Medical Policy

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Title: Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non–Orthopedic Conditions

See Also: *Orthopedic Applications of Platelet-Rich Plasma medical policy*

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Populations	Interventions	Comparators	Outcomes
Individuals: • With diabetic lower-extremity ulcers	Interventions of interest are: • Recombinant platelet-derived growth factor	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • With pressure ulcers	Interventions of interest are: • Recombinant platelet-derived growth factor	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events

Populations	Interventions	Comparators	Outcomes
			• Quality of life • Treatment-related morbidity
Individuals: • With venous stasis leg ulcers	Interventions of interest are: • Recombinant platelet-derived growth factor	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • With acute surgical or traumatic wounds	Interventions of interest are: • Recombinant platelet-derived growth factor	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • With chronic wounds	Interventions of interest are: • Platelet-rich plasma	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity
Individuals: • With acute surgical or traumatic wounds	Interventions of interest are: • Platelet-rich plasma	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Quality of life • Treatment-related morbidity

DESCRIPTION

The use of blood-derived growth factors, including recombinant platelet-derived growth factors (PDGFs) and platelet-rich plasma (PRP), has been suggested as a treatment of wounds or other miscellaneous non–orthopedic conditions, including but not limited to diabetic ulcers, pressure ulcers, venous stasis ulcers, and surgical and traumatic wounds.

Objective

The objective of the evidence review is to evaluate whether the use of recombinant platelet-derived growth factor or platelet rich plasma improves health outcomes compared with standard care for diabetic ulcers, pressure ulcers, venous stasis ulcers, and surgical and traumatic wounds.

Background

Wound Healing Treatment

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

Autologous platelet concentrate suspended in plasma, also known as platelet-rich plasma (PRP), can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets, releasing various growth factors, and results in the polymerization of fibrin from fibrinogen, creating a platelet gel. The platelet gel can then be applied to wounds or may be used as an adjunct to surgery to promote hemostasis and

accelerate healing. In the operating room setting, PRP has been investigated as an adjunct to a variety of periodontal, reconstructive, and orthopedic procedures. For example, bone morphogenetic proteins are a transforming growth factor, and thus PRP has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries.

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

Wound Closure Outcomes

This review addresses the use of recombinant PDGF products and PRP for non-orthopedic indications, which include a number of wound closure-related indications. For this review, the primary endpoints of interest for the study of wound closure are as follows, consistent with guidance from the U.S. Food and Drug Administration (FDA) for the industry in developing products for the treatment of chronic cutaneous ulcer and burn wounds[1,]:

- Incidence of complete wound closure;
- Time to complete wound closure (reflecting accelerated wound closure);
- Incidence of complete wound closure following surgical wound closure;
- Pain control.

REGULATORY STATUS

Regranex®

In 1997, becaplermin gel (Regranex®; Smith & Nephew), a recombinant PDGF product, was approved by the FDA for the following labeled indication:
"Regranex Gel is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control, Regranex Gel increases the complete healing of diabetic ulcers.

The efficacy of Regranex Gel for the treatment of diabetic neuropathic ulcers that do not extend through the dermis into subcutaneous tissue or ischemic diabetic ulcers … has not been evaluated…."

In 2008, the manufacturer added the following black box warning to the labeling for Regranex®: "An increased rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of Regranex Gel in a post marketing retrospective cohort study. Regranex Gel should only be used when the benefits can be expected to outweigh the risks. Regranex Gel should be used with caution in patients with known malignancy."

In 2018, the "Boxed Warning" and "Warnings and Precautions" were changed to remove "increased rate of cancer mortality" and "cancer mortality," respectively.

Platelet-Rich Plasma
The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, Title 21, parts 1270 and 1271. Blood products such as PRP are included in these regulations.

Under these regulations, certain products including blood products such as PRP are exempt and therefore, do not follow the traditional FDA regulatory pathway. To date, the FDA has not attempted to regulate activated PRP.[2,]

Numerous PRP preparation systems have been cleared for marketing by the FDA through the 510(k) process. These devices are intended to concentrate patient plasma at the point of care during bone grafting procedures. The use of different devices and procedures can lead to variable concentrations of active platelets and associated proteins, increasing variability between studies of clinical efficacy.

POLICY

A. Recombinant platelet-derived growth factor (ie, becaplermin) may be considered **medically necessary** when used as an adjunct to standard wound management for the following indications:

1. Neuropathic diabetic ulcers extending into the subcutaneous tissue
   Appropriate candidates for becaplermin gel for treatment of neuropathic ulcers should meet ALL of the following criteria:
   a. Adequate tissue oxygenation, as measured by a transcutaneous partial pressure of oxygen of 30 mm Hg or greater on the foot dorsum or at the margin of the ulcer
      AND
   b. Full-thickness ulcer (ie, stage III or IV), extending through dermis into subcutaneous tissues
      AND
   c. Participation in a wound-management program, which includes sharp debridement, pressure relief (ie, non-weight-bearing), and infection control

2. Pressure ulcers extending into the subcutaneous tissue
   Appropriate candidates for becaplermin gel for the treatment of pressure ulcers should meet ALL of the following criteria:
   a. Full-thickness ulcer (ie, stage III or IV), extending through dermis into subcutaneous tissues
      AND
   b. Ulcer in an anatomic location that can be offloaded for the duration of treatment
      AND
   c. Albumin concentration >2.5 dL
      AND
   d. Total lymphocyte count >1000/uL
      AND

e. Normal values of vitamins A and C

B. Other applications of recombinant platelet-derived growth factor (ie, becaplermin) are considered **experimental / investigational**, including, but not limited to:
   1. ischemic ulcers
   2. venous stasis ulcers, and
   3. ulcers not extending through the dermis into the subcutaneous tissue

C. Use of platelet-rich plasma (ie, autologous blood-derived preparations) is considered **experimental / investigational** for the treatment of acute or chronic wounds, including surgical wounds and nonhealing ulcers

Policy Guidelines

Becaplermin

1. Patients are typically treated once daily for up to 20 weeks or until completely healed. Application of the gel may be performed by the patient in the home.
2. Becaplermin is available in 2-, 7.5-, and 15-g tubes and is applied in a thin continuous layer, about 1/16 of an inch thick (ie, 1.6 mm or the thickness of a dime). The amount of the gel used will depend on the size of the ulcer, measured in square centimeters. However, an average-sized ulcer, measuring 3 cm^2, treated for an average length of time of 85 days, will require a little more than one 15-g tube. If the ulcer is treated for the maximum length of time of 140 days, 1.75 of the 15-g tubes would be required.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through December 1, 2020.

The platelet-rich plasma (PRP) portion of this evidence review on the platelet-derived wound healing formulae was originally based on a 1992 TEC Assessment that primarily focused on the Procuren process.[3,] This preparation method is no longer commercially available. Currently, a large number of devices are available for the preparation of PRP or PRP gel. The amount and mixture of growth factors produced by different cell-separating systems vary, and it is unknown whether platelet activation before an injection is necessary.[4,5,6,7,8,]

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function¾including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility

of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

RECOMBINANT PLATELET-DERIVED GROWTH FACTOR FOR DIABETIC LOWER-EXTREMITY ULCERS

Clinical Context and Therapy Purpose

The purpose of recombinant PDGF is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with diabetic lower-extremity ulcers.

The question addressed in this evidence review is: Does the use of recombinant PDGF improve health outcomes compared with standard care for diabetic ulcers?

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

Populations

The relevant population of interest is individuals with diabetic lower-extremity ulcers.

Interventions

The therapy being considered is recombinant PDGF.

Patients with diabetic lower-extremity ulcers are actively managed by dermatologists and endocrinologists in an outpatient clinical setting.

Comparators

Comparators of interest include standard wound care.

Patients with diabetic lower-extremity ulcers are actively managed by dermatologists and endocrinologists in an outpatient clinical setting.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, quality of life (QOL), and treatment-related morbidity.

Follow-up at 20 weeks is of interest for recombinant PDGF to monitor relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

The portion of this evidence review on the use of recombinant PDGF (becaplermin gel) was informed by a 1999 TEC Assessment, which found that the evidence supported the conclusion that becaplermin gel, in conjunction with good wound care, improves the health outcomes of patients with chronic neuropathic diabetic ulcers that met the patient selection criteria defined therein.[9,] Becaplermin gel plus good wound care resulted in a 43% complete wound closure rate, compared with 28% for patients treated with good wound care alone. Becaplermin gel also appeared to reduce the average time to complete wound closure. A 2014 systematic review identified 6 RCTs (total n=992 patients) that compared recombinant PDGFs with placebo or standard care.[10,] There was a combined odds ratio of 1.53 (95% confidence interval [CI], 1.14 to 2.04; p=0.004) favoring recombinant PDGF for complete healing rate.

A 2005 industry-sponsored study assessed the effectiveness of recombinant PDGF for diabetic neuropathic foot ulcers in actual clinical practice.[11,] Among a cohort of 24898 patients in wound care centers, those subjects whose wounds did not heal over an 8-week observation period were eligible for the study and were retrospectively assessed over 20 weeks or until they healed. Any subject with an open wound who was lost to follow-up was considered unhealed. Of the nearly 25000 patients treated for foot ulcers, 2394 (9.6%) received recombinant PDGF. A propensity score method with covariates to statistically model treatment selection was used to adjust for selection bias; results were stratified by 5 propensity score groups. Overall, the rate of healing was 26.5% in the control group and 33.5% in patients treated with recombinant PDGF. The relative risk (RR), controlling for the propensity to receive PDGF, was 1.32 (95% CI, 1.22 to 1.38) for healing and 0.65 (95% CI, 0.54 to 0.78) for amputation (6.4% in controls vs. 4.9% in the PDGF group). The analysis also indicated those who received PDGF were more likely to be younger, male, and have older wounds-factors not known to affect wound healing. These results support the clinical utility of recombinant PDGF for treatment of diabetic neuropathic foot ulcers in actual clinical practice.

Sridharan et al (2018) conducted a systematic review and meta-analysis of RCTs on topical growth factors compared with standard of care in patients with diabetic foot ulcers (DFUs). The primary outcome of concern was complete healing and the second outcome of concern was the existence of adverse events. Rankogram was generated based on the surface under the cumulative ranking curve. In total, 26 studies with 2088 participants and 1018 adverse events were included. The pooled estimates for recombinant human epidermal growth factor (rhEGF), autologous -PRP, recombinant human platelet-derived growth factor were 5.7 [3. 34, 10.37], 2.65 [1.65, 4.54], and 1.97 [1.54, 2.55] respectively. The surface under the cumulative ranking curve for rhEGF was 0.95; sensitivity analysis did not reveal significant changes from pooled estimates and rankogram. With regard to adverse events, no differences were observed for the overall risk of adverse events between the growth factors; however, the growth factors were observed to lower the risk of lower limb amputations compared to standard of care. The results lead the authors to conclude that rhEGF, recombinant human platelet-derived growth factor, and autologous PRP significantly improved the healing rate when used as adjuvants to the standard of care. Compared to other growth factors, rhEGF performed better. The limitations of this study include the following: the strength of most of the outcomes assessed was low, and the findings may not be applicable for DFU with infection or osteomyelitis.[12,]

Table 1. Systematic Reviews of Trials Assessing Recombinant Platelet-Derived Growth Factor for Diabetic Lower-Extremity Ulcers

Study (Year)	Literature Search	Studies	Participants	N	Design	Results
Sridharan et al (2018)	Dec 2016	RCTs	Patients with diabetic lower-extremity ulcers treated with platelet-derived growth factor	2088	RCTs	Pooled analysis estimated rhEGF, PRP, rhPDGF

PRP: autologous platelet-rich plasma; RCT: Randomized Controlled Trial; rhEGF: recombinant epidermal growth factor; rhPDGF: recombinant human platelet-derived growth factor

Section Summary: Recombinant PDGF for Diabetic Lower-Extremity Ulcers
Published evidence includes an industry-sponsored study and 2 systematic reviews that showed an improvement in treatment over control for tested outcome measures.

RECOMBINANT PLATELET-DERIVED GROWTH FACTOR FOR PRESSURE ULCERS

Clinical Context and Therapy Purpose
The purpose of recombinant PDGF is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with pressure ulcers.

The question addressed in this evidence review is: Does the use of recombinant PDGF improve health outcomes compared with standard care for pressure ulcers?

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

Populations
The relevant population of interest is individuals with pressure ulcers.

Interventions
The therapy being considered is recombinant PDGF.

Patients with pressure ulcers are actively managed by dermatologists in an outpatient clinical setting.

Comparators
Comparators of interest include standard wound care.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity.

Though not completely standardized, follow-up for pressure ulcer symptoms would typically occur in the months after starting treatment.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Rees et al (1999) conducted an RCT focusing on the use of becaplermin gel as a treatment for pressure ulcers.[13,] Patient selection criteria included full-thickness ulcers and an anatomic location where pressure could be offloaded during treatment. This latter patient selection criterion might have limited the number of patients with pressure ulcers who would have been considered candidates for becaplermin therapy. Patients were randomized to 1 of 4 parallel treatment groups and received either a placebo or 1 of 3 dosages of becaplermin. All patients received a standardized program of good wound care. In the 2 groups treated with the once-daily dosage (becaplermin 0.01% or 0.03%), the incidence of complete healing was significantly improved compared with the placebo group. There was no difference in outcome between the 0.01% and 0.03% groups, suggesting there is no clinical benefit in increasing the potency above 0.01%. A third group received becaplermin 0.01% twice daily. That group did not report improved outcomes compared with placebo, a finding that is unexplained.

Section Summary: Recombinant Platelet-Derived Growth Factor for Pressure Ulcers

Published evidence includes a multicenter, double-blind RCT that showed an improvement in treatment over control for tested outcome measures.

RECOMBINANT PLATELET-DERIVED GROWTH FACTOR FOR VENOUS LEG ULCERS

Clinical Context and Therapy Purpose

The purpose of recombinant PDGF is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with venous stasis leg ulcers.

The question addressed in this evidence review is: Does the use of recombinant PDGF improve health outcomes compared with standard care for venous stasis ulcers?

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

Populations

The relevant population of interest is individuals with venous stasis leg ulcers.

Interventions

The therapy being considered is recombinant PDGF.

Patients with venous stasis leg ulcers are actively managed by dermatologists and primary care providers in an outpatient clinical setting.

Comparators

Comparators of interest include standard wound care.

Patients with venous stasis leg ulcers are actively managed by dermatologists and primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity.

Though not completely standardized, follow-up for venous stasis leg ulcers symptoms would typically occur in the months after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Review of Evidence
Senet et al (2011) in France, published a multicenter, double-blind RCT of becaplermin gel for venous leg ulcers.[14,] There was no significant difference between the becaplermin (n=28) and control hydrogel (n=31) groups for any of the outcome measures, which included complete closure rates after 8 and 12 weeks, changed ulcer area and changed ulcer-related pain and QOL.

Section Summary: Recombinant Platelet-Derived Growth Factor for Venous Leg Ulcers
Published evidence includes a multicenter, double-blind RCT that showed no difference between treatment and control for tested outcome measures.

RECOMBINANT PLATELET-DERIVED GROWTH FACTOR FOR ACUTE SURGICAL OR TRAUMATIC WOUNDS

Clinical Context and Therapy Purpose
The purpose of recombinant PDGF is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with acute surgical or traumatic wounds.

The question addressed in this evidence review is: Does the use of recombinant PDGF improve health outcomes compared with standard care for surgical and traumatic wounds?

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

Populations
The relevant population of interest is individuals with acute surgical or traumatic wounds.

Interventions
The therapy being considered is recombinant PDGFs.

Patients with acute surgical or traumatic wounds are actively managed by dermatologists and primary care providers in an outpatient clinical setting.

Comparators
Comparators of interest include standard wound care.

Patients with acute surgical or traumatic wounds are actively managed by dermatologists and primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity.

Though not completely standardized, follow-up for acute surgical or traumatic wound symptoms would typically occur in the months after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Review of Evidence
Topical recombinant PDGF has also been investigated for repair of work-related fingertip injuries. A 2005 prospective controlled trial alternately assigned 50 patients (fingertip wound area ≥1.5 cm, with or without phalangeal exposure) to daily treatment with PDGF (n=25) or surgical reconstruction (n=25).[15,] Statistical analysis showed that baseline characteristics of the 2 groups were similar for patient age, wound area (2.2-2.4 cm), and distribution of fingertip injuries across the digits. Assessment by an independent physician showed that, compared with the surgical intervention, treatment with recombinant PDGF resulted in faster return to work (10 days vs. 38 days) and wound healing (25 days vs. 35 days), less functional impairment (10% vs. 22%), and less need for physical therapy (20% vs. 56%), respectively. Fingertips treated with PDGF were also reported to have satisfactory aesthetic results, while surgically treated fingertips were shorter and often unsightly. These results, if confirmed in additional RCTs, could lead to improvement in health outcomes for patients with fingertip injuries. However, this trial was limited by its small sample size, method of randomization, and potential for investigator bias (although examining physicians were blinded to treatment allocation, actual treatment might have been obvious).

Adverse Events

Growth factors cause cells to divide more rapidly. For this reason, the manufacturer of Regranex continued to monitor studies that started before its approval (in December 1997) for any evidence of adverse events, such as increased numbers of cancers. In a long-term safety study completed in 2001, more deaths from cancer occurred among patients who used Regranex than in those who did not. A subsequent study was performed using a health insurance database that covered the period from January 1998 through June 2003. This trial identified 2 groups of patients with similar diagnoses, drug use, and use of health services: 1 group used Regranex, and the other group did not. Results showed there were more deaths from cancer among patients who were given 3 or more prescriptions for Regranex than deaths for those not treated with Regranex. No single type of cancer was identified; deaths from all types of cancer were observed. In 2008, the U.S. Food and Drug Administration concluded that the increased risk of death from cancer in patients who used 3 or more tubes of Regranex was 5 times higher compared with those who did not use Regranex, prompting the manufacturer to add a black box warning to the labeling for Regranex. The risk of new cancers among Regranex users was not increased compared with nonusers, although the duration of follow-up of patients in this study was not long enough to detect new cancers.

Section Summary: Recombinant Platelet-Derived Growth Factor for Acute Surgical or Traumatic Wounds
Published evidence includes nonrandomized controlled trials reporting satisfactory aesthetic results. Larger RCTs are required to confirm and expound on these results.

PLATELET-RICH PLASMA FOR CHRONIC WOUNDS

Clinical Context and Therapy Purpose
The purpose of PRP is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with chronic wounds

The question addressed in this evidence review is: Does the use of PRP improve health outcomes compared with standard care for chronic wounds?

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

Populations
The relevant population of interest is individuals with chronic wounds.

Interventions
The therapy being considered is PRP.

Patients with chronic wounds are actively managed by primary care providers in an outpatient clinical setting.

Comparators
Comparators of interest include standard wound care.

Patients with chronic wounds are actively managed by primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity.

Though not completely standardized, follow-up for chronic wound symptoms would typically occur in the months after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews
A number of systematic reviews of the evidence on PRP have been published.[16,17,18,19,20,21,22,23,] These reviews are heterogenous in whether they pooled data from studies reflecting a variety of wound types[18,17,16,19,] or focused on specific wound types, primarily diabetic foot ulcers.[20,21,22,23,] Results from the reviews that pooled data from a variety of wound types[18,17,16,19,] are not discussed herein as their design precludes drawing conclusions about the applicability of the review findings to specific wound types. As the majority of the RCTs included in the systematic reviews were published post-2014, herein are summarized those systematic reviews that focused on specific wound types with search dates that extend to at least 2015.[21,22,23,]

Diabetic Foot Ulcers
Three recent systematic reviews have evaluated studies of PRP for individuals with diabetic foot ulcers.[21,22,23,] Table 2 provides a crosswalk of the studies included in the systematic reviews.

Table 2. Comparison of Trials of Platelet-Rich Plasma in Individuals with Diabetic Foot Ulcers Included in Systematic Reviews

Primary Study (Year)	**Del Pino-Sedeno 2018**[21,]	**Li 2019**[22,]	**Qu 2020**[23,]
Ahmed 2017[24,]	●	●	●
Chen 2008[a25,]		●	
Driver 2006[26,]	●	●	●
Elsaid 2020[27,]			●
Friese 2007 (conference proceeding)[28,]		●	
Game 2018[29,]			●
Gude 2019[30,]			●

Primary Study (Year)	Del Pino-Sedeno 2018[21,]	Li 2019[22,]	Qu 2020[23,]
Kakagia 2007[31,]	●	●	●
Karimi 2016[32,]	●		●
Li 2015[33,]	●	●	●
Liu 2016[a34,]		●	
Ma 2014[a35,]		●	
Milek 2017[36,]			●
Qi 2014[a37,]		●	
Saad Setta 2011[38,]	●	●	●
Saldalamacchia 2004[39,]	●	●	●
Serra 2013[40,]		●	●
Singh 2018[41,]			●
Steed 1992[42,]	●		
Steed 1996[43,]	●		
Xie 2020[44,]			●
Yang 2017[45,]			●
Zhang 2016[a46,]		●	
Zhou 2015[a47,]		●	
Zhu 2012[a48,]		●	

[a] In Chinese

Tables 3 and 4 summarize the characteristics and results of the 3 systematic reviews that have evaluated studies of PRP for individuals with diabetic foot ulcers.[21,22,23,]

A meta-analysis by del Pino-Sedeno et al (2018) assessed 8 RCTs and 2 longitudinal-observational studies (total participants N=525) to determine the safety and efficacy of PRP to treat diabetic foot ulcers.[21,] Results indicated PRP significantly increased chronic wound healing compared with standard treatment (RR=1.41; 95% CI: 1.08 to 1.84; p=.01; I^2=51%). Subgroup analysis showed that PRP source affected the proportion of completely healed diabetic foot ulcers (autologous RR=1.21; 95% CI: 1.04 to 1.42; p=.02; allogenic RR=3.20; 95% CI: 1.14 to 9.03; p=.03). PRP preparation method also influenced healing (homemade RR=1.22; 95% CI: 1.04 to 1.44; p=.02; commercial protocol RR=1.13; 95% CI: 0.58 to 2.20; p=.71; blood bank RR=3.20; 95% CI: 1.14 to 9.03; p=.03). The 2 trials that reported mean time for complete wound healing showed that PRP resulted in quicker healing (mean difference=-11.18 days; 95% CI: -20.69 to -1.68; p=.02; I^2=53%). Overall, the studies reported no significant differences in rates of wound complications or dermatitis, and rates of recurrences were similar between PRP and standard treatment. The authors noted, however, that results of their analysis should be interpreted cautiously because no statistical differences were found in the epithelialized area before and after

wound treatment (mean difference=0.70 cm^2; 95% CI: -0.96 to 2.35; p=.41; I^2=70%). This study was limited by the low number and quality of studies available on PRP for diabetic foot ulcers.

In their meta-analysis, Li et al (2019) assessed the efficacy and safety of autologous platelet-rich gel for topical treatment of diabetic chronic cutaneous ulcers[22,] Their analysis included 15 RCTs with 829 patients. Results indicated that autologous platelet-rich gel had a significant positive effect on healing rate, shorter healing time, and lower risk of infection than conventional treatment. Autologous platelet-rich gel also had a significantly lower incidence of infection when compared with conventional treatment (odds ratio=0.34; 95% CI: 0.15 to 0.77; p=.009). This meta-analysis was limited by a high or unclear risk of bias among the trials, which may indicate the trials were underpowered. Also, some studies had small sample sizes and limited outcome information. Further, 7 of the included trials are available only in the Chinese language. Finally, most of the trials were 8-12 weeks long and others only 2-5 weeks, making it difficult to analyze the relationship of time of observation to ulcer healing.

The Agency for Healthcare Research and Quality (AHRQ) (2020) published a Technology Assessment on Platelet-Rich Plasma for Wound Care in the Medicare Population. This Technology Assessment was requested by the Centers for Medicare & Medicaid Services to inform reconsideration of a National Coverage Decision on autologous blood-derived products for chronic non-healing wounds.[49,] This Technology Assessment evaluates evidence in lower extremity diabetic ulcers, lower extremity venous ulcers and pressure ulcers. Separate meta-analyses were conducted for each wound type. Here the focus is on findings for lower extremity diabetic ulcers and those for the other populations are discussed below. Risk of bias of individual studies was assessed using the Cochrane Collaboration's Risk of Bias 2 tool and rated high in 8 RCTs (57.14%), moderate in 6 RCTs (42.86%) and high in the 1 observational study (100%). Strength of the body of evidence was rated based on the Evidence-based Practice Center methods guide. The findings of this Technology Assessment indicated that there is moderate-strength evidence that PRP modestly increases complete wound closure (see meta-analysis results in Table 4 below) and low-strength evidence that PRP may shorten time to wound closure (meta-analysis not feasible). However, due to risk of bias and severe imprecision, evidence is insufficient to draw conclusions about other important outcomes, including wound infection, amputation, pain reduction, and wound recurrence. Important limitations of the literature were described as "inadequate description of offloading and wound care procedures, wound characteristics, PRP formulation techniques, concentration and volume; inadequate length of follow-up, and lack of stratification by comorbidities and other patient characteristics, such as diabetes control, vascular perfusion, and under representation of older adults."

Table 3. Characteristics of Key Systematic Reviews with Meta-Analyses in Individuals with Diabetic Foot Ulcers

Study	Dates	Trials	Participants	N (Range)	Design	Duration
del Pino-Sedeno (2018)[21,]	Inception-2017	10	Patients with diabetic foot ulcers	N=525 (13-117)	RCTs, longitudinal observational studies	3 wk to 128.57 wk

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Li (2019)[22,]	2004-2017	15	Patients with diabetic chronic cutaneous wounds/ulcers that do not show signs of healing in 4 weeks	N=829 (14-117)	RCTs	NR
Qu (2020)[23,]	Inception-2020	14	Adults with lower extremity diabetic ulcers, lower extremity venous ulcers, or pressure ulcers in any location, or a mix of these 3 etiologies	N=1,096 (range NR)	RCTs	Median = 6 wk (range, none to 11 months)

NR: not reported; wk: week(s); y: year(s).

Table 4. Results of Key Systematic Reviews with Meta-Analyses in Individuals with Diabetic Foot Ulcers

Study	Healing Rate	Healing Time	Complete Wound Healing	Risk of Infection	Wound complications	Pain Reduction	Recurrence
del Pino-Sedeno (2018)[21,]							
RR			1.41		0.57		2.76
MD		-11.18					
95% CI		-20.69 to -1.68	1.08 to 1.84		0.25 to 1.28		0.23 to 33.36
P-value		.02	.01		.17		.43
Li (2019)[22,]							
RR	1.39						
MD		-9.18					
OR				0.34			
95% CI	1.29 to 1.50	-11.32 to -7.05		0.15 to 0.77			
P-value	<.001	<.001		.009			
Qu (2020)[23,]							
RR			1.20	0.77			2.09
WMD						-1.10[a]	
95% CI			1.09 to 1.32	0.54 to 1.11		-1.81 to -0.39	0.31 to 13.93
P-value							

[a] Visual Analog Scale
CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio; WMD: weighted mean difference; Z: indicates overall effect.

Other Chronic Wound Types

The AHRQ (2020) Technology Assessment on Platelet-Rich Plasma for Wound Care in the Medicare Population described above also evaluated evidence on use of PRP in individuals with lower extremity venous ulcers and individuals with pressure ulcers.[23,]

For individuals with lower extremity venous ulcers, the evidence included 8 RCTs and 3 observational studies (total N=615). The majority compared PRP to management without PRP. Risk of bias was described as moderate due to randomization and outcome measurement limitations. There were no significant differences between PRP versus management without PRP in complete wound closure (RR=1.49; 95% CI: 0.72 to 3.06; 5 studies, N=250; I^2=29.4%), wound recurrence (RR=0.38; 95% CI: 0.09 to 1.57), wound infection (RR=0.79; 95% CI: 0.22 to 2.81), or quality of life as measured by the Chronic Lower Limb Venous Insufficiency Questionnaire (WMD=10.99; 95%CI: -50.5 to 72.5). For the outcomes time to complete wound closure and pain, meta-analysis of 2 studies was not possible due to insufficient data and findings were mixed between studies on both outcomes. The strength of evidence was rated as 'insufficient' to draw conclusions on all outcomes. Oliveira et al (2020) also conducted a meta-analysis of cost and effectiveness of studies of PRP for venous ulcers.[50,] Based on fewer studies identified from searches only through July 2018, although their findings indicated greater reductions in wound area for PRP, findings were consistent with the ARHQ review in finding no significant difference in complete wound closure (RR=2.54; 95% CI, 0.42 to 15.30; 4 studies, n=156; I^2=69%).

For individuals with pressure ulcers, the AHRQ Technology Assessment (2020)[23,] included 1 RCT and 1 comparative observational study (Total N not reported). The comparator was serum physiological dressing in the RCT and saline dressing in the observational study. Risk of bias of the primary studies was described as moderate, due to limitations in the randomization process and outcome measurement, deviations from intended interventions, and selective outcome reporting. Although both studies found that PRP significantly reduced wound size (strength of evidence=insufficient), neither study evaluated other important outcomes, such as complete wound closure.

Randomized Controlled Trials

One RCT of PRP for chronic wounds (Saha et al [2020])[51,] was identified as published subsequent to the AHRQ review (2020).[23,] Saha et al (2020) reported on a single-center, observer-blinded RCT that compared PRP plus total contact casting versus PRP alone in 118 individuals with trophic ulcers secondary to leprosy. Key characteristics and results of Saha et al (2020) are reported in Tables 5 and 6 below.

Analyses included 91.5% (n=108) of randomized individuals. Participants were mostly males in their late 40s with trophic ulcer duration of 13.4 months. Reduction in ulcer surface area, the primary outcome, was significantly greater for the PRP group from the first week (38.96% vs 12.46%; p<.001) through the fifth (and last) week of follow-up (91.10% vs 79.77%; p<.001). However, healing time and recurrence were not reported and there was no significant difference in complete healing rate.

Table 5. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Intervention	Control
Saha et al (2020)[51],	Iran	1	2016 to 2018	Individuals with clinically diagnosed trophic ulcers due to leprosy	Autologous PRP therapy with total contact casting (N=59)	Only total contact casting (N=59)

PRP: Platelet-rich plasma

Table 6. Summary of Key RCT Results

Study	Complete Healing	Healing Time	Pain	Quality of Life	Infection	Recurrence
Saha et al (2020)[51],	22 (39.29%) vs 11 (21.15%); p NR	NR	NR	NR	0 vs 0; p=.773	NR

NR: Not Reported

Tables 7 and 8 summarize the relevance and design and conduct limitations of Saha et al (2020).

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Saha et al (2020)[51],	4. Single site in Iran	4. Short duration of treatment; 8 weeks		1. Recurrence, quality of life not addressed 5. Clinical significance of difference in wound surface area not prespecified	1. 4 weeks follow-up post-treatment insufficient to assess long-term efficacy

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

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

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

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

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

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

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Saha et al (2020)						

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

Section Summary: Platelet-Rich Plasma for Chronic Wounds

The evidence for autologous PRP for a variety of chronic wounds includes systematic reviews, RCTs, which have been summarized in several systematic reviews, and nonrandomized trials. In individuals with lower extremity diabetic ulcers, PRP demonstrated an improvement over the control groups in complete wound closure and healing time, but moderate to high risk of bias and imprecision preclude drawing conclusions on other important outcomes such as recurrence, infection, amputation, and quality of life. In individuals with venous ulcers, PRP did not demonstrate an improvement over the control groups in complete wound closure, recurrence, wound infection or quality of life, although imprecision likely precluded identifying differences on these outcomes. In individuals with pressure ulcers, although PRP reduced wound size, other important outcomes such as complete wound closure were not measured. Overall, the studies are small and of low quality, and the results should be interpreted with caution.

PLATELET-RICH PLASMA FOR ACUTE SURGICAL OR TRAUMATIC WOUNDS

Clinical Context and Therapy Purpose

The purpose of PRP is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with acute surgical or traumatic wounds.

The question addressed in this evidence review is: Does the use of PRP improve health outcomes compared with standard care for surgical and traumatic wounds?

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

Populations

The relevant population of interest is individuals with acute surgical or traumatic wounds.

Interventions

The therapy being considered is PRP.

Patients with acute surgical or traumatic wounds are actively managed by primary care providers in an outpatient clinical setting.

Comparators

Comparators of interest include standard wound care.

Patients with acute surgical or traumatic wounds are actively managed by primary care providers in an outpatient clinical setting.

Outcomes
The general outcomes of interest are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity.

Though not completely standardized, follow-up for acute surgical or traumatic wound symptoms would typically occur in the months after starting treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

Review of Evidence

SURGICAL WOUNDS

Aortic Arch Repair
Zhou et al (2015) reported on a double-blind RCT with 80 patients that assessed the effect of PRP on the amount of blood transfused in the perioperative period for elective ascending and transverse aortic arch repair.[52,] An anesthesiologist prepared the PRP so that the surgeon was unaware of the treatment group. The volume of PRP transfused was 726 mL and led to a reduction in transfusion rates for red blood cells, frozen plasma, cryoprecipitate, and platelets by 34% to 70% ($p<0.02$). Hospital length of stay was also reduced (9.4 days vs. 12.7 days). There was no difference in mortality between the 2 groups (1 patient in each group) and no significant differences in postoperative complications or other outcome measures. Corroboration of the effect of PRP on perioperative blood transfusion is needed.

Sternotomy Wounds
Serraino et al (2015) reported on a large series with historical controls that assessed the occurrence of deep sternal wound infections in patients who underwent cardiac surgery either with (2010-2012, 422 consecutive patients) or without (2007-2009, 671 consecutive patients) application of PRP.[53,] The 2 groups were comparable at baseline. At the end of cardiac surgery, PRP gel was applied to the sternum before the closure of subcutaneous tissue. Rates of both deep and superficial wound infections were reduced in the patients treated with PRP (deep: 0.2% vs. 1.5%, superficial: 0.5% vs. 2.8%). Interpretation of these results is limited by likely differences in treatments over time. RCTs are needed to evaluate this potential use of PRP.

Otolaryngology
El-Anwar et al (2016) reported on an RCT that evaluated PRP in 44 children (age range, 12-23 months) undergoing repair of a complete cleft palate.[54,] Speech and velopharyngeal valve movement on follow-up were evaluated by 3 judges who "usually assessed every patient blindly," physical examination, video nasoendoscopy, and audio recording of audio perceptual assessment. At 6 months, PRP-treated patients had better nasality grade on audio perceptual assessment (p=0.024) and better velopharyngeal closure on endoscopy (p=0.016).

A 2008 double-blind RCT assessed the efficacy of PRP following tonsillectomy in 70 children (age range, 4-15 years).[55,] PRP was placed into the tonsil beds of half of the children, where it was directly visible. To compare pain symptoms and recovery, a daily diary was completed by the patient or a family member for 10 days after surgery. A FACES Pain Scale was used for children ages 4 to 7 years, while a numeric pain rating scale was used for children older than 7 years. Diaries from 83% of patients showed no differences in pain, medication doses, activity, and days eating solid foods between the 2 conditions.

Other Surgical Wounds
A 2011 Norwegian trial of PRP applied to saphenous vein harvest sites after wound closure found no differences in the incidence of wound infection or cosmetic result.[56,]

Alamdari et al (2018) published a clinical trial evaluating the efficacy of pleurodesis with a combination of PRP and fibrin glue compared with surgical intervention. The study population consisted of 52 esophageal cancer patients with postoperative chylothorax who did not respond to conservative management. Each member of the population was consecutively and randomly allocated to either a PRP fibrin glue pleurodesis arm or a surgical thoracic duct ligation arm. Twenty-six in each arm were treated with their respective interventions. The patients were distributed into the intervention arms in a way that made each group similar in terms of tumor size and patient demographics. This distribution procedure was not described. All patients (26) in the PRP treatment arm and 20 (76.9%) in the surgery arm were successfully treated (p=0.009). Seven patients (26.92%) of the PRP required a second application of the PRP fibrin glue after a week. The mean length of hospital stay was higher in the surgery group (53.50 ± 16.662 days) than the PRP group (36.04 ± 8.224 days; $p < 0.001$). The study was limited due to the fact the procedure for randomization was not described and, thus, its efficacy cannot be evaluated.[57,]

Mohamadi et al (2019) reported on an RCT of 110 participants in Tehran that evaluated the efficacy of PRP gel in wound healing time following pilonidal sinus surgery.[58,] Each group included 55 participants. Follow-up duration was 9 weeks. In the treatment group, PRP was both injected into the wound weekly, as well as applied to the wound surface and covered with latex. In the control group, wound dressing was described as "classic", but no other details were provided. Little to no detail was provided about specific outcome assessment methods *(ie,* "pain duration was inquired from participants"). All patients completed the study and were included in the outcome assessments. PRP significantly shortened mean healing time (4.8 vs 8.7 weeks; p<.001), pain duration (1.3 vs 3.4 weeks; p<.001), and antibiotic consumption duration (0.57 vs 1.74 weeks; p<.001). This RCT also performed regression analyses to evaluate the correlation between different factors in wound healing activity. Significant negative associations were found between healing time and wound volume and pain duration and angiogenesis. Notable limitations of this study included unclearly defined wound dressing in the comparator group, unblinded and

poorly defined outcome assessment, short-term follow-up and lack of assessment of other important health outcomes.

Slaninka et al (2020) published an RCT that evaluated PRP in 24 individuals in the Czech Republic who had undergone dermo-epidermal skin grafts taken from the thigh area.[59,] Indications for skin grafts were primarily hard-to-heal lower leg wounds. PRP was applied to 1 thigh and covered with Vaseline-impregnated, open-weave gauze and gauze. The control was the other thigh, which was also covered with open-weave gauze and gauze, but without PRP. Of the 24 included individuals, 3 (12.5%) were excluded after developing infections. The infections were described as first occurring on the non-PRP wound and only subsequently occurring on the PRP wound after several days. PRP significantly shortened median healing time (14 days vs 18 days; p=.026). No other outcomes were reported. Notable limitations of the RCT include its small sample size and that it did not address important health outcomes and harms.

Traumatic Wounds

Kazakos et al (2009) reported on a prospective RCT that evaluated treatment of acute traumatic wounds (open fractures, closed fractures with skin necrosis, friction burns) with platelet gel in 59 consecutive patients (27 PRP, 32 controls).[60,] Conventional treatment consisted of topical washing and cleaning of the wounds, removal of the necrotic tissue, and dressing in petroleum jelly gauze every 2 days. In all patients with open tibial fractures, an external fixation system was applied. PRP gel was applied to the wounds after surgical de bridement and placement of the external fixation system. The time needed for preparation and application of the PRP gel was 52 minutes. After that, PRP gel was applied to the wounds once weekly in the outpatient clinic until there was adequate tissue regeneration (mean, 21 days) sufficient to undergo reconstructive plastic surgery. Control patients receiving conventional treatment required a mean of 41 days for adequate tissue regeneration. Pain scores were significantly lower in PRP-treated patients at 2 and 3 weeks (visual analog scale score, 58 PRP vs. 80 controls). Although these results are encouraging, additional study with a larger number of patients is needed.

Marck et al (2016) reported on a randomized, double-blind, within-patient-controlled study in patients with deep dermal to full-thickness burns undergoing split-skin graft, comparing PRP with usual care.[61,] The study randomized 52 patients, 50 of whom received the allocated PRP intervention. There were no significant differences in short-term (5-7 days) rates in graft take in the intervention and control areas on each patient. At 3, 6, and 12 months, there were no significant differences in skin appearance or epithelialization scores.

Yeung et al (2018) performed a prospective RCT to test the efficacy of lyophilized platelet-rich plasma powder (LPRP) on the healing rate of wounds in patients with deep, second-degree burn injuries in comparison with a control group using a placebo. LPRP was dissolved in a solution and applied on deep second-degree burn wounds once per day for 4 consecutive days. Twenty-seven patients with deep second-degree burns were recruited and then those that met eligibility criteria were randomized into 2 groups. The LRPR group received the intervention (n=15) and the control group received a placebo application (n=12). A concentration of 1.0×10^7 platelets/cm^2 (wound area) was sprayed on the wound evenly. Function was assessed by the percentage of wound closure and bacteria picking out rate at weeks 2 and 3. The mean burn area of control for the LPRP was 75.65 ± 50.72 cm^2 and 99.73 ± 70.17 cm^2 (p=.0013), respectively. In the control group, the original wound area was 25.49 cm^2 at baseline, 23.79 cm^2 (6.67% healed) at week 2, and 4.34 cm^2 (86.40% healed) at week 3. In the LPRP group, the original wound area was 84.36

cm^2, followed by 23.96 cm^2 (71.59% healed) at week 2, and 0.63 cm^2 (99.24% healed) at week 3. The wound closure rate at week 2 in the LPRP group reached nearly 80% and was greater than 90% by week 3, showing a significant difference ($p<0.05$). Alternatively, in the control group, the wound closure rates were 60% and 80% in 2 and 3 weeks, respectively. The postoperative infection rate in the LPRP (26.67%) was lower than the control group (33.33%). Neither was significant, statistically. One limitation of this study is that the powder is made by an independent lab and dissolved in a specified amount of water. This provides an opportunity for accidental error-this may also be the case with some liquid PRP. [62,]

Section Summary: Platelet-Rich Plasma for Acute Surgical or Traumatic Wounds
The evidence for autologous PRP for a variety of acute surgical or traumatic wounds includes RCTs. For a variety of other conditions, studies have either not demonstrated a benefit or have demonstrated small benefits in studies with methodologic limitations.

Summary of Evidence

Recombinant PDGFs
For individuals who have diabetic lower-extremity ulcers who receive recombinant PDGF, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life (QOL), and treatment-related morbidity. Results have shown improved rates of healing with use of recombinant PDGF for diabetic neuropathic ulcers and pressure ulcers. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have pressure ulcers who receive recombinant PDGF, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. Results have shown improved rates of healing with use of recombinant PDGF for pressure ulcers. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have venous stasis leg ulcers or acute surgical or traumatic wounds who receive recombinant PDGF, the evidence includes small RCTs. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. The level of evidence does not permit conclusions whether recombinant PDGF is effective in treating other wound types, including chronic venous ulcers or acute traumatic wounds. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Platelet-Rich Plasma
For individuals who have chronic wounds who receive PRP, the evidence includes meta-analyses of a number of small controlled trials. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. In individuals with lower extremity diabetic ulcers, PRP demonstrated an improvement over the control groups in complete wound closure and healing time, but moderate to high risk of bias and imprecision preclude drawing conclusions on other important outcomes such as recurrence, infection, amputation, and quality of life. In individuals with venous ulcers, PRP did not demonstrate an improvement over the control groups in complete wound closure, recurrence, wound infection or quality of life, although imprecision likely precluded identifying differences on these outcomes. In individuals with

pressure ulcers, although PRP reduced wound size, other important outcomes such as complete wound closure were not measured. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have acute surgical or traumatic wounds who receive PRP, the evidence includes a number of small controlled trials. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. Current results of trials using PRP are mixed and the studies are limited in both size and quality. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American College of Physicians

In 2015, the American College of Physicians (ACP) published guidelines on treatment of pressure ulcers.[63,] The guidelines noted that "although low-quality evidence suggests that dressings containing PDGF [platelet-derived growth factors] promote healing, ACP supports the use of other dressings such as hydrocolloid and foam dressings, which are effective at promoting healing and cost less than PDGF dressings." A search of the ACP website on December 1, 2020 found that this 2015 guideline is now listed as inactive.

Association for the Advancement of Wound Care

The Association for the Advancement of Wound Care developed guideline recommendations for the management of pressure ulcers (2010)[64,] and venous ulcers (2015)[65,]:

- Pressure ulcer: "Growth factors are not indicated for PU [pressure ulcers] at this time." (level C evidence - no RCTs available comparing growth factors with A-level dressings)[64,]
- Venous ulcer: "Platelet-derived growth factor has shown no significant effects on VU [venous ulcer healing or recurrence]." (level A evidence)[65,]

National Institute for Health and Care Excellence

In 2019, the National Institute for Health and Care Excellence updated its guidance on the prevention and management of diabetic foot problems.[66,] The guidance stated that neither autologous platelet-rich plasma gel nor platelet-derived growth factors should be offered in the treatment of diabetic foot ulcers.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some larger studies that might influence this review are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT02312596[a]	A Prospective, Randomized Clinical Trial of PRP Concepts Fibrin Bio-Matrix in Chronic Non-Healing Pressure Ulcers	250	Jul 2021
NCT02312570[a]	A Prospective, Randomized Clinical Trial of PRP Concepts Fibrin Bio-Matrix in Chronic Non-Healing Pressure Ulcers	250	Jul 2021
NCT02307448[a]	Effectiveness of Autologous Platelet Rich Plasma in the Treatment of Chronic Non-Healing Wounds	80	Dec 2022
NCT02402374[a]	Randomized, Placebo-controlled, Blind-assessor Study to Evaluate the Safety and Efficacy of Autologous Platelet Rich Plasma Gel Prepared With the RegenKit-BCT Plus Family of Kits for the Treatment of Diabetic Foot Ulcer	192	Dec 2020
Unpublished			
NCT02071979[a]	Registry Trial of the Effectiveness of Platelet Rich Plasma for Chronic Non-Healing Wounds (CMS)	1500	Jan 2018(terminated; updated 01/16/18)
NCT02213952	Efficacy of Autologous Platelet-Rich Plasma in the Treatment of Vascular Ulcers in Primary Care: Clinical Trial Phase III	0	Dec 2017 (withdrawn Feb 2020)

NCT: national clinical trial; PRP: autologous platelet-rich plasma.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

86999	Unlisted transfusion medicine procedure
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed
G0460	Autologous platelet rich plasma (prp) for diabetic chronic wounds/ulcers, using an fda-cleared device (includes administration, dressings, phlebotomy, centrifugation, and all other preparatory procedures, per treatment) (new nomenclature 01-01-22)
P9020	Platelet rich plasma, each unit
S0157	Becaplermin gel 0.01%, 0.5 gm
S9055	Procuren or other growth factor preparation to promote wound healing

- There is a CPT category III code for injections of platelet-rich plasma: 0232T.
  - The instructions issued with the code state that it is not to be reported with codes 20550, 20551, 20600-20610, 20926, 76942, 77002, 77012, 77021 and 86965.
  - Code 0232T includes the harvesting and preparation of the platelet-rich plasma.
- For situations other than injection (when 0232T would be reported), no specific CPT codes describe the preparation of autologous blood-derived products but CPT code 86999 can be

used. It has been reported that providers have used CPT code 20926 (tissue graft, other) to describe the overall procedure. It is questionable whether platelet-rich plasma is appropriately considered a tissue graft.

- The American Medical Association's Department of Coding instructs that placement of PRP into an operative site is an inclusive component of the operative procedure performed and not separately reported.
- There is also a HCPCS code for this treatment: G0460.

ICD-10 Diagnoses

E10.41	Type 1 diabetes mellitus with diabetic mononeuropathy
E10.42	Type 1 diabetes mellitus with diabetic polyneuropathy
E10.43	Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy
E10.44	Type 1 diabetes mellitus with diabetic amyotrophy
E10.49	Type 1 diabetes mellitus with other diabetic neurological complication
E10.621	Type 1 diabetes mellitus with foot ulcer
E10.622	Type 1 diabetes mellitus with other skin ulcer
E10.628	Type 1 diabetes mellitus with other skin complications
E11.41	Type 2 diabetes mellitus with diabetic mononeuropathy
E11.42	Type 2 diabetes mellitus with diabetic polyneuropathy
E11.43	Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy
E11.44	Type 2 diabetes mellitus with diabetic amyotrophy
E11.49	Type 2 diabetes mellitus with other diabetic neurological complication
E11.621	Type 2 diabetes mellitus with foot ulcer
E11.622	Type 2 diabetes mellitus with other skin ulcer
E11.628	Type 2 diabetes mellitus with other skin complications
I70.231	Atherosclerosis of native arteries of right leg with ulceration of thigh
I70.232	Atherosclerosis of native arteries of right leg with ulceration of calf
I70.233	Atherosclerosis of native arteries of right leg with ulceration of ankle
I70.234	Atherosclerosis of native arteries of right leg with ulceration of heel and midfoot
I70.235	Atherosclerosis of native arteries of right leg with ulceration of other part of foot
I70.238	Atherosclerosis of native arteries of right leg with ulceration of other part of lower right leg
I70.241	Atherosclerosis of native arteries of left leg with ulceration of thigh
I70.242	Atherosclerosis of native arteries of left leg with ulceration of calf
I70.243	Atherosclerosis of native arteries of left leg with ulceration of ankle
I70.244	Atherosclerosis of native arteries of left leg with ulceration of heel and midfoot
I70.245	Atherosclerosis of native arteries of left leg with ulceration of other part of foot
I70.248	Atherosclerosis of native arteries of left leg with ulceration of other part of lower left leg
I70.25	Atherosclerosis of native arteries of other extremities with ulceration
I70.431	Atherosclerosis of autologous vein bypass graft(s) of the right leg with ulceration of thigh
I70.432	Atherosclerosis of autologous vein bypass graft(s) of the right leg with ulceration of calf
I70.433	Atherosclerosis of autologous vein bypass graft(s) of the right leg with ulceration of ankle
I70.434	Atherosclerosis of autologous vein bypass graft(s) of the right leg with ulceration of heel and midfoot
I70.435	Atherosclerosis of autologous vein bypass graft(s) of the right leg with ulceration of other part of foot
I70.438	Atherosclerosis of autologous vein bypass graft(s) of the right leg with ulceration of other part of lower leg
I70.441	Atherosclerosis of autologous vein bypass graft(s) of the left leg with ulceration of thigh
I70.442	Atherosclerosis of autologous vein bypass graft(s) of the left leg with ulceration of calf
I70.443	Atherosclerosis of autologous vein bypass graft(s) of the left leg with ulceration of ankle
I70.444	Atherosclerosis of autologous vein bypass graft(s) of the left leg with ulceration of heel and midfoot

I70.445 Atherosclerosis of autologous vein bypass graft(s) of the left leg with ulceration of other part of foot
I70.448 Atherosclerosis of autologous vein bypass graft(s) of the left leg with ulceration of other part of lower leg
I70.45 Atherosclerosis of autologous vein bypass graft(s) of other extremity with ulceration
I70.531 Atherosclerosis of nonautologous biological bypass graft(s) of the right leg with ulceration of thigh
I70.532 Atherosclerosis of nonautologous biological bypass graft(s) of the right leg with ulceration of calf
I70.533 Atherosclerosis of nonautologous biological bypass graft(s) of the right leg with ulceration of ankle
I70.534 Atherosclerosis of nonautologous biological bypass graft(s) of the right leg with ulceration of heel and midfoot
I70.535 Atherosclerosis of nonautologous biological bypass graft(s) of the right leg with ulceration of other part of foot
I70.538 Atherosclerosis of nonautologous biological bypass graft(s) of the right leg with ulceration of other part of lower leg
I70.541 Atherosclerosis of nonautologous biological bypass graft(s) of the left leg with ulceration of thigh
I70.542 Atherosclerosis of nonautologous biological bypass graft(s) of the left leg with ulceration of calf
I70.543 Atherosclerosis of nonautologous biological bypass graft(s) of the left leg with ulceration of ankle
I70.544 Atherosclerosis of nonautologous biological bypass graft(s) of the left leg with ulceration of heel and midfoot
I70.545 Atherosclerosis of nonautologous biological bypass graft(s) of the left leg with ulceration of other part of foot
I70.548 Atherosclerosis of nonautologous biological bypass graft(s) of the left leg with ulceration of other part of lower leg
I70.55 Atherosclerosis of nonautologous biological bypass graft(s) of other extremity with ulceration
I70.631 Atherosclerosis of nonbiological bypass graft(s) of the right leg with ulceration of thigh
I70.632 Atherosclerosis of nonbiological bypass graft(s) of the right leg with ulceration of calf
I70.633 Atherosclerosis of nonbiological bypass graft(s) of the right leg with ulceration of ankle
I70.634 Atherosclerosis of nonbiological bypass graft(s) of the right leg with ulceration of heel and midfoot
I70.635 Atherosclerosis of nonbiological bypass graft(s) of the right leg with ulceration of other part of foot
I70.638 Atherosclerosis of nonbiological bypass graft(s) of the right leg with ulceration of other part of lower leg
I70.641 Atherosclerosis of nonbiological bypass graft(s) of the left leg with ulceration of thigh
I70.642 Atherosclerosis of nonbiological bypass graft(s) of the left leg with ulceration of calf
I70.643 Atherosclerosis of nonbiological bypass graft(s) of the left leg with ulceration of ankle
I70.644 Atherosclerosis of nonbiological bypass graft(s) of the left leg with ulceration of heel and midfoot
I70.645 Atherosclerosis of nonbiological bypass graft(s) of the left leg with ulceration of other part of foot
I70.648 Atherosclerosis of nonbiological bypass graft(s) of the left leg with ulceration of other part of lower leg
I70.65 Atherosclerosis of nonbiological bypass graft(s) of other extremity with ulceration
L89.013 Pressure ulcer of right elbow, stage 3
L89.014 Pressure ulcer of right elbow, stage 4
L89.023 Pressure ulcer of left elbow, stage 3
L89.024 Pressure ulcer of left elbow, stage 4
L89.113 Pressure ulcer of right upper back, stage 3

L89.114 Pressure ulcer of right upper back, stage 4
L89.123 Pressure ulcer of left upper back, stage 3
L89.124 Pressure ulcer of left upper back, stage 4
L89.133 Pressure ulcer of right lower back, stage 3
L89.134 Pressure ulcer of right lower back, stage 4
L89.143 Pressure ulcer of left lower back, stage 3
L89.144 Pressure ulcer of left lower back, stage 4
L89.153 Pressure ulcer of sacral region, stage 3
L89.154 Pressure ulcer of sacral region, stage 4
L89.213 Pressure ulcer of right hip, stage 3
L89.214 Pressure ulcer of right hip, stage 4
L89.223 Pressure ulcer of left hip, stage 3
L89.224 Pressure ulcer of left hip, stage 4
L89.313 Pressure ulcer of right buttock, stage 3
L89.314 Pressure ulcer of right buttock, stage 4
L89.323 Pressure ulcer of left buttock, stage 3
L89.324 Pressure ulcer of left buttock, stage 4
L89.43 Pressure ulcer of contiguous site of back, buttock and hip, stage 3
L89.44 Pressure ulcer of contiguous site of back, buttock and hip, stage 4
L89.513 Pressure ulcer of right ankle, stage 3
L89.514 Pressure ulcer of right ankle, stage 4
L89.523 Pressure ulcer of left ankle, stage 3
L89.524 Pressure ulcer of left ankle, stage 4
L89.613 Pressure ulcer of right heel, stage 3
L89.614 Pressure ulcer of right heel, stage 4
L89.623 Pressure ulcer of left heel, stage 3
L89.624 Pressure ulcer of left heel, stage 4
L89.813 Pressure ulcer of head, stage 3
L89.814 Pressure ulcer of head, stage 4
L89.893 Pressure ulcer of other site, stage 3
L89.894 Pressure ulcer of other site, stage 4
L97.121 Non-pressure chronic ulcer of left thigh limited to breakdown of skin
L97.122 Non-pressure chronic ulcer of left thigh with fat layer exposed
L97.123 Non-pressure chronic ulcer of left thigh with necrosis of muscle
L97.124 Non-pressure chronic ulcer of left thigh with necrosis of bone
L97.211 Non-pressure chronic ulcer of right calf limited to breakdown of skin
L97.212 Non-pressure chronic ulcer of right calf with fat layer exposed
L97.213 Non-pressure chronic ulcer of right calf with necrosis of muscle
L97.214 Non-pressure chronic ulcer of right calf with necrosis of bone
L97.221 Non-pressure chronic ulcer of left calf limited to breakdown of skin
L97.222 Non-pressure chronic ulcer of left calf with fat layer exposed
L97.223 Non-pressure chronic ulcer of left calf with necrosis of muscle
L97.224 Non-pressure chronic ulcer of left calf with necrosis of bone
L97.311 Non-pressure chronic ulcer of right ankle limited to breakdown of skin
L97.312 Non-pressure chronic ulcer of right ankle with fat layer exposed
L97.313 Non-pressure chronic ulcer of right ankle with necrosis of muscle
L97.314 Non-pressure chronic ulcer of right ankle with necrosis of bone
L97.321 Non-pressure chronic ulcer of left ankle limited to breakdown of skin
L97.322 Non-pressure chronic ulcer of left ankle with fat layer exposed
L97.323 Non-pressure chronic ulcer of left ankle with necrosis of muscle
L97.324 Non-pressure chronic ulcer of left ankle with necrosis of bone
L97.411 Non-pressure chronic ulcer of right heel and midfoot limited to breakdown of skin
L97.412 Non-pressure chronic ulcer of right heel and midfoot with fat layer exposed

L97.413 Non-pressure chronic ulcer of right heel and midfoot with necrosis of muscle
L97.414 Non-pressure chronic ulcer of right heel and midfoot with necrosis of bone
L97.421 Non-pressure chronic ulcer of left heel and midfoot limited to breakdown of skin
L97.422 Non-pressure chronic ulcer of left heel and midfoot with fat layer exposed
L97.423 Non-pressure chronic ulcer of left heel and midfoot with necrosis of muscle
L97.424 Non-pressure chronic ulcer of left heel and midfoot with necrosis of bone
L97.511 Non-pressure chronic ulcer of other part of right foot limited to breakdown of skin
L97.512 Non-pressure chronic ulcer of other part of right foot with fat layer exposed
L97.513 Non-pressure chronic ulcer of other part of right foot with necrosis of muscle
L97.514 Non-pressure chronic ulcer of other part of right foot with necrosis of bone
L97.521 Non-pressure chronic ulcer of other part of left foot limited to breakdown of skin
L97.522 Non-pressure chronic ulcer of other part of left foot with fat layer exposed
L97.523 Non-pressure chronic ulcer of other part of left foot with necrosis of muscle
L97.524 Non-pressure chronic ulcer of other part of left foot with necrosis of bone
L97.811 Non-pressure chronic ulcer of other part of right lower leg limited to breakdown of skin
L97.812 Non-pressure chronic ulcer of other part of right lower leg with fat layer exposed
L97.813 Non-pressure chronic ulcer of other part of right lower leg with necrosis of muscle
L97.814 Non-pressure chronic ulcer of other part of right lower leg with necrosis of bone
L97.821 Non-pressure chronic ulcer of other part of left lower leg limited to breakdown of skin
L97.822 Non-pressure chronic ulcer of other part of left lower leg with fat layer exposed
L97.823 Non-pressure chronic ulcer of other part of left lower leg with necrosis of muscle
L97.824 Non-pressure chronic ulcer of other part of left lower leg with necrosis of bone
L98.491 Non-pressure chronic ulcer of skin of other sites limited to breakdown of skin
L98.492 Non-pressure chronic ulcer of skin of other sites with fat layer exposed
L98.493 Non-pressure chronic ulcer of skin of other sites with necrosis of muscle
L98.494 Non-pressure chronic ulcer of skin of other sites with necrosis of bone

REVISIONS	
06-05-2012	Policy added to the bcbsks.com web site. A stand alone policy was developed based on policy language previously contained in the Wound Care: Skin Substitutes and Growth Factors medical policy.
	In Policy section: ▪ The new stand-alone policy adds the following: "C. Use of autologous blood-derived preparations (i.e., platelet-rich plasma) is considered experimental / investigational. This includes, but is not limited to, use in the following situations: 1. Treatment of acute or chronic wounds including nonhealing ulcers 2. Adjunctive use in surgical procedures 3. Primary use (injection) for other conditions such as epicondylitis (i.e., tennis elbow), plantar fasciitis, or Dupuytren's contracture"
02-05-2014	Description section updated
	Policy section reformatted – no policy statement changes made.
	Rationale section updated
	In Coding section: ▪ HCPCS Code added: G0460 ▪ Coding information bullets updated ▪ ICD-10 Diagnoses Codes added
	References updated
10-29-2015	Description section updated
	In Policy section:

REVISIONS	
	▪ In Item C added "surgical sounds and" and removed "This includes, but is not limited to, use in the following situations:", "Adjunctive use in surgical procedures", and "Primary use (injection) for other condition such as epicondylitis(i.e. tennis elbow), plantar fasciitis, or Dupuytren's contracture" to read, "Use of autologous blood-derived preparations (ie, platelet-rich plasma) is considered experimental / investigational for the treatment of acute or chronic wounds, including surgical wounds and nonhealing ulcers."
	Rationale section updated
	In Coding section: ▪ Updated coding notations.
	References updated
04-25-2016	Description section updated
	Rationale section updated
	In Coding section: ▪ Coding notations updated
	References updated
03-01-2017	Title changed to "Recombinant and Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non–Orthopedic Conditions" from "Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Non–Orthopedic Conditions"
	Description section updated
	In Policy section: ▪ In Item A 2 d added "/uL" to correctly read "Total lymphocyte count >1000/uL" – no change in policy intent.
	Rationale section updated
	In Coding section: ▪ Removed ICD-10 Codes: E10.610, E10.618, E10.69, E11.610, E11.618, E11.69, I70.331, I70.332, I70.333, I70.334, I70.335, I70.338, I70.341, I70.342, I70.343, I70.344, I70.345, I70.348, I70.35, I70.731, I70.732, I70.733, I70.734, I70.735, I70.738, I70.741, I70.742, I70.743, I70.744, I70.745, I70.748, I70.75 ▪ Added ICD-10 Codes: L97.121, L97.122, L97.123, L97.124, L97.211, L97.212, L97.213, L97.214, L97.221, L97.222, L97.223, L97.224, L97.311, L97.312, L97.313, L97.314, L97.321, L97.322, L97.323, L97.324, L97.411, L97.412, L97.413, L97.414, L97.421, L97.422, L97.423, L97.424, L97.511, L97.512, L97.513, L97.514, L97.521, L97.522, L97.523, L97.524, L97.811, L97.812, L97.813, L97.814, L97.821, L97.822, L97.823, L97.824, L98.491, L98.492, L98.493, L98.494
	References updated
03-01-2018	Description section updated
	In Policy section: ▪ In Item B added "recombinant platelet-derived growth factor" to read "Other applications of recombinant platelet-derived growth factor (ie, becaplermin) are considered experimental / investigational, including, but not limited to:" ▪ Updated Policy Guidelines
	Rationale section updated
	References updated
04-10-2019	Description section updated
	Rationale section updated
	References updated
03-23-2021	Description section updated
	Rationale section updated
	References updated
01-01-2022	In Coding section:

REVISIONS	
	Revised nomenclature G0460 Autologous platelet rich plasma (prp) for diabetic chronic wounds/ulcers, using an fda-cleared device (includes administration, dressings, phlebotomy, centrifugation, and all other preparatory procedures, per treatment) effective 01-01-22

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