

Medical Policy



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

Professional

Original Effective Date: February 13, 2007
 Revision Date(s): June 5, 2012;
 February 5, 2014; October 29, 2015;
 April 25, 2016, March 1, 2017;
 March 1, 2018; April 10, 2019
 Current Effective Date: March 1, 2018

Institutional

Original Effective Date: December 15, 2008
 Revision Date(s): June 5, 2012;
 February 5, 2014; October 29, 2015
 April 25, 2016; March 1, 2017;
 March 1, 2018; April 10, 2019
 Current Effective Date: March 1, 2018

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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 • Quality of life • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
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 nonorthopedic indications, which include a number of wound closure-related indications.

For this review, the primary end points of interest for studies of wound closure are as follows, consistent with guidance from the U.S. Food and Drug Administration (FDA) for industry in developing products for treatment of chronic cutaneous ulcer and burn wounds¹:

1. Incidence of complete wound closure
2. Time to complete wound closure (reflecting accelerated wound closure)
3. Incidence of complete wound closure following surgical wound closure
4. 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 débridement, 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 three or more tubes of Regranex Gel in a postmarketing 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.”

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 cm², 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 with searches of the MEDLINE database. The most recent literature update was performed through October 29, 2018.

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 function^{3,4}including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two 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 randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

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 or PRP improve health outcomes compared with standard care for diabetic ulcers, pressure ulcers, venous stasis ulcers, chronic wounds, and surgical and traumatic wounds?

The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

The therapy being considered is recombinant PDGF.

Comparators

Comparators of interest include standard wound care.

Outcomes

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

Timing

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

Setting

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Studies with duplicative or overlapping populations were excluded.

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 five 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 (rhPDGF) were 5.7 [3034, 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, rhPDGF, 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	Pool 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 two 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 or PRP improve health outcomes compared with standard care for diabetic ulcers, pressure ulcers, venous stasis ulcers, chronic wounds, and surgical and traumatic wounds?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with pressure ulcers.

Interventions

The therapy being considered is recombinant PDGF.

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.

Timing

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

Setting

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Studies with duplicative or overlapping populations were excluded.

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 one of four parallel treatment groups and received either a placebo or one of three dosages of becaplermin. All patients received a standardized program of good wound care. In the two 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 PDGF 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 or PRP improve health outcomes compared with standard care for diabetic ulcers, pressure ulcers, venous stasis ulcers, chronic wounds, and surgical and traumatic wounds?

The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

The therapy being considered is recombinant PDGF.

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.

Timing

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

Setting

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Studies with duplicative or overlapping populations were excluded.

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 PDGF 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 or PRP improve health outcomes compared with standard care for diabetic ulcers, pressure ulcers, venous stasis ulcers, chronic wounds, and surgical and traumatic wounds?

The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

The therapy being considered is recombinant PDGFs.

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.

Timing

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

Setting

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Studies with duplicative or overlapping populations were excluded.

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 two 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 two groups of patients with similar diagnoses, drug use, and use of health services: one group used Regranex, and the other group did not. Results showed there were more deaths from cancer among patients who were given three 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 PDGF 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 recombinant PDGF or PRP improve health outcomes compared with standard care for diabetic ulcers, pressure ulcers, venous stasis ulcers, chronic wounds, and surgical and traumatic wounds?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with chronic wounds.

Interventions

The therapy being considered is PRP.

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.

Timing

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

Setting

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

A number of systematic reviews of the evidence on PRP have been published. A 2012 Cochrane review included 9 RCTs (total n=325 participants) of PRP for treating chronic wounds.¹⁶ This review was restricted to trials comparing PRP with no additional treatment or placebo. Four RCTs included patients with mixed chronic wounds, three included patients with venous leg ulcers, and two included patients with DFUs. Only one trial was considered to be at low-risk of bias. After a median treatment duration of 12 weeks, there was no significant difference between the PRP and control groups in complete healing of DFUs, venous leg ulcers, or mixed chronic wounds. There was no significant difference in the area epithelialized in three RCTs of mixed chronic wounds. In two RCTs of mixed chronic wounds, there was a significant difference favoring PRP in the wound area that was healed. Reviewers concluded there was no current evidence to suggest that autologous PRP would be of value for treating chronic wounds, given the small number of RCTs included, most of which were either at high or unclear risk of bias.

This Cochrane review was updated in 2016; it added a new RCT, for a total of 10 RCTs (total n=442 patients).¹⁷ Conclusions about the quality of the overall body of evidence were similar to the 2012 review. For the outcome of overall wound healing, autologous PRP did not significantly increase healing compared with standard treatment (RR=1.19; 95% CI, 0.95 to 1.50; $I^2=27%$, low-quality evidence). For wound healing in foot ulcers in people with diabetes, the evidence suggested that autologous PRP might increase healing compared with standard care (RR=1.22; 95% CI, 1.01 to 1.49; $I^2=0%$, low-quality evidence). It was unclear whether autologous PRP increased wound healing compared with standard care for venous leg ulcers (RR=1.05; 95% CI, 0.29 to 3.88; $I^2=0%$, low-quality evidence).

Other systematic reviews reached similar conclusions. For example, one from 2009 identified 42 controlled trials on PRP; of these, 20 were RCTs and were included in the systematic review, which found results to be inconclusive.¹⁸ The 20 RCTs comprised 11 trials on oral and maxillofacial surgery, 7 on chronic skin ulcers, and 2 on surgical wounds. An industry-funded systematic review from 2011 included 21 studies of PRP gel for cutaneous wound healing, 12 of which were RCTs.¹⁹ There were three main types of wounds, including open chronic wounds, acute surgical wounds with primary closure, and acute surgical wound with secondary closure. Study quality varied considerably, with three studies rated as high-quality and six rated as poor-quality. Two additional studies could not be rated because they were published only as an abstract and letter. Meta-analysis of the effect of PRP on complete wound healing of chronic wounds was limited by the inclusion of poor-quality studies. No high-quality RCTs showed improvement in complete healing with PRP. A 2015 systematic review of PRP for DFUs identified 6 small RCTs published between 1992 and 2011.²⁰ Although five of the studies reported positive results with PRP, the studies were small, and the possibility of selective publication bias was not assessed.

Since the publication of the 2015 update to the Cochrane review on PRP for wounds, Escamilla Cardenosa et al (2017) reported on an un-blinded RCT comparing PRP and saline for venous ulcer treatment.²¹ The trial included 61 patients (102 ulcers) who were randomized to the weekly application of a PRP dressing (31 patients, 55 ulcers) or weekly wet-to-dry dressing changes with saline (30 patients, 47 ulcers) over a 24-week period. The average percentage healed area in the PRP group was 67.7% and 11.2% in the control group ($p<0.001$). PRP group members had greater reductions in pain with the intervention.

Section Summary: PRP 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. For chronic wounds, including diabetic ulcers, pressure ulcers, and vascular ulcers, systematic reviews of RCTs have not found that PRP are associated with improved outcomes.

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 recombinant PDGF or PRP improve health outcomes compared with standard care for diabetic ulcers, pressure ulcers, venous stasis ulcers, chronic wounds, and surgical and traumatic wounds?

The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

The therapy being considered is PRP.

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.

Timing

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

Setting

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Studies with duplicative or overlapping populations were excluded.

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.²² 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 two groups (one 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.²³ The two groups were comparable at baseline. At the end of cardiac surgery, PRP gel was applied on the sternum before the closure of subcutaneous tissue. Rates of both deep and superficial wound infection 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.²⁴ Speech and velopharyngeal valve movement on follow-up were evaluated by three 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).²⁵ 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 ten days after surgery. A FACES Pain Scale was used for children ages four to seven years, while a numeric pain rating scale was used for children older than seven years. Diaries from 83% of patients showed no differences in pain, medication doses, activity, and days eating solid foods between the 2 conditions.

Other 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.²⁶

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 intervention. 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.²⁷

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).²⁸ Conventional treatment consisted of topical washing

and cleaning of the wounds, removal of the necrotic tissue, and dressing in petroleum jelly gauze every two days. In all patients with open tibial fractures, an external fixation system was applied. PRP gel was applied to the wounds after surgical débridement 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.²⁹ 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 four consecutive days. Twenty-seven patients with deep second-degree burns were recruited and then those that met eligibility criteria were randomized into two groups. The LPRP group received the intervention (n = 15) and the control group received a placebo application (n = 12). A concentration of 1.0×10^7 platelets/cm² (wound area) was sprayed on the wound evenly. Function was assessed by the percentage of wound closure and bacteria picking out rate at weeks two and three. The mean burn area of control for the LPRP was 75.65 ± 50.72 cm² and 99.73 ± 70.17 cm² (p=0013), respectively. In the control group, the original wound area was 25.49 cm² at baseline, 23.79 cm² (6.67% healed) at week 2, and 4.34 cm² (86.40% healed) at week 3. In the LPRP group, the original wound area was 84.36 cm², followed by 23.96 cm² (71.59% healed) at week 2, and 0.63 cm² (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.³⁰

Section Summary: PRP 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. The 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 diabetic neuropathic ulcers and pressure ulcers. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have pressure ulcers who receive recombinant PDGF, the evidence includes RCTs and systematic reviews. The 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 a meaningful 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. The 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 the effects of the technology on health outcomes.

Platelet-Rich Plasma

For individuals who have chronic wounds or acute surgical or traumatic wounds who receive PRP, the evidence includes a number of small controlled trials. The 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 the effects of the technology on health outcomes.

For individuals who have chronic wounds who receive PRP, the evidence includes a number of small controlled trials. The 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 the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American College of Physicians

The American College of Physicians (2015) published guidelines on treatment of pressure ulcers.³¹ 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.”

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) and venous ulcers (2015)^{32,33}:

- 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)
- Venous ulcer: “Platelet derived growth factor has shown no significant effects on VU [venous ulcer healing or recurrence]” (level A evidence).

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2016) updated its guidance on the prevention and management of diabetic foot problems.³⁴ 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.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (2012) revised its national coverage decision on autologous blood-derived products for chronic non-healing wounds.³⁵ This revision replaces prior noncoverage decisions.^{36,37}

The Centers for Medicare & Medicaid Services covers autologous PRP only for patients who have chronic non-healing diabetic, pressure, and/or venous wounds and when all of the following conditions are met:

“The patient is enrolled in a clinical research study that addresses the following questions using validated and reliable methods of evaluation...

The clinical research study must meet the requirements specified below to assess the effect of PRP for the treatment of chronic nonhealing diabetic, pressure, and/or venous wounds. The clinical study must address:

Prospectively, do Medicare beneficiaries that have chronic non-healing diabetic, pressure, and/or venous wounds who receive well-defined optimal usual care, along with PRP therapy, experience clinically significant health outcomes compared to patients who receive well-defined optimal usual care for chronic non-healing diabetic, pressure, and/or venous wounds as indicated by addressing at least one of the following:

- a. complete wound healing;
- b. ability to return to previous function and resumption of normal activities; or
- c. reduction of wound size or healing trajectory, which results in the patient’s ability to return to previous function and resumption of normal activities?”

Ongoing and Unpublished Clinical Trials

Some larger studies that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02307448 ^a	Effectiveness of Autologous Platelet Rich Plasma in the Treatment of Chronic Non-Healing Wounds	1500	Mar 2016 (ongoing)
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	Nov 2016 (ongoing)
NCT02213952	Efficacy of Autologous Platelet-Rich Plasma in the Treatment of Vascular Ulcers in Primary Care: Clinical Trial Phase III	150	Dec 2020
NCT02312596 ^a	A Prospective, Randomized Clinical Trial of PRP Concepts Fibrin Bio-Matrix in Chronic Non-Healing Pressure Ulcers	250	Jul 2020

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02312570 ^a	Clinical Trial of ECLIPSE PRP™ Wound Biomatrix in Chronic Non-Healing Pressure Ulcers	250	Sep 2019
NCT02071979 ^a	Registry Trial of the Effectiveness of Platelet Rich Plasma for Chronic Non-Healing Wounds (CMS) [Terminated]	1500	Dec 2021
Unpublished			
NCT02209662 ^a	A Multi-Center, Randomized Trial Comparing the Effectiveness of APIC-PRP to Control, When Added to Standard of Care in the Treatment of Non-healing Diabetic Foot Ulcers	274	Dec 2015 (unknown)

NCT: national clinical trial.

^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 for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment
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	<p>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.</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ 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: <ol style="list-style-type: none"> 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	<p>Description section updated</p> <p>Policy section reformatted – no policy statement changes made.</p> <p>Rationale section updated</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ HCPCS Code added: G0460 ▪ Coding information bullets updated ▪ ICD-10 Diagnoses Codes added <p>References updated</p>
10-29-2015	<p>Description section updated</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ 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." <p>Rationale section updated</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Updated coding notations. <p>References updated</p>
04-25-2016	<p>Description section updated</p> <p>Rationale section updated</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Coding notations updated

REVISIONS	
	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: <ul style="list-style-type: none"> ▪ 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: <ul style="list-style-type: none"> ▪ 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: <ul style="list-style-type: none"> ▪ 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

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