth, MA])

Literature Review
APDGF has been proposed for the treatment of chronic wounds (e.g., lower extremity wounds, pressure ulcers, graft-versus-host disease [GVHD] ulcers); persistent epithelial defects of the cornea; dry eye disease; periodontal disease; bone graft supplementation and regeneration; androgenetic (well-defined pattern) alopecia; neuropathic pain; wrinkles; depressed areas of the skin; ingrown toenails; degenerative cartilage lesions; tendonitis; joint capsular injuries; plantar fasciitis; soft tissue trauma (e.g., tendon and ligament ruptures); temporomandibular disorders;

carpal tunnel syndrome; fractures; osteoarthritis of the knee; as well as muscle injuries and disorders. Studies have also investigated the use of APDGF to enhance healing in various types of surgical procedures including: lipotransfer, hip arthoscopy, spinal fusion, blepharoplasty, mammoplasty, cleft lip and palate, maxillofacial surgery, LASIK surgery, dental implantology, mandibular degree II furcation defects, sinus floor augmentation, pediatric tonsillectomy, cystectomy, finger amputation, epithelialization of skin donor sites, skin autografts, saphenectomy, hemithyroidectomy, inguinal hernia repair and other abdominal surgeries, chest surgery, anterior colporrhaphy, and myringoplasty (Chen, et al., 2021; Al-Hamed, et al., 2020; Ali, et al., 2020; Yolcu, et al., 2020; Catapano, et al., 2019; Malahias, et al., 2018; Stähli, et al., 2018; Yadav, et al., 2018, Zhou, et al., 2018; Alves and Grimalt, 2016; Knezevic, et al., 2016; Kamakura, et al., 2015; Balbo, et al., 2010; Luaces-Rey, et al., 2010; Mishra, et al., 2009; Everts, et al., 2007). In addition, PRP is being investigated for use in promoting endometrium proliferation, improving embryo implantation rate and clinical pregnancy rate for women with thin endometrium in frozen embryo transfer cycles (Chang, et al., 2019). However, consensus on the terminology of the platelet products and standardization of the preparation of the platelet-leukocyte gel has not been established. No standard procedure for PRP production exists, which leads to varying concentration of platelets produced, varying number of growth factors within the PRP, and varying clinical results from PRP therapy. Overall, limitations of the studies include small patient populations and lack of a control group and/or comparison to standard therapy. Outcomes have been conflicting or reported that the application of APDGF did not make a significant difference in inflammation, closure, healing, bleeding, bone ingrowth, implant stability, reduction in recovery time or postoperative pain. Some studies reported that initial appearing benefits were not maintained. There is a safety concern that the increase growth factor in a local area with the use of PRP may have a cancer promoting effect. There is insufficient evidence in the published, peer-reviewed scientific literature to support the safety and effectiveness of platelet gel for these indications.

Aesthetic surgery: In a systematic review, Frautschi et al. (2017) evaluated the evidence for the safety and efficacy of platelet rich plasma (PRP) in aesthetic surgery. Eighteen studies were randomized controlled trials and 20 were case series. In the studies, PRP was injected for the following: aging skin rejuvenation (n=11 studies); scalp alopecia (n=10 studies); increase retention of fat grafts (n=8 studies); enhance the effect of fractional laser resurfacing (n=5 studies); and as an adjunct to facial cosmetic surgery to reduce ecchymosis and the incidence of hematomas (n=4 studies). Outcomes were conflicting and 53% of the studies did not include any objective measures to assess the outcome. The concentration of injected and/or baseline platelets was rarely described. Because of the poor quality and heterogeneity of the studies, meta-analysis could not be performed. There is insufficient data to support the use of PRP in aesthetic surgery.

Anterior Cruciate Ligament Repair: de Andrade et al. (2021) conducted a systematic review and meta-analysis to evaluate the efficacy of platelet rich plasma (PRP) to improve healing and rehabilitation when used in anterior cruciate ligament reconstruction (ACLR). Nine randomized control trials were included with 525 patients with ages ranged from 14–59 years. The control group did not receive PRP. The primary outcomes measured were graft ligamentization, tibial and femoral tunnel widening, knee laxity, and pain. Follow-ups ranged from 12–96 weeks. The PRP group did not show improved ligamentization of graft, lesser tunnel widening, knee laxity, international knee documentation committee (IKDC) or Tegner scores. PRP was associated with higher Lysholm score and lower visual analog scale for pain, however it was determined to be clinically insignificant. Author noted limitations included heterogeneity in PRP preparation, different rehabilitation protocols, small patient populations and low number of included studies.

Figueroa et al. (2015) conducted a systematic review of the literature to evaluate the efficacy of PRP for the treatment of anterior cruciate ligament (ACL) ruptures. A total of 11 studies (n=516) met inclusion criteria. The comparator was reconstruction without PRP (n=250). Four studies

reported a statistically significant difference in healing and two studies showed a tendency toward faster graft maturation but the clinical implication of these results was unclear. One study reported no difference between the groups with the addition of PRP. Regarding tunnel healing/widening, one study showed better clinical outcomes with PRP and five studies showed no benefits with its use. In conclusion, PRP showed no significant improvement in tunnel healing and its clinical improvement in ACL graft maturation is unclear due to the heterogeneity of the studies (e.g. volume and concentration of PRP, number of PRP applications, location of the injection, use of an anticoagulant or activating agent, various surgical techniques and rehabilitation schemes).

In a randomized controlled trial (n=100), Nin et al. (2009) evaluated the efficacy of APDGF when used for the treatment of initial anterior cruciate ligament (ACL) reconstruction with bone-patellar tendon-bone allograft. Fifty of the patients were treated with platelet gel and 50 were not (i.e., control group). In the study group during the surgical procedure, the ligament was covered with APDGF and sutured over itself. The gel was also introduced after implantation of the graft prior to closing the wound. Follow-up ranged from 18 to 36 months (mean 24.3 months). Postoperatively, there were no statistically significant differences between the two groups in the perimeters of the kneecap, C-reactive protein levels, magnetic resonance imaging (MRI) appearance of the graft, and clinical evaluation scores including range of knee motion, muscle torque, visual analog scale, International Knee Documentation Committee scores, and KT-1000 arthrometer scores. The pivot shift test was negative in 94% of all patients. There was no discernable clinical or biomechanical effect of APDGF for this patient population.

Vogrin et al. (2010) conducted a randomized controlled trial (n=50) to evaluate the effect of APDGF on postoperative knee stability following anterior cruciate ligament reconstruction for ligament rupture. Patients were divided into the study group (n=25) which received APDGF during surgical repair and the control group which was not treated with the platelet gel. The gel was applied locally following hamstring graft placement. Follow-up occurred at three and six months. Clinical evaluations were assessed using the Tagner activity score, Lyshol score and International Knee Documentation Committee (IKDC) score. Anteroposterior knee stability was measured using the KT-2000 arthrometer at 15, 20 and 30 pounds of force with knee flexion at 25 degrees and fixed patella at the same time. There was no significant difference in joint stability of the knee between the two groups at the three-month follow-up. At six months, there was a significant improvement ($p=0.011$) in the KT-2000 arthrometer scores in the study group compared to the control group. Limitations of the study include the small patient population, short-term follow-up and patients lost to follow-up (n=5).

Blepharoplasty: In 2006, Vick et al. conducted a randomized, controlled trial (n=33) to evaluate the effect of autologous platelet gel on postoperative edema and ecchymosis in one of the two eyes during bilateral blepharoplasty. Of the 33 patients, 28 (85%) completed the study. No significant differences between the treated and untreated sides were noted for discomfort and ecchymosis. A statistically significant difference was noted in photograding of edema on the treated side on day 1 ($p=0.03$), but the scores were equal on days three and seven. No clinically significant benefits to the use of autologous platelet gel during blepharoplasty were reported.

Breast Surgery: In a randomized controlled trial (n=111), Anzarut et al. (2007) studied the effectiveness of topical application of autologous platelet gel during breast surgery to reduce postoperative wound drainage in patients undergoing bilateral reduction mammoplasty. Each patient had one breast which received the gel and one breast which did not. No statistically significant differences in drainage, pain, size of open areas, clinical appearance, degree of scar pliability, or scar erythema were noted. The data did not support the use of autologous platelet gel to improve outcomes after breast reduction mammoplasty.

Cardiac Surgery: Kirmani et al. (2017) conducted a systematic review of the literature to determine if intraoperative application of PRP in adult patients undergoing cardiac surgery via median sternotomy, reduced the incidence of sternal surgical site wound infections, mediastinitis or bleeding compared to non-treatment. Inclusion criteria were studies that compared the use of PRP as a topical application to the sternum intraoperatively vs. standard closure technique without PRP. Due to the lack of randomized controlled trials (n=3), four observational studies were included. The observational studies showed a net effect of a significant reduction in wound infection with PRP (p=0.04). However, two RCTs showed no treatment effect with PRP. Two RCTs and three observational studies showed a significant reduction in mediastinitis with PRP (p=0.02). Two studies reported on postoperative bleeding and showed no significant difference with PRP (p=0.82). Limitations of the studies included: poor quality of data; paucity of RCTs; inclusion of four observational studies with no controls; heterogeneity of the preparation and application of PRP; lack of detail on surgical procedures; and heterogeneous patient populations. Large, well-designed randomized controlled trials are needed to establish the effectiveness of PRP for use in patients undergoing cardiac surgery via median sternotomy.

Patel et al. (2016) retrospectively reported results from a single surgery center on the effects of platelet rich plasma (PRP) on patients who underwent open cardiac operations requiring sternotomy. The outcomes of 1000 consecutive patients who received standard of care sternal closure plus autologous PRP, calcium and thrombin applied to the sternum at the time of closure were compared to the previous 1000 consecutive patients who received standard of care sternal closure without PRP. Deep and/or superficial sternal wound infections, readmission rates, and actual costs were analyzed for six months following surgery. Standard surgical methods were used for the performance of all median sternotomies and sternal closures. All patients who underwent sternotomy were included in the study. The procedures included: emergencies, reoperations, ventricular assist device implantations/heart transplants, aortic dissections and standard operations (i.e., coronary artery bypass grafting and valve repairs or replacements). Diagnosis of deep and superficial sternal wound infections (DSWI) was made based on one or more of the following: positive culture of mediastinal tissue or fluid; clinical evidence of mediastinitis during sternal reoperation; and/or chest pain, sternal instability, purulent discharge from the mediastinum associated with a positive blood culture. There were significant differences between the two groups. Age and body surface area were significantly lower in the control group and significantly more ventricular assist device implantations/heart transplants, emergency operations and blood transfusions occurred in the PRP group. Compared to the control group, the PRP group had a reduced incidence of deep sternal wound infection from 2.0% to 0.6%, and superficial wound drainage from 8.0% to 2.0%. The hospital readmission rate within 30 days of operation was reduced from 4.0% to 0.8% in the PRP group. Postoperative infections occurred within two months in the PRP group vs. four months in the control group but the study was not powered to validate this finding. There were no complications attributed to PRP. Limitations of the study include the retrospective study design, heterogeneity of surgical procedures, and significant differences in the patient characteristics in the study group vs. the control group. Prospective randomized controlled trials with matched patient populations and homogenous surgical procedure are needed to validate the efficacy of PRP in this subpopulation.

Cervical Fusion: Feiz-Erfan et al. (2007) conducted a double-blind randomized study in which platelet gel was used to treat 50 patients who underwent anterior cervical fusion with allograft bone and internal fixation. Altogether, 81-disc levels were treated. Forty-two levels were assigned to the gel group and 39 levels were assigned to the control group. Follow-up evaluations occurred at six weeks, 12 weeks, one year and two years. There were no significant differences in fusion rates between the groups at any follow-up evaluation. The data presented did not support the use of platelet gel to improve fusion rates in patients undergoing anterior cervical fusion.

Epicondylitis: Chen et al. (2021) conducted a systematic review of sixteen randomized control trials (n=927) to evaluate the effectiveness of platelet-rich plasma (PRP) on pain and functional outcomes for the treatment of lateral epicondylitis. Comparators included autologous whole blood (AWB) (four studies), corticosteroids (nine studies), saline (two studies), bupivacaine (one study), and laser therapy (one study). Nine studies (n=581) were included in a meta-analysis evaluating the efficacy of PRP versus AWB and/or PRP versus corticosteroids. The average patient age was 41.5 years with 56.8% females. The studies were conducted in Denmark, France, Iran, Greece, Netherlands, India, United Kingdom, Germany, Poland, Egypt, Pakistan, and Brazil. The mean follow up was 7.5 months. PRP compared to AWB had higher visual analog scale (VAS) scores at three ($p<0.01$) and six months ($p<0.01$) while Mayo Clinic performance index for the elbow (MAYO) scores were statistically equivalent. No significant difference in VAS and Disabilities of the Arm, Shoulder, and Hand (DASH) scores at three months when comparing PRP to corticosteroids with higher VAS and DASH scores for PRP at six months ($p<0.01$). No serious adverse events were reported. Self-resolving pain was reported in two studies. Author noted limitations included heterogeneity of PRP preparation methods and patient reported outcome measures, small patient populations and short-term follow-up.

Kemp et al. (2021) conducted a systematic review to evaluate the effectiveness of platelet rich plasma compared to corticosteroid (CS) injection for the treatment of lateral epicondylitis. The five systematic reviews (SR) included a range of 5–20 randomized control trials with 250–1271 patients. Demographic data on the patients was not provided. Patient reported outcome measures were assessed using the following: visual analogue scale for pain (VAS) (five SR), Disabilities of Arm, Shoulder and Hand (DASH) (five SR), Pain Pressure Threshold (PPT) (two SR), Patient-Related Tennis Elbow Evaluation (PRTEE) (three SR), modified Nirschl score for pain (MNS) (one SR), and modified MAYO score (MMS) (one SR). Four of five studies reported improved pain relief and function in short term (2–8 weeks) with CS injection and with PRP in the long term (>8 weeks). Adverse events were not reported. Author noted limitations included inconsistencies in reporting preparation techniques, injection techniques, and concentrations of PRP; varied patient reported outcome measures; small patient populations; and short term follow-up.

Systematic reviews and meta-analysis of RCT report conflicting outcomes when comparing PRP to other treatment modalities. Simental-Mendìa et al. (2020) conducted a systematic review and meta-analysis of five RCT (n=276) comparing PRP versus placebo (saline solution) for pain and joint function. Follow-up varied from two months to one year. Adverse events included post-injection pain. There was no significant change in pain or functional scores between PRP and placebo injections. Li et al. (2019) conducted a systematic review and meta-analysis of five RCT (n=515) comparing the effectiveness of PRP to corticosteroid injection. Follow up ranged from 4–24 weeks. The effectiveness of PRP and corticosteroid were comparable in the 4–8 week follow-up range. Although PRP showed more improvement in pain and function at 24 weeks, the studies were limited by small patient populations, short term follow up and lack of standard PRP treatment protocols.

Mi et al. (2017) conducted a systematic review and meta-analysis of eight randomized controlled trials (n=511) to compare the effectiveness of PRP (n=253) to steroid injections (n=258) in reducing pain and improving function of lateral epicondylitis. There was no significant difference in pain relief following PRP injection at 2–4 weeks ($p=0.03$), 6–8 weeks ($p=0.24$) and at 12 weeks ($p=0.35$). Steroid injections exhibited a significantly better improvement in function at 2–4 weeks ($p<0.001$) and at 6–8 weeks ($p<001$). PRP was significantly more effective for pain relief at six months ($p<.001$) and at one year follow-up ($p<001$) and function improvement at 12 weeks ($p<0.001$), six months ($p<0.001$), and one year ($p<0.001$). Three studies reported adverse events which included a higher rate of post-injection pain in the PRP groups. The steroid group had local skin atrophy and minor rash. Limitations of the studies included: small patient populations; heterogeneity of PRP concentrations and dosages; various types and dosages of

steroids; heterogeneity of the outcome measures used for pain and function scores; and lack of detail of randomization and blinding of patient and doctors. Additional high-quality, well-designed randomized controlled trails with large patient populations are needed to verify the results of this analysis.

Ahmad et al. (2013) conducted a systematic review to evaluate the evidence for platelet-rich plasma (PRP) for the treatment of lateral epicondylitis. Five randomized controlled trials, one nonrandomized comparison study and three case series met inclusion criteria. Comparators included blood, bupivacaine, normal saline injections or corticosteroids. Follow-ups ranged from six weeks to three months. Outcomes were conflicting with some studies reporting improvement and other studies reporting no significant differences with PRP. Limitations of the studies included: heterogeneity of outcomes measured; small, heterogeneous patient populations; variations in PRP preparation and post-injection protocol; lack of a non-treatment group; and short-term follow-ups. There is insufficient evidence to support PRP for the treatment of epicondylitis.

Peerbooms et al. (2010) conducted a two-center randomized controlled trial to evaluate the treatment of chronic lateral epicondylitis in patients randomly assigned to receive an APDGF injection (n=51) or a corticosteroid injection (n=49) (control group). Six months prior to onset of the trial, patients had been unresponsive to cast immobilization, corticosteroid injections and/or physiotherapy. Primary outcomes included visual analog scores (VAS) and Disabilities of the Arm, Shoulder, and Hand (DASH) scores. A successful outcome was a more than 25% reduction in VAS or DASH scores without repeat treatment within the first year following injection. Follow-ups occurred for up to 52 weeks. Patients engaged in a stretching protocol and a muscle- tendon-strengthening program following the injections. The VAS and DASH scores were significantly better in the APDGF group compared to the corticosteroid injection group at the six-month ($p<0.001$, $p=0.03$, respectively) and one-year ($p<0.001$, $p=0.001$, respectively) follow-ups. Although the scores were better in the corticosteroid injection group initially, improvement declined. In contrast the APDGF group showed progressive improvement over time. After an average five months, five APDGF-treated patients required reintervention compared to 13 control group patients. Limitations of the study include the small patient populations and patients lost to follow-up or patients with inadequate data sets (n=8).

Gingival Recession: Keceli et al. (2008) conducted a randomized controlled trial to evaluate the effectiveness of platelet gel used for the treatment of 40 patients with gingival recession. Patients were randomized to either connective tissue graft only or to connective tissue graft plus platelet gel. Outcomes were measured in terms of gingival index, plaque index, recession depth, probing depth, keratinized tissue width, recession width, clinical attachment level, and localization of mucogingival junction. Although significant improvements were seen within each group following treatment, no statistically significant differences were seen in outcomes between the two groups at the six-week, six-month and 12-month postoperative follow-up visits. No benefits from application of the platelet gel were identified.

Hip osteoarthritis: Gazendam et al. (2020) conducted a systematic review of eleven randomized control trials (n=1353) to compare the effectiveness (pain reduction and function improvement) of Intra-articular (IA) injections of corticosteroids (CCS), hyaluronic acid (HA) and platelet-rich plasma (PRP) in the treatment of hip osteoarthritis (OA). Patient populations of the studies ranged from 42–305, were 54% female with a mean age of 64±9.5 years. No intervention demonstrated significant improvement compared to saline IA injection at 2–4 and six months for pain or functional outcomes. Pooled data demonstrated that all interventions including placebo (except HA + PRP and the control group) led to clinical improvement of pain and function scores. Twenty-four major adverse events were reported: discontinued due to adverse events (n=20), deep vein thrombosis (n=1), rapid progression of OA (n=1), post hip arthroplasty infection (n=1) and superficial hematoma (n=1). Author noted limitations included heterogeneity of patient reported

outcome measures, small patient populations and short term follow-up. No IA injections demonstrate a statistically significant difference at up to six months post-injection for patients with hip OA.

Knee Pathology: Systematic reviews and meta-analysis of randomized control trials (RCT) contain overlapping studies and report conflicting outcomes. Limitations of the studies include heterogeneity of grade of osteoarthritis (OA) and outcome measure tools/scales, small patient populations, short term follow up and lack of standard PRP treatment protocols. Dong et al. (2020) conducted a systematic review and meta-analysis of 24 RCT (21 knee OA, three hip OA) (n=2057) comparing PRP versus control (hyaluronic acid, saline, prolotherapy, acetaminophen) for pain and joint function. Follow ups varied from 12 weeks to 18 months. Outcome measures included: Western Ontario and McMaster (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analog Scale (VAS), Harris Hip Score (HHS), and International Knee Documentation Committee (IKDC). Although PRP showed significant improvement in the short term in total WOMAC scores (14 studies), WOMAC pain scores (14 studies), WOMAC stiffness scores (13 studies), WOMAC physical function scores (12 studies), VAS (12 studies), KOOS quality of life (four studies), IKDC (four studies) and HHS (two studies), there was significant heterogeneity for each test and no benefits at long term follow up. There were no reported differences in the KOOS symptoms outcomes (four studies), KOOS pain (four studies), KOOS function (four studies), and KOOS sport (four studies). Limitations of the studies include heterogeneity of the studies, outcome measures and PRP regimens; short term follow up, and small patient populations.

Chen et al. (2020) conducted a systematic review and meta-analysis of 14 RCT (n=1350) comparing PRP to hyaluronic acid for the treatment of knee osteoarthritis. Follow ups ranged from three to 60 months. Outcome measures varied from study to study and included visual analog scale (VAS) score, subjective International Knee Documentation Committee (IKDC) score, Western Ontario and McMaster Universities (WOMAC) score, Knee Injury and Osteoarthritis Outcome Score (KOOS), and adverse events. There were no statistically significant differences between the groups in short term outcomes for the VAS (three studies); short-term (three studies) and mid-term outcomes (one study) for subjective IKDC; mid-term WOMAC-Total score (two studies); short-term (three studies) and mid-term (four studies) for the WOMAC-pain; short-term (two studies) and mid-term (three studies) for the WOMAC-stiffness score; mid-term WOMAC-physical function score (three studies); short-term (three studies) and long-term (two studies) KOOS-symptoms score; short-term (three studies), mid-term (one study), and long-term (two studies) KOOS-pain score; short-term (three studies), mid-term (one study), and long-term (two studies) KOOS-ADL score; short-term (three studies), mid-term (one study), and long-term (two studies) KOOS-sport score; short-term (three studies), mid-term (one study), and long-term (two studies) KOOS-QoL. There was no statistical difference in adverse events between the groups. However, results were favorable for PRP in the mid-term (p=.02) and long-term (p=.0003) VAS score (four studies), long-term (p=.001) IKDC score (six studies), mid-term (p=.01) (four studies) and log-term (p=<0.00001) (six studies) WOMAC-total, long-term (p<0.00001) WOMAC-pain score (six studies), long-term (p<0.00001) WOMAC-stiffness score (five studies), short-term (p=.03) (two studies) and long-term (p=.001) (five studies) WOMAC-physical function, and mid-term (p=.02) KOOS-symptoms (one study). Limitations of the studies include: small patient populations, short term follow ups, heterogeneity of the outcome indicators, and lack of standardization of preparation and injection of PRP.

Hohmann et al. (2020) conducted a systematic review and meta-analysis of 12 RCT (n=1248) comparing efficacy of intra-articular knee injections of PRP to hyaluronic acid. Follow ups ranged from 6–12 months. Outcomes were assessed using Western Ontario and McMaster Universities (WOMAC) score, International Knee Documentation Committee (IKDC) score, and visual analog scale (VAS) score and varied from study to study. There were no significant improvements in

clinical outcomes at six (p=0.069) or 12 months (p=0.188) (eight studies). PRP showed significant improvement in pooled estimates of pain scores (eight studies) at six months (p=0.001) and 12 months (p=0.001). Limitations of the studies include: heterogeneity of outcome measure tools, small patient populations, short term follow up and lack of standard PRP treatment protocols.

Delanois, et al. (2019) conducted a systematic review of studies investigating the management of knee osteoarthritis using platelet-rich plasma injections (PRPs), bone marrow-derived mesenchymal stem cells (BMSCs), adipose-derived mesenchymal stem cells (ADSCs), and amnion-derived mesenchymal stem cells (AMSCs). Eleven randomized control trials investigating PRP were included. The intervention consisted of intra-articular PRP injections ranging from one to three at varying intervals of time. Comparators were oral acetaminophen, oral hyaluronic acid (HA), intra-articular HA, intra-articular corticosteroid, or intra-articular saline. Follow-up ranged from 1–12 months. Studies reported conflicting results about the efficacy of PRP. Because of the poor quality and heterogeneity of the studies, no meta-analysis was able to be performed. Author noted limitations include the small patient populations and short-term follow-ups. Additional high-level, well designed human studies with large patient populations utilizing standardized protocols are needed to validate the efficacy and clinical utility of PRP in the management of knee osteoarthritis.

Di et al. (2018) conducted a systematic review of seven randomized control trials (RCT) (n=908) comparing the effectiveness of platelet-rich plasma (PRP) to hyaluronic acid (HA) for the treatment of knee osteoarthritis (OA). RCTs were included if they identified knee OA and compared autologous PRP with HA via intra-articular injection. Excluded were studies with unknown data and methodology and those conducted on patients with knee OA with additional diagnosis of pain or swelling associated with knee joint disease, ligament or meniscus injury, arthritis, blood diseases, serious cardiovascular disease, or infection or those receiving immunosuppressive or anticoagulation therapy. Primary outcomes were efficacy and response to treatment as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (n=4 studies), International Knee Documentation Committee (IKDC) (n=2 studies), Knee Injury and Osteoarthritis Outcome Score (KOOS) (n=3 studies), EuroQol visual analogue scale (EQ VAS) (n=4 studies), and Tegner score (n=1 study). Reported adverse events included mild pain and infiltration, swelling or effusion after injection. Author noted limitations included: risk of selection bias, small sample sizes and lack of placebo groups. Other limitations include the lack of standardized injection protocol and differences in PRP preparation and type (fresh, frozen, leukocyte poor or rich). Multicenter, randomized trials with large patient populations are needed to further assess the efficacy of PRP treatment for patients with knee OA.

Muchedzi and Roberts (2018) conducted a systematic review of the literature to evaluate the evidence of PRP in the treatment of knee osteoarthritis (OA) and following total knee arthroplasty (TKA). Seventeen studies (n=2328) were included: 11 compared intraoperative PRP gel injection vs. control groups (without intraoperative PRP injection) during TKA; and six compared intra-articular PRP injections vs. placebo/control groups in the non-surgical management of knee OA. Inclusion criteria were: randomized control trials (RCTs), pseudorandomized, comparative clinical trials and systematic reviews performed since 2006 using PRP in the management of knee OA and following TKA in patients of any age. Studies were excluded if they were cross sectional studies, case series, case reports, or included patients with previous knee surgery. The primary outcomes measured were patient reported including pain (visual analog scale [VAS]), quality of life scores, and knee function. Secondary outcomes were wound scores, length of hospital stay, and postoperative blood loss. Length of follow-up was classified as short term, medium term and long term. Regarding the effects of PRP on OA there were no statistically significant differences in pain (p=0.013), quality of life (p=0.06), and knee function (p=0.09). No clinical statistical benefits were seen with PRP on reducing blood loss during TKA (p=0.07) or in reducing hospital length of stay (p=0.31). Author-noted limitations included the heterogeneity of the studies (PRP preparation

and characteristics, different outcome measures) and missing data elements. Additional high quality, well-designed randomized controlled trials with large patient populations are needed to verify the results of this analysis.

Dai et al. (2017) conducted a systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy and safety of platelet-rich plasma (PRP) injections for the treatment of osteoarthritis of the knee. Ten randomized controlled trials (n=1069) met inclusion criteria. Eight studies compared PRP with hyaluronic acid (HA) and three studies compared PRP with saline. The primary outcome measures were pain and function scores reported by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Follow-ups ranged from 3–12 months. Outcomes at six months (three studies; n=339) showed that PRP compared with HA had similar effects on WOMAC pain scores and functional improvement. At the 12-month follow-up (three studies; n=302) PRP injections were associated with significantly better WOMAC pain scores (p=0.0001) and WOMAC functional scores (p<0.00001) compared to HA. PRP also showed better pain relief and functional improvement than saline in one study. There was no significant difference in adverse events of PRP vs. HA (four studies). Author-noted limitations of the studies included the heterogeneity of PRP preparation (e.g., single- vs double-spinning technique, speed, length of centrifugation, use of an activator or not), PRP and HA administration (frequency of injections, injection volume), and HA types. The studies included small, heterogeneous patient populations (age, sex, body mass index, activity level, OA grade) and there was a high risk of bias in eight studies. The short-term follow-ups and few numbers of studies included in the meta-analysis contributed to the low quality of the analysis.

Shen et al. (2017) conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the effectiveness of intra-articular platelet rich plasma (PRP) for the treatment of osteoarthritis of the knee. Fourteen RCTs (n=1423) met inclusion criteria. Studies that enrolled patients age ≥◦18 years with symptomatic knee OA and had a follow-up of at least 12 weeks were included. The comparators (controls) included saline placebo, hyaluronic acid (HA), ozone and corticosteroids. Follow-ups ranged from 12 weeks to 12 months. The primary outcome was the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscores, physical function subscores, and total scores. Follow-ups occurred at three, six, and 12 months (n=5 studies) following treatment. The secondary outcome was the number of patients reporting adverse events. Sample sizes for PRP groups ranged from 12–96 patients. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was the most frequently used outcome (n=9 studies). Compared with controls at the 3-, 6-, and 12-month follow-ups, PRP injections significantly reduced the WOMAC pain subscores (p=0.02, 0.004, <0.001, respectively); significantly improved the WOMAC physical function subscores (p=0.002, p=0.01, p<0.001, respectively); and significantly improved total WOMAC scores (p<0.001 each). Subscores were based on 3–6 studies each. PRP did not significantly increased the risk of post-injection adverse events (p=0.24). Limitations of the studies included: moderate to high risk of bias in ten studies; heterogeneity of outcome measures; variations in PRP treatment protocols (e.g., preparation devices, use of exogenous activators) and injection regimen (e.g., dose, times, intervals); short-term follow-ups; limited number of studies and small patient populations for each comparator and subscores; and lack of blinding. Due to the heterogeneity of the studies a firm conclusion could not be made as to whether or not PRP is more effective than the comparators. The duration period of the beneficial effect of PRP injections is unknown.

Meheux et al. (2016) conducted a systematic review to determine if platelet rich plasma (PRP) injections improved outcomes in patients with symptomatic knee osteoarthritis (OA) at 6–12 months following injection. Secondary objectives of the review were to evaluate the differences in outcomes between PRP and corticosteroid injections or hyaluronic acid (HA) or placebo injections, and the similarities and differences in outcomes based on the PRP formulations. Six randomized controlled trials (739 patients, 817 knees), with an average follow-up of 38 weeks, met inclusion

criteria. Five studies compared PRP injections to hyaluronic acid (HA) injection and one study compared PRP to placebo (saline). No study compared PRP to corticosteroid injection. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was the most frequently used outcome. Other outcome measures included: Knee Injury and Osteoarthritis Outcome Score (KOOS); Short Form-36, Tegner, Visual Analog Scale (VAS), and Lequesne. No study compared leukocyte-poor PRP to leukocyte-rich PRP. According to self-reported WOMAC and IKDC scores, most studies reported significant improvements with PRP including pain, physical function, and stiffness. Mean post-treatment WOMAC scores for PRP were significantly better than HA at 3–6 months (p=0.0008) and at 6-12 months (p=0.0062). There were numerous limitations to this review including: limited number of studies (n=6) with small, heterogeneous patient populations (n=7–176); heterogeneity of PRP preparation and dosage and HA dosage and injection techniques; lack of blinding; two studies did not report the randomization procedure; short-term follow-ups; lack of radiographic data on follow-up; use of various outcome measures; heterogeneity of classification systems used to determine severity of knee OA; and limited evidence comparing leukocyte-rich versus leukocyte-poor PRP. Knee range of motion was not recorded for any trial. Because of the heterogeneity of the studies, meta-analysis could not be performed. Well-designed randomized controlled trials with large, homogenous patient populations, PRP preparation and dosage and injection techniques are needed to validate the effectiveness of PRP for the treatment of OA of the knee.

Lai et al. (2015) conducted a systematic review of the literature to evaluate the efficacy of PRP for intra-articular injections for the treatment of knee osteoarthritis (OA). A total of eight studies met inclusion criteria (two randomized controlled trials, two comparative and four observational studies). Comparators were hyaluronic acid or saline. The studies reported improved function and reduction of pain but effects were only stable in the short term. Some outcomes were reported as worsening of symptoms over longer follow-up periods (up to two years). Two studies reported maintenance of improved outcomes for 12 months. Outcomes with PRP were better than saline and outcomes were mixed when PRP was compared to hyaluronic acid. Due to the small patient populations, short-term follow-ups, and lack of a comparator, firm conclusions could not be made regarding the efficacy of PRP in the treatment of knee OA. The subgroup of patients with OA of the knee who would benefit from PRP has not been established.

Campbell et al. (2015) conducted a systematic review of overlapping meta-analyses to evaluate platelet-rich plasma (PRP) injection used in the treatment of knee joint cartilage degenerative pathology. Three meta-analyses (n=577–1543) met eligibility criteria. Follow-ups ranged from 2–12 months. The studies compared outcomes of treatment with intra-articular platelet-rich plasma (IA-PRP) to treatment with intra-articular hyaluronic acid or intra-articular placebo. Use of IA-PRP led to significant improvements in patient outcomes for up to 12 months following injection. However, there were varying reports of patient satisfaction from no statistically significant difference to increased satisfaction following injection. There appeared to be an increased risk of local adverse reactions after multiple PRP injections and IA-PRP offered better symptomatic relief to patients with early knee degenerative changes. Limitations of the study include the heterogeneity of the number of PRP injections given (1–4), intervals between injections (1–3 weeks), injection volume, spinning techniques, and activating agents. Whether or not these variations affected outcomes was unable to be assessed. Other limitations included the heterogeneity of standardized and nonstandardized patient outcome measures that were reported.

Chang et al. (2014) conducted a systematic review to evaluate the effectiveness of PRP for the treatment of knee cartilage degenerative pathology. Adults with degenerative disorders were diagnosed through clinical and image findings. Sixteen randomized and non-randomized controlled trials met inclusion criteria (n=1543). Follow-ups ranged from 6– 24 months with the latest point of assessment for most trials occurring 12 months after PRP injections. Comparators included saline and hyaluronic acid (HA). Meta-analysis comparing before and after PRP treatment showed

a continual efficacy for 12 months. Results varied depending on the severity of the degeneration. Eight trials reported adverse events of transient local swelling and regional pain. Limitations of the studies included: low methodological quality; short-term follow-up; lack of controls and randomization; and heterogeneity of degenerative grades of arthritis, PRP preparation and dosage, and functional assessment outcome measures.

Khoshbin et al. (2013) conducted a systematic review (n=577) to evaluate the use of PRP for the treatment of symptomatic knee osteoarthritis (OA). Four randomized controlled trials and two case series met inclusion criteria. Comparators included injections of hyaluronic acid (HA) or normal saline (NS). Based on the Western Ontario and McMaster Universities Arthritis Index scale, pooled results of four studies showed that PRP was significantly better than HA or NS ($p<0.001$). The International Knee Documentation Committee scores (three studies) favored PRP as a treatment modality ($p <0.001$). There was no difference in the pooled results for visual analog scale score or overall patient satisfaction. There were significantly more adverse events in patients treated with PRP than in those treated with HA or placebo ($p=0.002$). Limitations of the studies included: heterogeneity of study designs, patient populations, treatment regimens and PRP preparation techniques; short-term follow-up (≤ 6 months); and use of various outcome measures. The authors noted that the ideal number, frequency, and timing of treatments; the grade of OA best treated; the concurrent use of nonsteroidal anti-inflammatory agents, corticosteroids, or analgesic agents; the optimal post-treatment rehabilitation protocol; and the most bioavailable delivery method are unknown.

Kon et al. (2010) conducted a prospective case series (n=100 patients/115 knees) to evaluate the efficacy of APDGF in the treatment of monolateral or bilateral degenerative lesions of articular cartilage of the knee. Patients had experienced at least four months of pain or swelling of the knee and had radiographic findings of degenerative joint changes. Intra-articular injections were administered every 21 days, and follow-up occurred for 12 months. Compared to baseline, statistically significant improvements in the International Knee Documentation Committee (IKDC) objective scores were seen following APDGF injections at the six and 12 month follow-ups ($p<0.0005$, each). However, a statistically significant worsening of scores was seen between six and 12 months ($p<0.0005$). The same results were seen with the IKDC subjective scores with significant improvements at six- and 12-month follow-ups ($p<0.005$, each), but significant worsening at the 12-month follow-up ($p=0.02$). The Euroqol Visual Analogue Scale (EQ VAS) scores improved significantly at the six- and 12-month follow-ups compared to baseline ($p<0.0005$, each), but had a tendency to worsen over time ($p=0.2$), even though not statistically significant. Limitations of the study include the lack of a control group and randomization, short-term follow-up and the number of patients lost to follow-up or who did not complete the study (n=12).

Long-Bone Union or Nonunion: An et al. (2021) conducted a meta-analysis of randomized and non-randomized controlled trials (RCT and NRCT) to assess the efficacy of platelet-rich plasma (PRP) combined with autologous bone grafting compared with autologous bone grafting alone for the treatment of long bone delayed union or non-union. Included were six RCTs and two NRCTs with 420 patients and were performed in China, Iran, Mexico, and Iraq. Mean age of patients varied between 26–38 years with 59%–85% being male. Follow-ups varied from 9–25 months. Patients who received combined treatment of PRP and autologous bone graft were not associated with higher rates of radiographic bone healing ($p=0.09$) or excellent/good post-treatment limb function ($p=0.37$). Combined treatment was associated with a shorter healing time (mean difference: -1.35 months; $p<0.001$). Adverse events were not reported. Author noted limitations included heterogeneity of PRP preparation methods and patient reported outcome measures, small patient populations and short-term follow-up.

Lenza et al. (2013) conducted a systematic review to evaluate the effectiveness of PRP as an adjunctive therapy for the union of long bones. Two randomized controlled trials (RCT) (n=148) met inclusion criteria. Outcomes included bone regeneration, adverse events, pain, quality of life and cost. One RCT compared PRP to recombinant human morphogenic bone protein-7 for the treatment of pseudoarthrosis and the second RCT evaluated the effects of platelet-rich plasma, platelet-rich plasma plus bone marrow stromal cells, and no adjuvant treatment. Follow-ups occurred for up to 12 months. Overall, there was no significant difference with the use of PRP.

Periodontal Intraosseous Defects: Del Fabbro et al. (2018) conducted a Cochrane review to assess the effectiveness of autologous platelet concentrates (APC) used as an adjunct to periodontal surgical therapies (open flap debridement [OFD], OFD combined with bone grafting [BG], guided tissue regeneration [GTR], OFD combined with enamel matrix derivative [EMD]) for the treatment of infrabony defects. Thirty-eight randomized controlled trials were included (n=1402 defects). The four surgical techniques without PRP were the comparators. Primary outcomes were probing pocket depth, clinical attachment level, and radiographic bone defect filling. Secondary outcome was patients' quality of life. Follow-ups ranged from 3–6 months and 9–12 months. Reported outcomes included the following:

1. APC + OFD versus OFD alone (n=12 studies, n=510 defects). Significant improvements were seen with APC for all three primary outcomes ($p<0.001$).
2. APC + OFD + BG versus OFD + BG (n=17 studies, n= 569 defects). Significant improvements were seen with APC for all three primary outcomes ($p<0.001$).
3. APC + GTR versus GTR alone (n=7 studies, n=248 defects). No statistically significant differences were seen with APC.
4. APC + EMD versus EMD (n=2 studies, n=75 defects). No statistically significant differences were seen with APC.

Very low quality of evidence showed some improvement in use of APC in open flap debridement and open flap debridement with bone graft in the treatment of infrabony defects. There were no statistically significant differences with APC for guided tissue regeneration and enamel matrix derivative. Although the use of APC appeared to improve the outcomes for some indications, the body of evidence was considered to be low quality due to high risk of bias, high heterogeneity of studies, and imprecision in outcomes measures.

Kotsovilis et al. (2009) conducted a systematic review of randomized controlled trials (n=10 studies) to evaluate the efficacy of APDGF for the treatment of periodontal intraosseous defects. Seven trials had a parallel group design and three exhibited a split-mouth design. Four studies were conducted by the same research group. Various parameters of APDGF preparations and applications were used (e.g., type of centrifuge, pattern of centrifuge steps, baseline and treatment platelet concentration, growth factor concentration in platelets) and APDGF was combined with various types of bone grafts or substitutes, alloplastic materials, and/or guided tissue regeneration. According to the authors, overall primary and secondary outcomes failed to confer statistically significant additive benefits of APDGF in the therapy of periodontal intraosseous defects. There were no safety issues identified.

Plantar Fasciitis: Yang et al. (2017) conducted a systematic review and meta-analysis of nine randomized controlled trials (p=430) to evaluate the safety and efficacy of PRP as a treatment for plantar fasciitis compared to steroid treatments. Outcome measures included the visual analogue scale (VAS), the Foot and Ankle Disability Index (FADI), American Orthopedic Foot and Ankle Society (AOFAS) scale, and the Roles and Maudsley Score (RMS). Control subjects were treated with dexamethasone (one study), triamcinolone (two studies), methylprednisolone (five studies) and an unidentified steroid in one study. A combination of local anesthetics, such as prilocaine or lidocaine, was applied in six studies. Nine studies described the detailed process used to produce PRP. Follow-up times were divided into short periods (2–4 weeks), intermediate periods (4–24 weeks), and long periods (≥ 24 weeks through 48 weeks). No significant differences in the VAS

scores were observed between the two groups in the short term (p=0.51) and intermediate term (p=0.30). PRP demonstrated significantly better long-term efficacy than steroid treatments (p=0.03). There were no significant differences in the FADI (p=0.28) (two studies; n=88), AOFAS Scale (p=0.79) (three studies; n=138), and RMS (p=0.56) (two studies; n=138) between the groups at 12 weeks. Author-noted limitations included the small patient populations, heterogeneity of the studies, subjective outcomes (VAS, FADI, AOFAS, RMS), and short-term follow-ups. Another limitation was the heterogeneity of the steroid treatments used. Additional well-designed, long-term randomized controlled trials are needed to establish the role of PRP for the treatment of plantar fasciitis.

Rotator Cuff Repair: Chen et al. (2020) conducted a systematic review and meta-analysis of 18 randomized control trials (RCT) (n=1116) evaluating the effectiveness of PRP (n=545) versus no PRP for rotator cuff tears. Patient populations ranged from 35–120 and follow up ranged from six months to two years. The following outcome measures were used: Constant-Murley (Constant) score (10 studies), University of California, Los Angeles (UCLA) score (6 studies), visual analog scale (VAS) for pain, (10 studies), retear rate (11 studies), American Shoulder and Elbow Surgeons (ASES) score (4 studies), and Simple Shoulder Test (SST) (4 studies). PRP significantly improved Constant scores (short and long term and overall [p<0.01]), VAS scores (short term [p<0.01] and overall [p<0.02]) and SST scores (long term [p=0.01]). No significant differences were reported in ASES score between PRP and no PRP. PRP patients reported higher UCLA scores at short- and long-term follow-ups and overall (p<0.01). The odds of a retear (long term and overall [p<0.01]) were reported as being reduced in the PRP treated group. Functional outcomes did not meet the minimal clinically important difference (MCID) (10% difference threshold). Study limitations include small patient populations, heterogeneity between the types of PRP treatments (activating agents, preparation kits) and volumes that were administered. Other limitations include variability in degree of injury, which rotator cuff tendons were treated, and injection technique. The authors state that even though the findings were statistically significant, PRP may not provide clinically meaningful improvements in pain or function.

Cai et al. (2016) conducted a systematic review and meta-analysis evaluating arthroscopic repair of full-thickness rotator cuff tears with (n=150) and without PRP (n=153). Five randomized controlled trials with 12-month follow-ups met inclusion criteria and were used for meta-analysis. There were no statistically significant differences between the groups for overall outcome scores (p>0.05) or use in patients with full-thickness rotator cuff repairs. The PRP-treated group did exhibit better postoperative healing rates than the no-PRP group (p=0.03) in small to moderate full-thickness tears but there were no differences in the clinical outcomes. Limitations of the studies include small patient populations; risk of reporting bias; and high level of heterogeneity of surgical techniques, tear size and PRP products and volume used.

Zhao et al. (2015) conducted a systematic review to evaluate the retear rate and clinical outcomes of PRP used during arthroscopic full-thickness rotator cuff repair. Eight randomized controlled trials met inclusion criteria and overall, the methodological quality was rated as high. Patient populations ranged from 28–88 and follow-ups ranged from 1–2 years. Significant differences were not seen in the retear rates, Constant scores and the University of California at Los Angeles (UCLA) scores. The meta-analysis did not support the use of PRP in arthroscopic repair of these tears. PRP did not increase the tendon healing rate or improve the UCLA and Constant shoulder scores.

Chahal et al. (2012) conducted a systematic review and meta-analysis to determine the efficacy of PRP when used in patients with full thickness rotator cuff tears who underwent arthroscopic repair. Two randomized and three nonrandomized studies met inclusion criteria (n=261). The primary outcome was the rotator cuff retear rate after arthroscopic repair. There was no significant difference in retear rates among patients including those who had large or at-risk tears regardless

of PRP treatment status or in patients who underwent a double-row rotator cuff repair. There were no statistically significant differences in the Constant Murley score; Simple Shoulder Test score; American Shoulder and Elbow Surgeons score; University of California, Los Angeles shoulder score; or Single Assessment Numeric Evaluation score. Due to the inclusion of nonrandomized trials, true meta-analysis could not be performed. Limitations of the studies included: the small patient populations; heterogeneity of repair techniques, differences in rotator cuff tear sizes and number of tendons involved, and the use of various PRP products.

Sinus Augmentation Procedures: Lemos et al. (2016) conducted a systematic review and meta-analysis to evaluate the effect of combining platelet-rich plasma (PRP) with bone grafts on bone formation and implant survival in maxillary augmentation (sinus lift). Seventeen studies were selected for qualitative analysis and 13 studies for quantitative analysis. Twelve studies were RCTs and five were prospective studies. A total of 369 patients and 621 maxillary sinus augmentations were evaluated. The results showed no significant difference in implant stability (p=0.32), marginal bone loss (p=0.31), alveolar bone height (p=0.10), implant survival (p=0.22) or bone formation (p = 0.81). PRP with bone graft had no influence on bone formation and implant survival in maxillary sinus augmentation.

Arora et al. (2010) conducted a systematic review of randomized controlled trials (n=5 trials; 5–39 patients per trial) of at least six months duration to evaluate the efficacy of APDGF when used with bone and bone substitutes in sinus augmentation procedures. Limitations noted by the authors included heterogeneity of the study designs, small patient populations and inconsistent single outcome variables for sinus elevation. A meta-analysis of the data was not possible due to the heterogeneity of the outcome variables. The authors concluded that "the disparity in the study design, surgical techniques, and different outcome assessment variables used makes it difficult to assess the practical benefit of using APDGF in sinus grafting procedures."

Tendon Disorders: Karjalainen et al. (2021) conducted a Cochrane review to assess the safety and efficacy of autologous whole blood or platelet-rich plasma (PRP) injections for the treatment of lateral elbow pain. Thirty randomized and two quasi-randomized trials met inclusion criteria (n=2337). Comparators included: placebo injection, glucocorticoid injection, autologous whole blood, dry needling, surgery, extracorporeal shock wave therapy, laser, and tennis elbow strap with exercise. Compared to placebo injection, no clinically significant improvement for mean pain or function was observed with autologous blood or PRP injection at three, six and twelve months. Following review of the evidence the authors concluded that no clear indications for using autologous blood or PRP injection for treatment of lateral elbow were supported.

Liu et al. (2019) conducted a meta-analysis of five randomized control trials (n=189) that compared the efficacy of PRP to placebo injections in conjunction with eccentric training as treatment for Achilles tendinopathy (AT). Outcome measurements included the Victorian Institute of Sports Assessment-Achilles (VISA-A), visual analog scale (VAS) or Achilles tendon thickness. No VISA-A differences were observed in the PRP and placebo groups after 12 weeks, 24 weeks, and one year. The VAS scores of the PRP and control groups at six and 24 weeks after treatment were not significantly different. Author noted limitations were the high level of heterogeneity, differing scoring standards and methods, different types of PRP used and limited patient information such as age and disease severity.

Filardo et al. (2018) conducted a systematic review of the literature on the effectiveness of PRP for the following tendon disorders: Achilles tendon (n=24 studies), patellar tendon (n=19 studies), rotator cuff tendons (n=32 studies), and lateral elbow tendons (n=29 studies). Randomized control trials, prospective comparative trials, retrospective comparative trials, retrospective cohort studies, cohort studies, case series and comparative studies were included. Patellar tendons and lateral elbow tendinopathy "seemed" to show benefit. However, the studies reported

heterogeneous findings as well as difficulties in determining indications, results and limitations of PRP treatment. Achilles tendon and rotator cuff pathology showed no beneficial effects. Due to the low quality of the studies, no conclusions could be drawn about the effectiveness of PRP for these conditions. Additional limitations of the studies include poor study designs (lack of control group) and small patient populations.

Franchini et al. (2018) conducted a systematic review and meta-analysis of 36 randomized control trials (n=2073) to evaluate the benefit of platelet-rich plasma (PRP) in non-surgical orthopedic procedures. Disorders included: lateral epicondylitis (n=11 studies), Achilles tendinopathy (n=4 studies), plantar fasciitis (n=14 studies), patellar tendinopathy (n=2 studies), and rotator cuff tendinopathy (n=3 studies). Studies investigating PRP use in surgical orthopedic procedures, platelet-poor plasma and autologous conditioned plasma were excluded. The comparators were local steroid injection (n=19 studies), saline injection (n=6 studies), autologous whole blood (n=4 studies), local anesthetic injection (n=3 studies), dry needling injection (n=3 studies), and other comparators (n=4 studies). Primary outcomes included pain as measured by standard validated pain scale (Visual Analogue Score [VAS]) and functional measurement by any standard validated scale (American Orthopedic Foot and Ankle Society Score [AOFAS] and Disabilities of the Arm, Shoulder and Hand [DASH]). Secondary outcomes included tendon thickness in millimeters (mm) evaluated by ultrasounds. Follow-ups ranged from three weeks to 24 months, however analysis was reported into two-time periods: short-term (within three months from the intervention) and medium-term (from four to six months). Due to the few number of studies reporting on results beyond six months a long term period (12 months) was not evaluated. No significant differences in the VAS scores were observed between the short-term or medium-term groups in elbow tendinopathy, plantar fasciitis, or other conditions. Short-term adverse events included post-injection pain, local pain, and initial worsening of pain. No adverse events were reported to have occurred in 22 studies. Author noted limitations include heterogeneity of the studies, short term follow-ups, and the lack of standardization for PRP production. The meta-analysis did not support the use of PRP as a conservative treatment in these orthopedic disorders.

Del Fabbro et al. (2015) conducted a systematic review of the literature to evaluate PRP for the treatment of patellar tendinopathy. Two randomized controlled trials, six nonrandomized controlled trials, two prospective case-series, three case reports and two retrospective reviews were included in the review. Follow-ups ranged from three weeks to 24 months. Study limitations included: small patient populations; short-term follow-ups; lack of a comparator; heterogeneity of PRP preparation, injection dosage and injection methods. Due to the limitations of the studies, a clear conclusion could not be made.

de Vos et al. (2014) conducted a systematic review of randomized controlled trials to evaluate the efficacy of PRP for the treatment of chronic lateral epicondylar tendinopathy. Included studies had outcome measures described in terms of pain and/or function. Six studies met inclusion criteria of which four were rated as high quality and two as low quality. Follow-ups ranged from 3–6 months. The method and composition of PRP varied from study to study. In five studies, there was no significant effect of PRP on outcomes when compared with corticosteroids, autologous whole blood, saline or needling with bupivacaine. PRP does not improve clinical outcomes on patients with this condition.

Andia et al. (2014) conducted a systematic review and meta-analysis of 13 studies (12 randomized controlled trials and one case series) (n=886) to evaluate outcomes of PRP for the treatment of painful tendinopathy. Data on 636 patients were included in the meta-analysis. Follow-ups ranged from one month to two years. The various studies investigated PRP for the treatment of upper limb tendinopathy (n=9 studies), chronic elbow tendinopathy (n=7 studies), supraspinatus tendinopathy (n=2 studies), lower limb tendinopathy (n=4 studies) and patellar tendinopathy (n=3 studies). Due to the heterogeneity of the studies including various

comparators, outcome measures, follow-up periods, number of injections and the diverse injection protocols, the effectiveness of PRP for the treatment of chronic tendinopathy was not proven.

de Vos et al. (2010) conducted a single-center, double-blind, randomized controlled trial (n=54) to determine if autologous platelet gel would improve the pain and functional outcomes of patients with chronic midportion Achilles tendinopathy. Randomization was stratified by activity level to the study group (n=27; mean age 49 years) or to the saline injection placebo group (n=27; mean age 50 years). Both groups were also involved in an eccentric exercise program. Stratification into one of two treatment groups was based on the ankle activity score that objectively quantified ankle-related activity into a high activity group or a low activity group. The primary outcome measure was the self-reported Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, which quantified pain and activity levels. The secondary outcome measures were subjective patient satisfaction, return to sports, and adherence of the eccentric exercises. At the 24-week follow-up, the VISA-A score improved significantly in both groups (study group 21.7 points; placebo group 20.5 points), but the difference between the two groups was not significant, and there were no significant differences in the secondary outcomes. The injection of platelet gel did not result in greater improvements than placebo. Two author-noted limitations of the study were the amount of platelets and the quantity of activated growth factors in the platelet gel injections were unknown and the use of eccentric exercises.

Tooth Extraction: Del Fabbro et al. (2017) conducted a systematic review of 33 comparative studies (n=911) to assess the effectiveness of autologous platelet concentrates (APCs) on alveolar bone preservation, soft tissue healing, and quality of life following tooth extraction. To be included, studies had to be controlled clinical trials or randomized clinical trials, have a parallel (n=9 studies) or split-mouth design (n=24 studies), and have a sample size of at least five patients per group or five patients with bilateral treatment. The APC could be used alone or in conjunction with another material (such as bone graft materials), but the only difference between the control and experimental groups had to be the use of APC. The primary outcome measures were complications, adverse events (e.g., alveolar osteitis, acutely infected or inflamed alveolus), postoperative discomfort and quality of life (e.g., self-reported postoperative pain on a visual analog scale, swelling). Results of meta-analysis following extraction included the following:

- soft tissue healing was statistically better for sockets treated with APC at the seventh postoperative day ($p<0.05$) (n=3 studies)
- probing depth in the distal aspect of the second mandibular molar was statistically significant in the APC group at the third postoperative month ($p<0.05$) (n=3 studies)
- no statistical differences were reported between APC and control group in alveolar osteitis, and acute inflammation and infection of alveolus ($p>0.05$, each) (n=10 studies and 11 studies, respectively)
- bone metabolism was similar for the APC and control groups ($p>0.05$) (n=2 studies)
- bone density was statistically better in the APC group at the first, third and sixth month follow-ups ($p<0.05$, each) (n=2 studies)
- percentage of new bone at the twelfth postoperative week was not statistically significant ($p>0.05$) (n=2 studies)

Seven studies reported a significant decrease in pain in the APC group and five studies reported no significant difference. Because of the heterogeneity of the studies and the lack of standard deviation reported, meta-analysis could not be performed for these outcomes. Limitations of the studies included: small patient populations (n=5-78); heterogeneity of the PRP preparation; high risk of bias (n=13 studies); heterogeneity among studies (e.g., follow-up duration, postsurgical timing of when outcomes were assessed); and conflicting outcomes. Additional studies are needed to support the effectiveness and clinical role of PRP following tooth extraction.

Total Knee Arthroplasty: Ma et al. (2017) conducted a systematic review and meta-analysis of six randomized controlled trials (n=529) to evaluate the efficacy of platelet rich plasma (PRP) in

preventing postoperative bleeding after total knee arthroplasty (TKA). Significant differences were reported in less total blood loss (p=0.0005) (n=355); lower hemoglobin (Hb) drop (p=0.008) (n=388) on the first postop day, and decreased length of hospital stay (p=0.002) (n=61) in the PRP groups. However, there were no significant differences with the use of PRP in drain volume, Hb level, transfusion rate, range of motion, WOMAC scores, and complications (p>0.5 for each) (n=94–486). The majority of the outcomes were analyzed based on the results of two studies. The administration of PRP did not increase the risk of postoperative complications. Limitations of the studies included: limited number of studies; small patient populations; variation of the doses of PRP; heterogeneity of clinical practice and methodology of the studies; and the different kinds of drainage and methods used to calculate the drainage volume. Due the heterogeneity of the studies no firm conclusions could be made regarding the effectiveness of PRP after TKA.

Li et al. (2017) conducted a systematic review and meta-analysis to evaluate the effects of PRP vs. placebo on range of motion (ROM) and pain control after total knee arthroplasty (TKA). Seven randomized controlled trials (RCTs), one case series and three retrospective reviews (n=1316) were included in the meta-analysis. The primary endpoint was range of motion (ROM). Western Ontario McMaster Universities Osteoarthritis Index Bellamy (WOMAC) was used to assess function and pain after TKA. Three months postoperative data from six studies (n=655) reported a significant improvement in ROM (p=0.000). Three studies (n=163) showed no statistical difference in WOMAC questionnaire scores at three months. There was no statistical difference in postoperative pain scores at 24 hours (p=0.077), 48 hours (p=0.760) and day seven (p=0.988) (three studies; n=217) or in the occurrence of infection (p=0.464) (six studies; n=511). Author-noted limitations of the studies include the small patient populations; short-term follow-up; unknown duration of follow-up in some studies; and heterogeneity of PRP preparation (obtaining, preparing and applying). Another limitation is the inclusion of non-RCTs with retrospective study designs. Large, well-designed randomized controlled trials are needed to establish the clinical effectiveness of PRP following TKA.

Kuang et al. (2016) conducted a systematic review and meta-analysis to evaluate the safety and effectiveness of platelet rich plasma (PRP) for postoperative bleeding and functional recovery following total knee arthroplasty. Twelve studies (n=1234), including five randomized controlled trials (RCTs) (n=262), non-randomized comparative studies and retrospective reviews met inclusion criteria. Compared to placebo, there was a significant decrease in pain scores on the visual analogue scale in the PRP group (n=397) (p=0.02 in RCTs; p<0.001 non-RCTs). There were no significant differences in drop in hemoglobin, knee society scores, Western Ontario McMaster osteoarthritis index, length of hospital stay, postoperative narcotic use, and range of motion. Author-noted limitations of the analysis included: RCTs only represented 262 patients; small-patient populations; short-term follow-up; and heterogeneity of study methodology (e.g., surgical techniques; age and gender) and quality of the studies. The authors concluded that PRP should not be used in TKA. The production of PRP is complicated and the use of PRP does not improve clinical outcomes.

Peerbooms et al. (2009) conducted a randomized controlled trial (n=102) to evaluate the efficacy of platelet gel in wound healing following total knee arthroplasty. Patients were randomly assigned to a control group who received no platelet gel (n=52) or to the study group treated with platelet gel (n=50). Due to insufficient data, the final analysis included 32 study group patients and 41 control group patients. There were no significant differences in the two groups based on comparison of postoperative wound scores, visual analog scale, Western Ontario MacMaster (WOMAC) questionnaire scores, knee function, use of analgesics, and the pre- and postoperative hemoglobin values. Results of the study indicated that the application of platelet gel "did not promote wound healing" and had "no effect on pain, knee function, or hemoglobin values."

Wound Healing: Hossam et al (2022) conducted a single center, prospective, randomized control trial to compare the safety and efficacy of autologous platelet rich plasma (PRP) versus standard care in the healing of non-ischemic diabetic foot ulcer (DFU). Eighty patients were randomized 1:1 to receive either local application of PRP injection in the healing edge and the floor of the targeted DFU (Group A) (n=40) or standard wound care (Group B) (n=40). Patients were included if they were classified as American Society of Anesthesiologists (ASA) type II, had either type 1 or type 2 diabetes, previously treated DFU of more than six months duration with no signs of infection and an intact pedal pulse with an arterial duplex showing a patent arterial tree with a peak systolic velocity > 60 cm/sec. Patients were excluded if they were ASA > II. Group A was comprised of 70% males with a mean age of 54.9 ± 2.37 years and Group B was 85% males with a mean age of 54.8 ± 3.9 years. Prepared PRP was applied to the DFU in Group A every two weeks for up to three times. Standard wound care for group B consisted of moist dressing with or without collagenase ointment. The primary outcomes measured were improvements in the total surface area (TSA) of the DFU and the rate of complete healing. The secondary outcomes were rate of wound infection and major limb amputation. Follow-up was 12 weeks. In the first five weeks, there was a statistically higher reduction in DFU size in Group A than in Group B. A 50% reduction in TSA of DFU occurred at 2.5 weeks in Group A compared to 4.5 weeks in Group B ($p<0.001$). Group A achieved a 90% reduction in TSA of DFU at five weeks versus seven weeks for Group B ($p<0.001$). Ninety-five percent of Group A had complete wound healing at week six compared to 77.8% at week nine for Group B ($p<0.01$). Adverse events included four superficial wound infection in Group A and eighteen superficial or deep wound infection and cellulitis in Group B ($p<0.001$). No major amputations occurred in Group A. Four major amputations in Group B. Author noted limitations included lack of standardization of PRP fabrication method and treatment usage. Additional study limitations included small patient population and short-term follow-up. Additional high-quality, well-designed randomized controlled trails with large patient populations are needed to verify the results of this analysis.

The outcomes of systematic reviews, randomized controlled trials, and case series investigating the efficacy of autologous platelet gel in the treatment of wounds including lower extremity ulcers, pressure ulcers, diabetic ulcers, and venous ulcers have been conflicting. Qu et al. (2021) conducted a systematic review and meta-analysis to evaluate the safety and effectiveness of autologous platelet-rich plasma (PRP) compared to any other wound care for the treatment of lower-extremity diabetic ulcers, lower-extremity venous ulcers, and pressure ulcers. A total of 25 studies met inclusion criteria (20 randomized control trials (RCT) and five observational studies): 14 studies of lower-extremity diabetic ulcers, nine lower-extremity venous ulcers, and two pressure ulcers in any location. Five studies were conducted in Africa, nine in Asia, nine in Europe, and two in the United States. Average age of patients with lower-extremity diabetic ulcers was 57.5 years, 37% female and 73% white. Lower-extremity venous ulcer patients' average age was 60.28 years with 47.7% female and average age for pressure ulcer patients was 57.6 years with 41% females. Primary outcomes measured included complete wound closure, time to complete wound closure, wound recurrence, hospitalization, amputation, and wound infection. Secondary outcomes measured included pain, wound size (area and depth), quality of life, and adverse events (AEs). Length of follow up for lower-extremity diabetic ulcers ranged from none to five months, lower-extremity venous ulcers was less than four weeks, and pressure ulcers was none to six months. Outcomes results in patients with lower-extremity diabetic ulcers (n=1083; 13 RCTs and one observational study) showed PRP was associated with more complete wound closure, shorter time to complete wound closure and wound depth reduction when compared with management without PRP. However, there was no significant difference on amputation, hospitalization, pain reduction, wound infection, and wound recurrence. In patients with lower-extremity venous ulcers (n=424; six RCTs and three observational studies), there was no significant difference in outcomes of complete wound closure, wound infection, wound recurrence, and wound area. The evidence was insufficient to estimate an effect on any outcome for pressure ulcers (one RCT and one observational study). There was no significant difference on total number

of adverse events (AE), number of withdrawals, and number of withdrawals due to AE in patients with lower-extremity diabetic ulcers, lower-extremity venous ulcers, and pressure ulcers. Author noted limitations of the study included lack of standard reporting of PRP preparation and dosage, lack of consistent approach for reporting and evaluation, small patient population and short term follow up. There is insufficient published evidence to estimate an effect of autologous PRP on wound healing in individuals with lower-extremity venous ulcers or pressure ulcers.

In a systematic review and meta-analysis of ten randomized controlled trials (n=442), Martinez-Zapata et al. (2016) assessed the outcomes of autologous platelet-rich plasma (PRP) for the treatment of chronic wounds. The range of participants per study was 10–117 (median 29). Follow-ups ranged from 8–40 weeks (median 12 weeks). Four studies included subjects with a range of chronic wounds (wounds caused by more than one etiology and wounds of several etiologies in the same trial), three studies included subjects with venous leg ulcers and three studies considered patients with diabetic foot ulcers. It is unclear if PRP improves healing of chronic wounds or venous ulcers compared to standard treatment with or without placebo. Two randomized controlled trials reported that PRP may increase healing in diabetic foot ulcers, but the evidence is of low quality. Limitations of the studies included: the heterogeneous, small patient populations; heterogeneity of PRP preparation; short-term follow-up; and risk of bias.

Carter et al. (2011) conducted a systematic review and meta-analysis to evaluate the use and clinical outcomes of APDGF for the treatment of cutaneous skin wounds compared to standard wound care. A total of 24 studies met inclusion criteria (i.e., three systematic reviews, 12 randomized controlled trials, two prospective cohort studies, three prospective comparative studies and four retrospective reviews). Three main types of wounds were treated: open chronic wounds, acute surgical wounds with primary closure and acute surgical wounds with secondary closure. Follow-ups ranged from 1 week to six months. A meta-analysis including four randomized controlled trials on chronic wound healing showed results in favor of platelet gel compared to saline gauze, saline gel or no treatment. A meta-analysis for acute wound primary closure was not undertaken because there were only two studies, and their outcome measures were incompatible. A meta-analysis of infection and pain for acute wounds showed that there was no significant difference in superficial infection rates using platelet gel compared to no topical treatment. There was also no significant difference in postoperative pain using platelet gel compared to saline spray or no topical treatment. Limitations of the studies included the heterogeneous patient populations, short-term follow-ups, heterogeneous outcome measures, conflicting results, various types of APDGF products and regimens, and multiple heterogeneous wound care regimens.

Kazakos et al. (2009) performed a randomized controlled trial to evaluate the benefit of APDGF in the treatment of soft tissue acute wounds (n=59). The wounds included open fracture of the tibia (n=37), closed fracture of the tibia with skin necrosis (n=9), wide friction burns in the femur (n=11), and one each acute injury of the Achilles tendon and open bimalleolar fracture. The study group (n=27) was treated with topical APDGF and the control group (n=32) was treated with conventional dressings. Follow-up ranged from 2.5–21 months (mean six months). The wound healing rate was significantly faster in the study group at weeks 1, 2 and 3 ($p=0.003$, $p<0.001$ and $p<0.001$, respectively). The mean time to plastic reconstruction in the APDGF group was significantly shorter (21.26 days) compared the control group (40.59 days) ($p<0.001$). The control group reported higher pain scores at the end of the second and third weeks. No adverse events were observed. Limitations of the study include the small, heterogeneous patient population.

In a prospective double-blind randomized controlled trial (n=44), Litmathe et al. (2009) evaluated the efficacy of APDGF for wound healing following cardiac surgery in high-risk patients (e.g., obesity, diabetes, smokers, peripheral vascular disease, heart failure). All patients underwent either isolated coronary artery bypass grafting (CABG) or combined coronary surgery and valve

replacement. APDGF was applied to the wound in the study group (n=22) but not in the control group (n=22). There were no statistically significant differences in sternal wound healing or wound healing at the vein harvesting sites. No beneficial effects of APDGF were noted in this study.

Driver et al. (2006) (n=40) reported that 68.4% of patients with nonhealing diabetic foot ulcers randomized to platelet gel healed compared to 42.9% in the control group. Two randomized controlled trials reported no significant difference in outcomes in treatment of chronic venous ulcers (Senet, et al., 2003; Stacey, et al., 2000) (n=15, 42, respectively) using platelet gel. Additional randomized controlled trials with larger sample sizes are indicated to establish the role of platelet gel in the treatment of lower extremity ulcers.

Multiple Indications/Products: Cohn et al. (2015) conducted a systematic review to evaluate PRP for the treatment of orthopedic conditions. A total of 12 randomized controlled trials and one controlled cohort study were included (four lateral epicondylitis, two chronic Achilles tendinopathy, two anterior cruciate ligament injury, and five rotator cuff injuries). Comparative controls included: corticosteroids, saline and no PRP. Follow-ups ranged from four weeks to 24 months. Four trials reported some benefit compared to controls, but eight studies reported no benefit of PRP vs. control. The authors noted that there were no standardized criteria that defined PRP regimens and treatments varied widely in terms of platelet count and concentration. The heterogeneity made it difficult to compare studies and draw conclusions regarding the efficacy of PRP in these orthopedic conditions.

Moraes et al. (2014) conducted a Cochrane review to assess the safety and efficacy of PRP for the treatment of musculoskeletal soft tissue injuries. Seventeen randomized and two quasi-randomized trials met inclusion criteria (n=1088). Comparators included: placebo, autologous whole blood, dry needling or no PRP. Clinical conditions included: shoulder impingement syndrome surgery (n=1 study); elbow epicondylitis (n=3 studies); anterior cruciate ligament (ACL) reconstruction (n=4 studies), ACL reconstruction (donor graft site application) (n=2 studies), patellar tendinopathy (n=1 study), Achilles tendinopathy (n=1 study), and acute Achilles rupture surgical repair (n=1 study). Sixteen of the studies were rated as having high or unclear risk of bias and the preparation of PRP varied, lacking standardization and quantification. Overall and for individual conditions, the evidence was insufficient to support the use of PRP for the treatment of these conditions.

Vannini et al. (2014) conducted a systematic review of the evidence to determine the clinical effectiveness of PRP for the treatment of foot and ankle pathologies. Four randomized controlled trials, one comparative study and 12 case series met inclusion criteria. Studies included treatment for Achilles tendon, plantar fasciitis, talar osteochondral lesions, total ankle replacement, and foot and ankle fusions. Following review of the evidence the authors concluded that no clear indications for using PRP in foot and ankle pathologies were supported. The studies were of poor methodology with heterogeneous PRP applications and conflicting outcomes.

Sheth et al. (2012) conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) (n=23) and prospective cohort series (n=10) to assess outcomes regarding decrease in pain and improved healing and function of autologous blood concentrates compared with control therapy in the treatment of orthopedic injuries (e.g., anterior cruciate ligament [ACL] reconstruction, spinal fusion, total knee arthroplasty, humeral epicondylitis, and Achilles tendinopathy). Patient populations ranged from 10–165 subjects per study with follow-ups ranging from two days to two years. Primary outcome measures to define healing and patient-reported quality of life measures included functional parameters (e.g., knee stability, tenderness threshold, visual analog scale [VAS], and Disabilities of the Arm, Shoulder and Hand [DASH] score) and radiographic imaging parameters (e.g., computed tomography, magnetic resonance imaging). Regarding functional outcome measures, six RCTs showed that platelet-rich plasma (PRP)

provided a significant functional benefit, fifteen studies demonstrated no difference between PRP and the control, and one study reported a significant benefit from the control. Three prospective cohort studies showed a significant functional benefit with PRP, six reported no difference and one study reported significant benefit with the control. There were no significant differences in VAS scores between the PRP groups and the control groups (p=0.10). Regarding imaging outcomes, there were no significant differences with regard to solid fusion (p=0.33) or the number of patients with low MRI signal intensity of the autograft used in ACL reconstruction between the platelet-rich plasma and control groups (p=0.19). Limitations of the studies included heterogeneity of the preparation (e.g., number of centrifugations, or use of anticoagulation or activating agents) and dosage (volume and number of applications) of the blood concentrates, study protocol, outcome measures and orthopedic indications. Additional limitations included the variability across all pooled outcomes in terms of follow-up due to a lack of consistent study time lines, and the potential for bias in the observational, nonrandomized data.

Martinez-Zapata et al. (2009) conducted a systematic review of the literature to evaluate the safety and efficacy of autologous platelet gel in tissue regeneration reported in randomized controlled trials (n=20). The trials that met inclusion criteria included oral and maxillofacial surgery (n=11), chronic skin ulcers (n=7), and surgical wounds (n=2). In four oral and maxillofacial surgery studies (n=153), which included patients suffering from chronic periodontitis, a meta-analysis was completed. A significant improvement was seen in the depth reduction of gingival recession following the use of platelet gel. The clinical attachment level of a subgroup of patients with more severe disease was better than the results in patients with incipient illness. Meta-analysis revealed no significant differences in patients treated with platelet gel for chronic skin ulcers or surgical wounds. Because of the poor quality of the studies (e.g., small patient populations, large confidence intervals, lack of reporting of adverse events, and heterogeneous outcome measures), well-designed large randomized controlled trials are needed to validate the finding of this analysis.

Technology Assessment
The Washington State Health Care Authority (WSHCA) (2016) conducted a technology assessment to evaluate the safety and efficacy of the use of PRP and/or autologous blood injection (ABI), for the treatment of musculoskeletal soft tissue injuries, tendinopathies, osteoarthritis, and low back pain in adults. The systematic review included 54 randomized controlled trials and eight prospective and retrospective cohort studies. PRP was evaluated for the treatment of elbow epicondylitis, Achilles tendinopathy, patellar tendinopathy, rotator cuff tendinosis and/or partial tears, plantar fasciitis, acute muscle injuries, acute Achilles tendon rupture, ankle sprain, osteochondral lesions of the talus, knee osteoarthritis, and hip and TMJ osteoarthritis. Comparators included: conservative therapy, hyaluronic acid (HA), steroid injections, saline injections, autologous blood injections, anesthetic injections, dry needling and exercise with and with/out transcutaneous nerve stimulation (TENS). Overall, no serious adverse events were reported. Limitations of the studies included the small patient populations, short-term follow-ups, conflicting outcomes, high risk of bias, and insufficient or low-quality of evidence. The authors concluded that although PRP is used for healing applications for these conditions, the safety and efficacy are not well established. There is a lack of standardization of PRP preparation and although the technology to obtain PRP is FDA-approved, PRP itself is currently not indicated for direct injection.

In 2023, WSHCA conducted a re-review to focus on symptomatic adults with knee or hip osteoarthritis (OA) who may be treated with PRP as a primary form of treatment or in conjunction with conservative therapies. The systematic review included 32 randomized controlled trials. Comparators for studies addressing knee OA included placebo, steroid, oral analgesics, PRP plus exercise versus (vs.) exercise alone, physical therapy, prolotherapy, fewer vs. greater number of PRP injections, and leukocyte-poor (LP)-PRP vs. leukocyte-rich (LR)-PRP. Limitations of the studies

included the small patient populations, short-term follow-ups, conflicting outcomes, high risk of bias, and insufficient or low-quality of evidence. The committee found the evidence sufficient to determine that use of PRP for knee and hip osteoarthritis to be unproven for being safer, more effective, or more cost-effective than comparators.

Professional Societies/Organizations

Agency for Healthcare Research and Quality (AHRQ): In a 2020 AHRQ technology assessment program, Qu et al. conducted a systematic review of 27 studies (22 randomized control trials [RCT] and five observational) on platelet-rich plasma for wound care in the Medicare population. The assessment was specifically evaluating the effectiveness of PRP in lower extremity diabetic ulcers (15 studies), lower extremity venous ulcers (11 studies), and pressure ulcers (2 studies). Follow up ranged from none to 11 months. Moderate strength of evidence (SOE) supported that PRP increases complete wound closure or healing with a low SOE supporting shortened healing time and reduction of wound size in lower extremity diabetic ulcers. There was insufficient evidence to estimate the effect of PRP on wound healing of lower extremity venous ulcers or pressure ulcers. There were no statistically significant difference in death, total adverse events or serious adverse events between PRP and management without PRP. Author noted limitations of the studies included inadequate description of wound care procedures and wound characteristics; heterogeneity of PRP formulation, concentration and volume; short term follow up; and lack of stratification by comorbidities and other patient characteristics including older adults. It was noted that Medicare eligible older adults were underrepresented in the included studies.

A 2017 AHRQ comparative effectiveness review on the treatment of osteoarthritis of the knee included five randomized controlled trials investigating the use of platelet rich plasma (PRP). The studies compared PRP to sham control or analgesic. The longest follow-up was six months. Low strength of evidence (four studies) supported a beneficial effect of PRP compared to saline injections on medium-term (12–26 weeks) pain and quality of life. However, the evidence was insufficient to draw conclusions regarding the effects of PRP on medium-term function and outcomes at shorter or longer times. Two studies reported on adverse events and results were conflicting. One study reported an increase in pain and stiffness with single injection which doubled with two injections. There was a high risk of bias in the studies.

American Academy of Orthopaedic Surgeons (AAOS): In the 2020 evidence-based guidelines on management of glenohumeral joint osteoarthritis (OA), the American Academy of Orthopedic Surgeons (AAOS) stated in the absence of reliable evidence, platelet rich plasma cannot be recommended for the treatment of glenohumeral osteoarthritis. AAOS stated better standardization and high-quality evidence from clinical trials is needed to provide evidence of the benefits and efficacy of biologics in glenohumeral OA.

Chu et al. (2019) reported on the 2018 AAOS/NIH U-13 collaborative symposium on optimizing clinical use of biologic treatments including platelet-rich plasma (PRP) and cell-based therapies in treating orthopaedic conditions. A consensus framework for improving and accelerating the clinical evaluation, use, and optimization of biologic therapies for musculoskeletal diseases was established. The recommendations are as follows:

- "Define terminology to clearly distinguish uncharacterized minimally manipulated autologous cell products from rigorously characterized, culture expanded and purified stem cell and progenitor cell populations.
- Standardize reporting requirements
- Establish registries for postmarket monitoring and quality assessments of biologic therapies
- Designate osteoarthritis as a serious medical condition
- Clarify, by disease state, a consensus approach for biological markers of interest and clinical trial design
- Establish the framework for a multicenter knee osteoarthritis clinical trial consortium

- Explore accelerated pathways for FDA approval of new drug applications for biologics to treat musculoskeletal conditions."

LaPrade et al. (2016) reported on the AAOS Research Symposium on the biologic treatment of orthopedic injuries. The use of platelet rich plasma (PRP) for the treatment of orthopedic injuries was reviewed. AAOS noted that there are several barriers to the clinical use of PRP for these indications. The barriers include lack of standardization of PRP preparation methodology procedures; lack of a widely adopted PRP classification system; inability to compare results between studies due to the heterogeneity of PRP preparations; effects of PRP formulation on clinical efficacy are not well understood; and protocols for PRP application (e.g., volume of PRP delivered, timing of injections) have not been established. The AAOS consensus statements on PRP included the following:

- "An accepted nomenclature and classification system that encompasses autologous blood/plasma products and categorizes preparations in sufficient detail is required to facilitate comparison across studies. Efforts should be made to involve academics, clinicians, and industry representatives in this process to encourage widespread adoption of the system.
- The influence of donor variance and processing and delivery factors on the composition of PRP must be established.
- A validated assay of the efficacy of PRP should be established for each clinical application.
- The relationship between PRP composition and efficacy should be established.
- Minimum standards of reporting for all studies (preclinical and clinical) evaluating PRP must be established to facilitate communication and the interpretation and synthesis of scientific investigations. These standards must include measured characteristics of the PRP and factors relating to the donor, processing, and delivery of the PRP.
- Specific formulations of PRP should be matched with specific pathologic indications.
- Methods for establishing proof of safety and efficacy of PRP should be determined. This process may require evidence of phenotype stability or viability for each indication".

In the 2013 evidence-based guidelines on osteoarthritis of the knee, the American Academy of Orthopedic Surgeons (AAOS) stated that they are unable to recommend for or against growth factor injections and/or platelet-rich plasma for the treatment of symptomatic osteoarthritis of the knee. AAOS stated that there is a lack of compelling evidence that has resulted in an unclear balance between benefits and potential harm. In 2021, AAOS updated their guidelines and downgraded their recommendation two levels to limited due to inconsistent evidence. They stated that it is extremely important for future research to include comprehensive platelet rich plasma characterization and description of platelet rich plasma preparation protocol.

U.S. Department of Veterans Affairs/Department of Defense (VA/DoD): The VA/DoD clinical practice guidelines on the non-surgical management of hip and knee osteoarthritis (OA) (2020) states there is insufficient evidence to recommend for or against platelet-rich plasma injections for the treatment of osteoarthritis of the hip or knee.

Wound Healing Society: The Wound Healing Society guidelines on diabetic foot ulcer treatment stated that platelet rich plasma has not demonstrated an increase in the healing rate and number of wounds that healed. One systematic review and four randomized controlled trials suggested no improved wound healing effects (Lavery, et al., 2016).

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Blood-Derived Products for Chronic Non-Healing Wounds (270.3)	4/13/2021
LCD	CGS Administrators, LLC	Wound Application of Cellular and/or Tissue Based Products (CTPs), Lower Extremities (L36690)	9/5/2024

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed

HCPCS Codes	Description
G0460	Autologous platelet rich plasma for nondiabetic chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment

***Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.**

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Revision Details

Type of Revision	Summary of Changes	Date

Annual review	• No clinical policy statement changes.	10/15/2024
Annual review	• Updated to new template and formatting standards • No changes to criteria	10/15/2023

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