

## Clinical Review Criteria

### Platelet Rich Plasma

- Autologous Platelet Derived Wound Healing Factors for Non-Healing Cutaneous Wounds (Autogel, Procuren, SafeBlood)
- Injections for the Treatment of Non-Healing Fractures and Tendinopathy
- Platelet Rich Plasma for Knee Osteoarthritis
- Platelet Rich Plasma for Plantar Fasciitis

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## Criteria

### For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	<a href="#">Blood-Derived Products for Chronic Non-Healing Wounds (270.3)</a>
Local Coverage Determinations (LCD)	<a href="#">Platelet Rich Plasma Injections for Non-Wound Injections (L39060)</a>
Local Coverage Article	<a href="#">Billing and Coding: Platelet Rich Plasma Injections for Non-Wound Injections (A58790)</a>

### For Non-Medicare Members

Kaiser Permanente has elected to use the Platelet Rich Plasma (A-0630) MCG\* for medical necessity determinations. The use of platelet rich plasma is not covered for any indications by MCG guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.

\***The MCG\* are proprietary and cannot be published and/or distributed.** However, on an individual member basis, Kaiser Permanente can share a copy of the specific criteria document used to make a utilization management decision. If one of your patients is being reviewed using these criteria, you may request a copy of the criteria by calling the Kaiser Permanente Clinical Review staff at 1-800-289-1363 or access the MCG Guideline Index using the link provided above.

### If requesting review for this service, please send the following documentation:

- Last 6 months of clinical notes from requesting provider &/or specialist (Orthopedics, sports medicine, physiatrist)

Service	Criteria
<ul style="list-style-type: none"> <li>• Platelet Rich Plasma for Plantar Fasciitis</li> <li>• Platelet Rich Plasma for Knee Osteoarthritis</li> </ul>	There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

## Background

Platelets are rich in growth factors that play an essential role in tissue healing. Platelet-rich plasma (also known as platelet-enriched plasma, platelet-rich concentrate, autogenous platelet gel, or platelet releasate) is used to enhance bone and soft tissue healing by placing supraphysiologic concentrations of autologous platelets at the site of tissue damage. Platelet-rich plasma has been tried for a wide variety of clinical applications, including orthopedics, otolaryngology, and oral and maxillofacial, plastic, gynecologic, cardiac, and general surgeries. Platelet-rich plasma can be prepared from blood collected in the immediate pretreatment period using standard cell separators and salvage devices. After activation, platelet-rich plasma is usually administered by either direct application or injection into the affected area. There is little consensus regarding the production and characterization of platelet-rich plasma.

### **Bone Fracture Healing (GEM 21STM)**

Bone fracture healing is a biological process that involves both local and systemic acute phase reactants. The physiological events occurring at the site of injury include hematoma formation, recruitment and transformation of mesenchymal cells, induction of angiogenesis, and the production and remodeling of the extracellular matrix. Radiographic healing of a bone fracture is normally achieved in 4-13 months depending on type and location of the fracture. The rate of bone union also depends on several other factors as patient's health, compliance, nutritional status, stability of the fracture and others. Disruption of any of these factors would lead to delayed or non-union of the fracture. It was reported that approximately 10% of the bone fractures in the US are complicated by impaired healing, which has a high impact on the quality of life and burden of health costs. Several compounds and technologies have been and are being developed to enhance fracture healing and accelerate repair. These include prostaglandins, gene therapy, growth hormone, parathyroid hormone, and growth factors. Among the growth factors studied are the bone morphologic proteins, transforming growth factor B, vascular endothelial growth factor, and platelet derived growth factor (PDGF) (Axelrad 2007, Hollinger 2008).

In vitro and animal studies indicate that PDGF has the potential of accelerating the bone healing process. The experimental studies showed that PDGF receptors increase in osteoblasts as they mature, but that the response varies inversely to the number of receptors. This indicates that there is an optimal concentration and time during bone regeneration to deliver the PDGF in order to be effective (Axelrad 2007).

The GEM 21STM a device for bone grafting material containing a therapeutic tri- calcium phosphate or PDGF was approved by the FDA for periodontally related defects in November 2005.

### **Tendinopathy**

Painful tendon disorders are common among professional and recreational athletes, and also among sedentary individuals. It is estimated that 30-50% of all sports-related injuries are painful tendon injuries. These injuries are classified as tendinitis during the acute inflammatory process and tendinosis when healing becomes chronically impaired. Clinicians are increasingly using the term tendinopathy to refer to tendon disorders without implying a specific pathology, and chronic tendinopathy for cases that are refractory to conventional treatment. If the triad of pain, swelling, and reduced load bearing capacity are present, then the correct term for the diagnosis is tendinopathy, which is a clinical and not a histopathological diagnosis. The pathophysiology of chronic tendinopathy involves the presence of degenerative changes, including disorganized collagen fibers, increased granular substance and neovascularity. Tendinopathy leads to reduction in activity levels and sometimes cessation of all sports activities. The three most common sites affected are the Achilles, patellar, and rotator cuff tendons. Other tendons affected include those around the elbow (medial and lateral epicondylitis), wrist extensors, supraspinatus tendon, and plantar fasciopathy (Maffulli 2003, de Vos 2010, Creaney 2011, Mautner 2013).

Tendinopathies are difficult to treat, and the healing response differs between load-bearing tendons such as the patellar and Achilles tendons, and non-load-bearing tendons such as the wrist extensors. Traditionally tendinopathy have been treated with oral and injectable anti-inflammatory medications, bracing, physical therapy, and heavy load eccentric training programs. The rationale for anti-inflammatory therapies for tendinopathy has been questioned recently, and currently heavy load eccentric training programs are being used by many practitioners as a first-line therapy. These training programs require high levels of patient motivation and are not always successful. When conservative therapies fail, surgery may be recommended (Krogh 2013, Mautner 2013).

Recently, research focused on the use of complex growth factor preparations derived from the patient's blood to drive the body's own tissue healing mechanisms. The use of autologous growth factors is thought to lead to tendon repair through collagen regeneration and stimulation of angiogenesis. This concept of delivering humoral mediators to promote normal tendon healing was first reported in 2003. Platelets are the major player; in addition to their central role in the clotting cascade, they are involved in the normal healing response. The exact mechanism by which platelets promote tendon healing is unclear; however, it is theorized that the growth factors and cytokines contained in the platelets speed tissue regeneration and healing. Platelets contain alpha granules and dense granules, which when stimulated release platelet-derived growth factor, transforming growth factor (TGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF) I and II, and fibroblast growth factor. These factors play an important role in cellular proliferation, chemotaxis, cellular differentiation, extracellular matrix production, and angiogenesis. The dense granules contain adenosine, serotonin, histamine, and calcium, which play a role in tissue modulation and regeneration (Foster 2009, Maffulli 2010, Thanasis 2011).

There is no standard technique for harvesting growth factors for administration, and several preparations are described in the literature as the autologous blood injection (ABI), and platelet rich plasma (PRP). PRP is defined as autologous blood with concentration of platelets higher than its physiologic concentration found in healthy whole blood. PRP contains a 2- to 8-fold increase in platelets concentration (150,000-350,000 $\mu$ L in blood and at least 1,000,000 $\mu$ L in PRP), and 1- to 25-fold growth factor concentration depending on which factor is examined. PRP is commonly prepared in the laboratory, operating suite, outpatient sports medicine clinic, or at a radiology setting. It begins with venipuncture and collection of autologous whole blood from the patient into a syringe containing anticoagulant at the point of care. The collected blood is then centrifuged in a tabletop centrifuge machine. This separates the whole blood into three layers: red blood cells, platelet poor plasma, and platelet concentrate that contains white blood cells. Typically, the red blood cells are discarded after the first spin, and a second spin yields a more concentrated platelet layer. The PRP amount is approximately 10% of the volume of whole blood collected. PRP can be categorized according to its leukocyte content into leukocyte depleted pure PRP (P-PRP) in which leukocytes are purposely eliminated, or PRP that contains a high concentration of leukocytes (L-PRP). Once prepared the PRP is maintained in a sterile environment and used immediately for the procedure (Foster 2009, de Vos 2010, Maffulli 2010, Creaney 2011, Gosens 2011, Thanasis 2011, Lee 2013).

Earlier use of PRP included its application in maxillofacial surgery, plastic surgery, cardiac bypass surgery, and orthopedics. The positive effects observed in these surgical applications have stimulated its use in sports medicine outpatient clinic setting. The use of PRP is accepted by the patients because it is produced from their own blood and the risk of adverse effects is minimal. Different types of centrifuge machines used vary in their ability to separate red blood cells from platelets which affects the platelet concentration, separating leukocytes from platelets, or shearing platelets during the centrifuge process that may cause premature platelet activation and degranulation. The variation in centrifuge machines and PRP preparation techniques cannot provide a consistently similar or standardized final product. There is also no clear definition for the optimal dose of PRP or the number of injections needed. Most physicians perform one injection, although sometimes PRP injections are given as a series of injections over several weeks. Some physicians may choose to add an activating agent (thrombin or calcium chloride) to PRP before its injection, while others only inject just the platelets based on the assumption that they can be slowly activated with the exposure to thrombin or tendon collagen. Potential risks related to PRP injection include infection, hemorrhage, and soft tissue injury. Concerns have also been raised about the potential harms of PRP in delaying tissue remodeling, excessive growth, and excessive scarring (de Vos 2011, Lee 2013),

To date, platelet rich plasma for the treatment of tendinopathy has not received FDA approval. The FDA has cleared several devices used in the preparation of PRP and has standards for the procedure of preparation of PRP.

## Medical Technology Assessment Committee (MTAC)

### ***Autologous Platelet Derived Wound Healing Factors for Non-Healing Cutaneous Wounds (Procuren)***

#### BACKGROUND

Wound healing is a dynamic process that involves a complex interaction of several cellular and biochemical events. Tissue repair begins with a clot formation and platelet degranulation which release the growth factors necessary for wound repair. Generally, the process of normal healing takes few days to 2 weeks and involves three phases that may overlap in time: 1. inflammatory phase, 2. proliferative phase, and 3. remodeling phase. If any of these phases is compromised, healing will be delayed. Treatment of chronic non-healing

cutaneous wounds has challenged health care providers for generations, and various strategies including devices, biologics and drug have been used to accelerate the healing process. These agents are designed to affect one of processes involved in healing (Robson 1999). Advances in biology of wound healing, showed that macrophages and platelets are the chief regulatory cells in the repair process. Platelets are known for their role in haemostasis where they help prevent blood loss at site of vascular injury. They adhere, aggregate, and form a procoagulant surface leading to thrombin generation and fibrin formation. Activated platelets release potent locally acting growth factors substances that initiate division and migration of fibroblasts and formation of new capillaries promoting wound healing (Knighton 1986, Fu 2005). Becaplermin, a topical treatment with platelet derived growth factor as its active ingredient was approved by the FDA in 1997 to treat diabetic foot and leg ulcers that extend into the subcutaneous tissue or beyond and have adequate blood supply. Platelet derived growth factor (Procuren) for the treatment of non-healing cutaneous wounds was reviewed by MTAC in February 1999, and failed MTAC evaluation criteria due to the lack of scientific evidence to determine its safety and efficacy. It is being re-reviewed based on requests for coverage from Eastern WA. **Bone Fracture Healing (GEM 21STM)** Bone fracture healing is a biological process that involves both local and systemic acute phase reactants. The physiological events occurring at the site of injury include hematoma formation, recruitment and transformation of mesenchymal cells, induction of angiogenesis, and the production and remodeling of the extracellular matrix. Radiographic healing of a bone fracture is normally achieved in 4-13 months depending on type and location of the fracture. The rate of bone union also depends on several other factors as patient's health, compliance, nutritional status, stability of the fracture and others. Disruption of any of these factors would lead to delayed or non-union of the fracture. It was reported that approximately 10% of the bone fractures in the US are complicated by impaired healing, which has a high impact on the quality of life and burden of health costs. Several compounds and technologies have been, and are being developed to enhance fracture healing and accelerate repair. These include prostaglandins, gene therapy, growth hormone, parathyroid hormone, and growth factors. Among the growth factors studied are the bone morphologic proteins, transforming growth factor B, vascular endothelial growth factor, and platelet derived growth factor (PDGF) (Axelrad 2007, Hollinger 2008). In vitro and animal studies indicate that PDGF has the potential of accelerating the bone healing process. The experimental studies showed that PDGF receptors increase in osteoblasts as they mature, but that the response varies inversely to the number of receptors. This indicates that there is an optimal concentration and time during bone regeneration to deliver the PDGF in order to be effective (Axelrad 2007). The GEM 21STM a device for bone grafting material containing a therapeutic tri- calcium phosphate or PDGF was approved by the FDA for periodontally related defects in November 2005.

**Tendinopathy** Tendinopathy is a general term that is used to describe a tendon injury. It is characterized by pain, stiffness, and loss of strength in the affected area. Treatments for tendinopathy include, but are not limited to: rest, anti-inflammatory medication, analgesia, orthotics, physical therapy, and local steroid injections. Another more recent technology that has been proposed for the treatment of tendinopathy is platelet rich plasma injections into the ailing tendon (Kampa 2010). Platelets are small nonnucleated blood cells that are involved in wound healing. The exact mechanism by which platelet rich plasma promotes tendon healing is unclear; however, it is thought that the growth factors and cytokines contained in the platelets speed tissue regeneration and healing. Platelets contain alpha granules and dense granules, which when stimulated release growth factors and cytokines. The alpha granules release: platelet-derived growth factor, transforming growth factor-beta, vascular endothelial growth factor, epidermal growth factor, insulin-like growth factor I and II, and fibroblast growth factor. These factors play an important role in cellular proliferation, chemotaxis, cellular differentiation, extracellular matrix production, and angiogenesis. The dense granules contain adenosine, serotonin, histamine, and calcium, which play a role in tissue modulation and regeneration (Foster 2009, Maffulli 2010). Platelet rich plasma is derived from anti-coagulated autologous whole blood, which is centrifuged to concentrate platelets in plasma. Normal platelet counts in the blood range from 150,000-350,000  $\mu$ L. The goal of the devices used to create platelet rich plasma is to raise the concentration to at least one million platelets per  $\mu$ L. After separation, the platelet rich plasma must be clotted to allow for delivery to the desired site. This clotting leads to platelet activation, resulting in the release of growth factors and cytokines. Bovine thrombin, calcium chloride, and type I collagen are different agents used to stimulate platelet activation (clotting) (Foster 2009). One of the advantages of this approach is that because the platelet rich plasma is derived from the patient's own blood there is a low chance of rejection. However, the optimal dose range has not been defined. The injection of platelet rich plasma is a procedure and therefore not regulated by the FDA. However, several devices used in the preparation of platelet rich plasma have received FDA approved.

**Evidence Conclusion:** The published evidence on the effect of Procuren for treating non-healing cutaneous wounds consists of two small randomized controlled trials, one of which reports improvements in wound healing for Procuren as compared to placebo and the other trial reports worse outcomes with Procuren. The available evidence does not allow any conclusion about the effects of Procuren on non-healing cutaneous wounds.

**Articles:** Knighton DR, et al. Stimulation of repair in chronic, nonhealing cutaneous ulcers using platelet-derived wound healing formula. *Surgery, Gyn, Obstet* 1990;170:56-60.

There is insufficient scientific evidence that Procuren is medically effective and therefore does not meet *Kaiser Permanente Medical Technology Assessment Criteria*.

## **06/17/2003: MTAC REVIEW**

### **Autologous Platelet Derived Wound Healing Factors in the treatment of Tendinopathy**

**Evidence Conclusion:** *Achilles tendinopathy*\_De Vos and colleagues' study (2010), reviewed by MTAC earlier in 2010, is a double-blind, placebo-controlled, randomized, controlled trial that compared the effect of injecting platelet rich plasma (PRP) versus isotonic saline (placebo) in 54 patients with chronic midportion Achilles tendinopathy. After PRP injection, patients in the two study groups underwent standardized rehabilitation program including a daily eccentric exercise program for 12 weeks. The primary outcome was pain and activity level as measured with the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire. The first publication of the trial (de Vos et al, 2010) reported on the clinical outcomes at 24 weeks, and the second (de Vos, et al 2011) reported on the effect of PRP on ultrasonographic tendon structure and neovascularization at 24 weeks. This was followed by another report (de Jonge, et al 2011) on the one-year clinical and ultrasonographic outcomes for the same group of patients (evidence table 1). The results of the trial showed significant improvement in pain and activity level among patients in both the PRP group and the placebo group at 24 weeks and at one year compared to baseline values. There were no statistically significant differences for these outcomes between the two study groups. The 24-weeks follow-up also showed a significant increase in the neovascularization scores among patients in the two treatment groups when compared to baseline, but with no between-group differences at any point of time (6,12,24 weeks, or 1 year). The one-year follow-up also showed that the ultrasonographic tendon structure improved significantly in both groups with no significant difference between them. Overall, the results of the trial indicate that adding PRP injection therapy to eccentric exercises for patients with midportion Achilles tendinopathy was not superior to the addition of saline injection as regards clinical outcomes, tendon structure, or neovascularization. The trial did not compare PRP head to head with eccentric exercises, nor did it include a comparison group that received PRP without exercises, which makes it hard to determine the effect of PRP used alone, and whether the eccentric exercises have a dominating positive effect that overshadows the benefit of PRP therapy. In addition, saline injection in the tendon may have had more than a placebo effect as either or both the trauma of introducing a needle (needling) into the tendon, and the volume increase due to saline injection into the tendon may initiate a healing response as noted by several investigators. *Lateral epicondylitis (tennis elbow)*

The few published RCTs on the use of PRP injections for the treatment of lateral epicondylitis, had their limitations and showed conflicting results. In these trials PRP was compared to the injection of corticosteroids, whole autologous blood, or saline. No comparisons were made to standardized eccentric muscle strengthening exercises used alone or to watchful waiting. Patients were included in the trials if they had symptoms of epicondylitis for at least 3 or 6 months (depending on study), not allowing for the natural healing of the condition (Peerbooms 2010 indicated that the "Natural history of lateral epicondylitis predominantly results in healed patients [80%] in one year). The studies used different definitions for success as well as different tools and questionnaires for measuring the outcomes. All, except for one trial, did not use ultrasonography to evaluate the effect of PRP therapy on tissue healing. Peerbooms (2010), Gosens (2011) and colleagues (Evidence table 2) conducted a double-blind RCT to compare the efficacy of a platelet rich plasma injection versus corticosteroid injection for the treatment of lateral epicondylitis in 100 patients who had failed non-operative treatment. Patients in the two treatment groups also participated in an eccentric exercise program. The primary outcome of the trial was the difference in successful outcomes (25% reduction in the pain according to VAS score or disabilities of the arm, shoulder, and hand according to DASH Outcome Measure), without a re-intervention after one year and 2 years of follow-up. The one-year follow-up results of the trial showed a statistically significant greater improvement in pain and function in the PRP group versus the corticosteroid group. Patients in the corticosteroid group experienced a decline in function after an initial short-term improvement. The 2-year follow-up results of the trial (Gosens et al 2011) showed that the mean improvement in the pain and function scores continued to favor the PRP group. The study had valid design and analysis, however, PRP was compared to corticosteroid, the use of which in tendinopathy is currently controversial as is known to have a short-term pain relief effect and may lead to permanent adverse changes in the tendon (according to the authors). The study did not include a placebo arm to determine whether the improvement observed with the PRP was due to the treatment or to the natural course of the lateral epicondylitis. The authors indicated that the natural history of lateral epicondylitis usually results in

healed patients (80%) within 1 year, but they included patients with lateral epicondylitis for as short as 6 months. Ultrasound evaluation was not used to determine the effect of PRP on tissue healing. There was a discrepancy in the figures and numbers presented in the two published articles reporting on the 1-year and 2-year follow-up results. [Creaney and colleagues \(2011\)](#) compared the injection of blood versus PRP in 150 patients who had elbow tendinopathy for at least 6 months and had failed conservative therapy including physical therapy exercises (stretches and eccentric loading). The authors did not clearly indicate whether all patients had undergone a standardized muscle strengthening eccentric exercises. Study participants were randomly assigned to receive 2 injections (one month apart) of either PRP or autologous blood injection (ABI). The primary outcome was improvement in patient-related tennis elbow-evaluation (PRTEE) score at 6 months (PRTEE is a 0- 100 composite scale that measures pain and physical function). 20 patients (13%) were lost to follow-up at six months. Analysis of the results of the remaining 130 patients (authors considered it ITT analysis) showed a higher but statistically insignificant success rate in the ABI group (72%) vs. the PRP group (66%). Success was defined as an improvement in the PRTEE score of 25 points at 6 months. The study was randomized and controlled, but it compared two forms of growth factor preparations and did not include a placebo or sham therapy group that did not undergo tendon penetration, nor did it compare growth factor injection versus a standardized program of eccentric muscle exercises that are known to have a beneficial effect. The needling effect or placebo effect of injection cannot be ruled out. The investigators were not blinded, and no ultrasound evaluation was used to determine the effect of PRP on tissue healing. In addition, the trial does not allow studying the natural course of lateral epicondylitis, and its short follow-up duration does not allow studying the long-term effects or harms associated with the therapy. In a small trial [Thanasas and colleagues \(2011\)](#) also compared PRP versus autologous whole blood injection (ABI) for the treatment of lateral epicondylitis. In this trial the injection of either 3 mL PRP or 3 mL whole blood was given only once under ultrasound guidance and followed by a standardized eccentric muscle strengthening. The trial had only six months of follow-up and the primary outcome was improvement in pain (using VAS score) and function (using the Liverpool elbow score). The results of the study showed that PRP was more effective than ABI in reducing pain at 6 weeks, but not at 3 or 6 months. There was no significant difference between the two treatment groups in the functional score of Liverpool. Similar to Creaney and colleagues' trial, the study does not determine whether any benefit observed was due to the injected substance, needling procedure, or the natural course of the disease. The authors of a [network meta-analysis \(Krogh 2012\)](#) of RCTs that assessed the comparative effectiveness and safety of injection therapies in patients with lateral epicondylitis, concluded that autologous blood products either as whole blood or PRP may have benefits over placebo, only one trial (Peerbooms 2010) was considered to be at low risk of bias, and that further high quality RCTs are needed to evaluate these therapies before any recommendation can be made. A more recent double-blind RCT ([Krogh et al 2013, evidence table 3](#)) compared the effect of a single injection of PRP to the injection of corticosteroid or saline for the treatment of lateral epicondylitis in 60 patients. The primary outcome was pain reduction at 3 months (a change from 12 months in the initial protocol due to the high dropout rate resulting from unsatisfactory pain reduction). The study had other limitations including but not limited to the inclusion of patients who were not naive to corticosteroids (58% of the participants had received corticosteroid therapy, and 35% had received more than one injection at study entry). The study also included patients with lateral epicondylitis symptoms for as short as 3.8 months (not allowing for natural healing of the condition), and as long as 232 months and combined them in the analysis. Saline injection may not have been the appropriate placebo as it was applied through 5-7 tendon perforations. Needling and/or volume increase due to saline injection could initiate a healing process. It is reported that needling, also known as microtenotomy, involves treating a chronic tendon injury, by attempting to change a chronic injury to an acute lesion that may have greater healing potential. The disruption of the tendinosis or scar tissue by needling and consequent bleeding is thought to release tissue growth factors that stimulate a healing response (Rha et al 2012). The authors of the trial also indicated that they did not test the actual platelet content but relied on the manufacturer's description. Overall, the results of the trial show that the effect of PRP or glucocorticoids on pain was not superior to saline injection, and that steroid injection was superior to PRP and saline in reducing color Doppler activity and tendon thickness.

#### *Rotator cuff*

A published RCT (Rha et al, 2012) compared the therapeutic effect of platelet rich plasma with dry needling in 38 patients with rotator cuff disease. The trial was randomized and blinded, but had a small size, included patients with tendon tear or tendinosis, had a short follow-up of six months, and a 25% dropout rate. The study participants were randomized to receive either two PRP injections or two dry needling procedures at 4-week intervals. The primary outcome measure was Shoulder Pain and Disability Index (SPADI). This was measured at baseline, two weeks after the first injection, immediately before the second injection, two weeks after the second injection, and at the 3- and 6-month follow-up visits. The authors did not indicate whether the analysis performed was intention to treat or completer analysis. Overall, the results indicated that patients in the two treatment groups showed a significant reduction in the Shoulder Pain and Disability Index and improvement of range of motion during follow-up. The PRP injections provided more symptomatic relief and functional improvement than dry needling at six months, but there was no difference in range of motion improvement between the two groups.

These results should be interpreted with caution due to the limitations of the trial. *Plantar Fasciitis* Aksahin and colleagues (2012) compared the effect of corticosteroids and platelet rich plasma in 60 patients diagnosed with plantar fasciitis who had failed conservative therapy. The trial was not randomized which is a potential source of selection bias. The first 30 consecutive patients received corticosteroid injections and the second 30 patients received PRP injections. All participants were followed up for 6 months and the primary outcome was improvement in the mean VAS heal pain scores. The results showed significant improvement in each of the two groups compared to baseline, but there were no significant differences between the two groups. *Conclusion:* There is some evidence that the adding PRP injection therapy to eccentric exercises for patients with Achilles tendinopathy is **not** more effective than injecting the tendon with saline also in addition to eccentric exercises. There is insufficient evidence to determine that PRP injections given alone are effective at reducing pain and improving function in patients with lateral epicondylitis. There is insufficient evidence to determine the effect of PRP injections on rotator cuff disease, plantar fasciitis or other tendinopathies. The published studies do not allow making any conclusion on whether the effect of PRP injections is due to the therapy or due to healing initiated with needling of the tendons. There is insufficient evidence to determine the effect of PRP on tissue healing. There is insufficient evidence to determine whether there is an optimal PRP dose, concentration, or number and interval of injection that would potentially reduce pain and improve function in patients with tendinopathy. There are variations among the studies as regards the preparation of PRP products, platelet concentration, presence of white blood cells, and number of injections uses, which would limit generalization of the negative or positive results of the trials published to date. Definition of treatment success varied between studies. Larger RCTs with longer follow-up duration are needed to determine the efficacy and safety of PRP in tendinopathy.

**Articles:** The literature search for studies published after the last MTAC review of platelet rich plasma for the treatment of tendinopathy revealed 4 randomized controlled studies on PRP injections for lateral elbow epicondylitis, one for Achilles tendon, one for rotator cuff, and one for plantar fasciitis, as well as a number of case series with no control groups. A meta-analysis of studies on the use of platelets in the treatment of Achilles tendon injuries, and another network meta-analysis on the comparative effectiveness of injection therapies were also identified by the search. The meta-analyses were not selected for critical appraisal as the one that examined the role of platelets in the treatment of Achilles tendon injuries also included models and trials on the use of the therapy for tendon rupture repairs. The network meta-analysis on injection therapies included all types of injection therapy including PRP. The individual trails on PRP in either meta-analysis was reviewed separately. The following RCTs were critically appraised: *Achilles Tendinopathy* de Vos RJ, Weir A, van Schie HTM, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy. *JAMA* 2010; 303:144-149. de Vos, Weir A, Tol JL, et al. No effects of PRP on ultrasonographic tendon structure and neovascularization in chronic midportion Achilles tendinopathy. *Br J Sports Med* 2011; 45:387-392. [See Evidence Table](#) De Jonge S, de Vos RJ, Weir A, et al. One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial. *Am J Sports Med* 2011; 39:1623-1629. *Lateral Epicondylitis* Gosens T, Peerbooms JC, van Laar W, et al. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. *Am J Sports Med* 2011; 39:1200-1208. Peerbooms JC, Sluimer J, Bruijn DJ, and Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial. *Am J Sports Med* 2010; 38:255-262. [See Evidence Table](#). Krogh TP, Fredberg U, Stengaard-Pederson K, et al. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial. *Am J Sports Med* 2013; 41:625-635. [Peerbooms \(2010\), Gosens \(2011\) and colleagues Krogh et al 2013, \[See Evidence Table\]\(#\)](#)

The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Tendinopathy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*

## **Autologous Platelet Derived Wound Healing Factors**

### **06/04/2008: MTAC REVIEW**

**Evidence Conclusion:** *Wound Healing (Procuren)* The reviewer's conclusion in the previous MTAC report of 1999 was, "The published evidence on the effect of Procuren™ for treating non-healing cutaneous wounds consists of two small randomized controlled trials, one of which reports improvements in wound healing for Procuren™ as compared to placebo, and the other trial reports worse outcomes with Procuren™. The available evidence does not allow any conclusion about the effects of Procuren™ on non-healing cutaneous wounds." The literature search for the current review did not reveal any additional evidence that would determine the efficacy and safety of platelet derived growth factor for the treatment of non-healing cutaneous wounds.

*Bone Fracture Healing (GEM 21STM)* There insufficient published evidence to determine the efficacy and safety of autologous platelet derived wound healing factors for the treatment of non-healing fractures.

**Articles:** *Wound Healing* The search yielded around 100 articles. Many were review articles or publications not related to the current review. No meta-analyses of empirical studies, randomized or non-randomized controlled

studies, published after the last review, were identified. *Bone Fracture Healing* The literature search did not reveal any empirical studies on the use of PDGF for bone fractures. The published studies were all related to the use of PDGF for of dental implants, periodontal wounds, defects, or bone turnover during periodontal repair. None was selected for critical appraisal.

The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Non-Healing Wounds does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Non-Healing Fractures does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

### ***Autologous Platelet Derived Wound Healing Factors in the treatment of Tendinopathy***

#### **02/14/2011: MTAC REVIEW**

**Evidence Conclusion:** *Achilles tendinopathy* A recent double-blind, placebo-controlled RCT evaluated the effects of adding a platelet rich plasma (PRP) injection to an eccentric exercise program in 54 patients with chronic midportion Achilles tendinopathy. The primary outcome measures were pain and activity level, measured using the Victorian Institute of Sports Assessment-Achilles (VISA-A). In both groups, VISA-A scores improved significantly after 24 weeks; however, there was no significant difference in VISA-A score between the two groups. With regard to safety, no microbial growth was found in the collected PRP samples, and no complications (infections, hematomas, or ruptures) were reported after the treatment (de Vos 2010). *Lateral epicondylitis (tennis elbow)* A double-blind RCT that included 100 subjects compared the efficacy of a platelet rich plasma injection to a corticosteroid injection for the treatment of lateral epicondylitis in patients who had failed non-operative treatment. In addition to a platelet rich plasma injection or a corticosteroid injection subjects also participated in an eccentric exercise program. The primary outcome measures were pain, measured using the visual analog scale (VAS), and disability, measured using the disability of the arm, shoulder, hand (DASH) outcome measure. Successful treatment was defined as more than a 25% reduction in VAS or DASH without a re-intervention after 1 year. According to the VAS, treatment was successful for 73% of subjects in the platelet rich plasma group and 49% in the corticosteroid group ( $P < 0.001$ ). When using the DASH, treatment was successful for 73% of subjects in the platelet rich plasma group and 51% in the corticosteroid group ( $P = 0.005$ ). This trial did not address safety. Results from this study should be interpreted with caution as there are several methodological limitations (Peerbooms 2010). *Conclusion:* There is insufficient evidence to support the use of platelet rich plasma injection for the treatment of Achilles tendinopathy. There is evidence from one small RCT that supports the use of this technology for patients with lateral epicondylitis; however, because of methodological limitations results from this trial are insufficient to determine the safety and efficacy of this procedure. Several trials are currently underway to determine the safety and efficacy of platelet rich plasma injections for the treatment of tendinopathy.

**Articles:** Studies were selected for review if they included at least 25 subjects and assessed either the safety or efficacy of platelet rich plasma injections for the treatment of tendinopathy. Studies were excluded if they lacked a valid comparison group. Two RCTs were selected for review. The following studies were critically appraised: de Vos RJ, Weir A, van Schie HTM, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy. *JAMA* 2010; 303:144-149. See [Evidence Table](#). Peerbooms JC, Sluimer J, Bruijn DJ, and Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial. *Am J Sports Med* 2010; 38:255-262. See [Evidence Table](#).

The use of Autologous Platelet Derived Wound Healing Factors in the treatment of Tendinopathy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

### ***Platelet Rich Plasma for Knee Osteoarthritis***

#### **04/21/2018: MTAC Review**

##### **Evidence Conclusion:**

- The published evidence on the use of PRP for knee OA is inconclusive and do not allow making a recommendation for or against using PRP for the treatment of knee osteoarthritis. The published studies have methodological limitations and their results are mixed. It is difficult to determine whether the inconsistency in the outcomes of the individual trials and their pooled results is due to the severity of the knee OA, differences in platelet separation technique, concentration or activation, timing and frequency of administration of PRP, variations in response between the individuals, quality of the studies including blinding of the patients, or the outcome measures used. None of the published studies evaluated the effect of PRP therapy on any structural changes or remodeling of the knee joint.



- The published literature does not provide sufficient evidence to determine the long-term comparative efficacy and safety of PRP to other standard recommended pharmacological or non-pharmacological therapies for knee osteoarthritis.
- Additional studies are needed to determine the optimal protocol for delivering PRP, the criteria for selecting the patients who may benefit from the treatment, as well as the long-term efficacy and safety of PRP for the treatment of knee OA. An ideal study would be double-blinded RCTs with sufficient statistical power, adequate randomization, standardized inclusion/exclusion criteria for patient selection, standardized protocol for PRP preparation and delivery, valid comparator, with objective as well as the subjective outcome measures, and long-term follow-up.
- A search of the National Institute of Health Clinical Trials website for ongoing trial identified several active trials including:
  - Bone Marrow Aspirate Compared to Platelet Rich Plasma for Treating Knee Osteoarthritis ClinicalTrials.gov Identifier NCT03289416
  - Efficacy of Hyaluronic Acid and Platelet-rich Plasma Combination in Knee Osteoarthritis ClinicalTrials.gov Identifier NCT03211650
  - Steroids, Hyaluronic Acid or Platelet Rich Plasma versus Placebo for Knee Osteoarthritis the (KIT). ClinicalTrials.gov Identifier NCT02776514
  - Intraarticular Platelet Rich Plasma Injections versus Intraarticular Corticosteroid Injections in Primary Knee Osteoarthritis. ClinicalTrials.gov Identifier NCT01923909

**Articles:** The literature search for studies on the comparative efficacy and safety of PRP and standard therapies used for knee OA revealed eight meta-analyses (MAs) published in the last 4 years, 19 relevant randomized and nonrandomized trials published in the last 10 years, and less than 10 case series/reports. The published meta-analyses were overlapping, 4 included randomized controlled trials (RCTs) as well as quasi-randomized trials and observational studies, and 4 included only RCTs. The meta-analyses of RCTs were given preference over the individual RCTs, which were small, had insufficient statistical power, and conflicting results. A meta-analysis of RCTs provides greater statistical power to detect significant differences and allows performing subgroup analyses. Three of the 4 identified meta-analyses of RCTs were selected for critical appraisal, based on their methodological quality, inclusiveness, inclusion of the more recently published RCTs, grading the quality the studies included, quantitative synthesis of the results of RCTs as a primary analysis, and/or comparing the outcomes of PRP versus an active treatment separately either as the primary analysis or in a subgroup analysis.

A more recently published meta-analysis ([See Evidence Table 1](#) - Zhang et al, 2018) was identified by the search but was not selected for critical appraisal as it pooled the results of prospective non-randomized trials together with the RCTs, and had no subgroup analysis for the RCTs.

Two recent trials ([See Evidence Table 2](#) - Cole et al, 2017, and [See Evidence Table 3](#) - Joshi Jubert et al, 2017) not included in the three meta-analyses reviewed was also selected for critical appraisal.

The use of Platelet Rich Plasma (PRP) for the Treatment of Knee Osteoarthritis (OA) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

### ***Platelet Rich Plasma (PRP) for the treatment of Plantar Fasciitis (PF) (Plantar Fasciopathy)***

**04/21/2018: MTAC REVIEW**

#### **Evidence Conclusion:**

- There is insufficient published evidence to determine that the effectiveness and safety of the local injection of platelet rich plasma is equivalent or superior to local steroid injection or to other pharmacological or nonpharmacological therapies currently used for the treatment of patients with plantar fasciitis. The overall quality of published studies is poor, with some trials reporting improvement with PRP and others reporting no improvement. It is difficult to determine whether the differences in the reported results are due to differences in the platelet separation technique, concentration or activation; or due to differences in the timing and frequency of administration or outcome measures.
- There is insufficient published evidence to determine the long-term efficacy and safety of PRP in treating patients with chronic plantar fasciitis.
- Large-scale, high-quality randomized controlled trials with blinding of outcome assessment and longer follow-up are required to provide evidence on the long-term safety and effectiveness of PRP for treating patients with plantar fasciitis.
- Ongoing trials:

- RCT Comparing Steroid Injections and Platelet Rich Plasma Injections in the Treatment of Plantar Fasciitis. ClinicalTrials.gov Identifier: NCT01957631.
- RCT Comparing ESWT with PRP for Plantar Fasciitis in High Demand Cohort. ClinicalTrials.gov Identifier: NCT02668510

**Articles:** The literature search for studies on the efficacy and safety of platelet rich plasma injections, published after the 2010 MTAC review identified three systematic reviews with meta-analyses, one network meta-analysis, two qualitative systematic review, and 14 small trials (10 RCTs and 4 non-randomized) that compared local injection of platelet rich plasma versus steroid injection in the majority of trials. PRP was compared to shock wave therapy in one trial, dextrose prolotherapy in another and to low-dose radiation also in one trial. One meta-analysis (Tsikopoulos, 2016) included only 3 earlier studies and was excluded from the review. The other two meta-analyses ([See Evidence Table 1](#) - Yang, 2017 and [See Evidence Table 2](#), 2017 and) as well as the randomized controlled trial with the lowest risk of bias ([See Evidence Table 3](#) - Mahindra, 2016) were selected for critical appraisal.

The use of Platelet Rich Plasma (PRP) for the treatment of Plantar Fasciitis (PF) (Plantar Fasciopathy) does not meet the *Kaiser Permanente Medical Technology Assessment Criteria*.

## Applicable Codes

**Medicare- Considered Medically Necessary when criteria in the applicable policy statements listed above are met**

**Non-Medicare-Considered Not Medically Necessary**

CPT® or HCPC Codes	Description
<b>0232T</b>	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed
<b>G0460</b>	Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment
<b>P9020</b>	Platelet rich plasma, each unit
<b>S9055</b>	Procuren or other growth factor preparation to promote wound healing

**\*Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

\*\*To verify authorization requirements for a specific code by plan type, please use the [Pre-authorization Code Check](#).

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Date Created	Date Reviewed	Date Revised
04/1999	10/05/2010 <sup>MDCRPC</sup> , 04/05/2011 <sup>MDCRPC</sup> , 11/01/2011 <sup>MDCRPC</sup> , 09/04/2012 <sup>MDCRPC</sup> , 07/02/2013 <sup>MDCRPC</sup> , 08/06/2013 <sup>MPC</sup> , 06/03/2014 <sup>MPC</sup> , 04/07/2015 <sup>MPC</sup> , 02/02/2016 <sup>MPC</sup> , 12/06/2016 <sup>MPC</sup> , 10/03/2017 <sup>MPC</sup> , 09/04/2018 <sup>MPC</sup> , 09/03/2019 <sup>MPC</sup> , 09/01/2020 <sup>MPC</sup> , 09/07/2021 <sup>MPC</sup> , 09/06/2022 <sup>MPC</sup> , 09/05/2023 <sup>MPC</sup> , 04/02/2024 <sup>MPC</sup>	09/13/2021

<sup>MDCRPC</sup> Medical Director Clinical Review and Policy Committee

<sup>MPC</sup> Medical Policy Committee

Revision History	Description
11/22/2017	Added non-covered services LCD
05/01/2018	Added MTAC reviews for Platelet Rich Plasma (PRP) for the treatment of Plantar Fasciitis (PF) (Plantar Fasciopathy) & Knee Osteoarthritis
09/01/2020	Added Medicare LCA A57642
04/15/2021	Added CPT code S9055
08/02/2021	Removed LCD L35008 and LCA A57642; added LCA A58351

09/13/2021	Updated NCD version 270.3
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