Title: Recombinant and Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other Non-Orthopedic Conditions

Description/Background

WOUND HEALING TREATMENT
A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factors (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 has also 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 the 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 type of transforming growth factors, and thus PRP has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries.

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) and Hemaseel® (Haemacure Corp.) are examples of commercially available fibrin sealants. Autologous fibrin sealants can 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 the purposes of this review, the primary end points of interest for studies of wound closure are as follows, consistent with guidance from the FDA for industry in developing products for treatment of chronic cutaneous ulcer and burn wounds: (1)

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.

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**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 this 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 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.”

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 (CFR) title 21, parts 1270 and 1271. Blood products such as platelet-rich plasma are included in these regulations.
Under these regulations, certain products including blood products such as PRP are exempt and therefore, do not follow the traditional FDA regulatory pathway. To date, FDA has not attempted to regulate activated PRP. (2)

Numerous PRP preparation systems that have been cleared for marketing by 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.

Medical Policy Statement

The safety and effectiveness of recombinant platelet-derived growth factor (Regranex®) have been established; it is a useful therapeutic option when indicated.

The use of platelet-rich plasma (ie, autologous blood-derived growth factor or autologous platelet gel) has not been established. There is insufficient evidence to draw definitive conclusions regarding the clinical efficacy of autologous platelet concentrate or gel, therefore, they are considered experimental/investigational.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Inclusions:
Recombinant platelet-derived growth factor (Regranex®) when used as an adjunct to standard wound management for the following indications:
- When used according to the U.S. Food and Drug Administration (FDA)-labeled indication, (i.e., neuropathic diabetic ulcers extending into the subcutaneous tissue)
- As a treatment of pressure ulcers extending into the subcutaneous tissue

Exclusions:
Recombinant platelet-derived growth factor (Regranex®) for:
- Ischemic ulcers
- Venous stasis ulcers
- Ulcers not extending through the dermis into the subcutaneous tissue.

The use of platelet-rich plasma (ie, autologous blood-derived growth factors or autologous platelet gel [eg, Aurix™ / Autologel™ and SafeBlood®]) for the treatment of acute or chronic wounds, including surgical wounds and nonhealing ulcers, is considered experimental/investigational.
CPT/HCPCS Level II Codes (Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)

**Established codes:**
- S0157

**Other codes (investigational, not medically necessary, etc.):**
- G0460
- P9020
- S9055
- 0232T

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

**Rationale**

The platelet-rich plasma portion of this evidence review on platelet-derived wound-healing formulae was originally based on a 1992 Blue Cross Blue Shield Association 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 platelet-rich plasma (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 injection is necessary.(4-8)

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.
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 wound specialists, dermatologists and endocrinologists 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, quality of life, 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 longer 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 Blue Cross Blue Shield Association 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 meet the patient selection criteria defined therein.(9) Beca
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. 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. Among a cohort of 24,898 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 25,000 patients treated for foot ulcers, 2394 (9.6%) received 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 randomized controlled trials on topical growth factors compared with standard of care (SOC) 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 (SUCRA). In total, 26 studies with 2088 participants and 1018 adverse events were included. The pooled estimates for recombinant 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.

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

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Literature Search</th>
<th>Studies</th>
<th>Participants</th>
<th>N</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
</table>

PRP: autologous platelet-rich plasma; RCT: Randomized Controlled Trial; rhEGF: recombinant epidermal growth factor; rhPDGF: recombinant human platelet-derived growth factor
Section Summary: Recombinant Platelet-Derived Growth Factor 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 platelet-derived growth factor 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 diabetic lower-extremity ulcers are actively managed by wound specialists, dermatologists and endocrinologists 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, quality of life, and treatment-related morbidity.

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

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

REVIEW OF EVIDENCE

Rees et al (1999) conducted a 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 of patients 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 that there is no clinical benefit in increasing the potency above 0.01%. A third group of patients received becaplermin 0.01% twice daily. This group did not report an improved outcome 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 wound specialists, dermatologists and primary care providers 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, quality of life, and treatment-related morbidity.

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

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.
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 quality of life.

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 populations of interest are individuals with acute surgical or traumatic wounds.

Interventions
The therapy being considered is recombinant PDGF.

Patients with acute surgical or traumatic wounds are actively managed by wound specialists, dermatologists and primary care providers 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, quality of life, 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 principles described in the first indication.
REVIEW OF EVIDENCE

Topical recombinant PDGF has also been investigated for repair of work-related fingertip injuries. A 2005 prospective controlled trial in the United States alternately assigned 50 patients (fingertip wound area ≥1.5 cm or more, 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 study was limited by its small sample size, the method of randomization, and the potential for investigator bias (although examining physicians were blinded to treatment allocation, actual treatment may 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 prior to its approval (in December 1997) for any evidence of adverse effects, 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 that there were more deaths from cancer among patients who were given 3 or more prescriptions for Regranex than deaths for those who were not treated with Regranex. No single type of cancer was identified; deaths from all types of cancer were observed. In 2008, the FDA 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 platelet-rich plasma 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 platelet-rich plasma (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.

Patient with chronic wounds are actively managed by wound specialists and primary care providers 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, quality of life, 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 principles described in the first indication.

**REVIEW OF EVIDENCE**

**Systematic Reviews**
A number of systematic reviews of the evidence on PRP have been published.(16-23) 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.(20-23) 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, the summaries of those systematic reviews that focused on specific wound types with search dates that extend to at least 2015 are included.(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

<table>
<thead>
<tr>
<th>Primary Study (Year)</th>
<th>Del Pino-Sedeno 2018 21</th>
<th>Li 2019 22</th>
<th>Qu 2020 23</th>
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<td>Ahmed 2017 24</td>
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<td>Chen 2008 25</td>
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<td>Driver 2006 26</td>
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<td>Elsaid 2020 27</td>
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<td>Friese 2007 (conference proceeding) 28</td>
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<td>Game 2018 29</td>
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<td>Gude 2019 30</td>
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<td>Kakagia 2007 31</td>
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<td>Karimi 2016 32</td>
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<td>Milek 2017 36</td>
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<td>Qi 2014 37</td>
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<td>Saad Setta 2011 38</td>
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<td>Saldalamacchia 2004 39</td>
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<td>Serra 2013 40</td>
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<td>Singh 2018 41</td>
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<td>Steed 1992 42</td>
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<td>Steed 1996 43</td>
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<td>Xie 2020 44</td>
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<td>Yang 2017 45</td>
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<td>Zhang 2016 46</td>
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<td>Zhou 2015 47</td>
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<tr>
<td>Zhu 2012 48</td>
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* 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.

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 cm2; 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. 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. 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 one 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>del Pino-Sedeno (2018)</td>
<td>Inception-2017</td>
<td>10</td>
<td>Patients with diabetic foot ulcers</td>
<td>N=525 (13-117)</td>
<td>RCTs, longitudinal observational studies</td>
<td>3 wk to 128.57 wk</td>
</tr>
<tr>
<td>Li (2019)</td>
<td>2004-2017</td>
<td>15</td>
<td>Patients with diabetic chronic cutaneous wounds/ulcers that do not show signs of healing in 4 weeks</td>
<td>N=829 (14-117)</td>
<td>RCTs</td>
<td>NR</td>
</tr>
<tr>
<td>Qu (2020)</td>
<td>Inception-2020</td>
<td>14</td>
<td>Adults with lower extremity diabetic ulcers, lower extremity venous ulcers, or pressure ulcers in any location, or a mix of these 3 etiologies</td>
<td>N=1,096 (range NR)</td>
<td>RCTs</td>
<td>Median = 6 wk (range, none to 11 months)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Healing Rate</th>
<th>Healing Time</th>
<th>Complete Wound Healing</th>
<th>Risk of Infection</th>
<th>Wound complications</th>
<th>Pain Reduction</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>del Pino-Sedeno (2018)</td>
<td>RR</td>
<td>-1.11</td>
<td>1.41</td>
<td>0.57</td>
<td>2.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MD</td>
<td>-11.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>-20.69 to -1.68</td>
<td>1.08 to 1.84</td>
<td>0.25 to 1.28</td>
<td>0.23 to 33.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>.02</td>
<td>.01</td>
<td>.17</td>
<td>.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li (2019)</td>
<td>RR</td>
<td>1.39</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>MD</td>
<td>-9.18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
<td></td>
<td>0.34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>1.29 to 1.50</td>
<td>-11.32 to -7.05</td>
<td>0.15 to 0.77</td>
<td>95% CI</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>P-value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.009</td>
<td>P-value</td>
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</tr>
<tr>
<td>Qu (2020)</td>
<td>RR</td>
<td>1.20</td>
<td>0.77</td>
<td>2.09</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>WMD</td>
<td></td>
<td></td>
<td></td>
<td>-1.10 a</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>1.09 to 1.32</td>
<td>0.54 to 1.11</td>
<td>-1.81 to -0.39</td>
<td>0.31 to 13.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td>P-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carter (2011)</td>
<td>Risk difference</td>
<td>0.22</td>
<td>-0.02</td>
<td>-0.75</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>0.05 to 0.38</td>
<td>-0.06 to 0.01</td>
<td>-2.38 to 0.89</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Z</td>
<td>2.54</td>
<td>1.42</td>
<td>0.90</td>
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</tr>
</tbody>
</table>

*Visual analog scale
CI: confidence interval; MD: mean difference; OR: odds ratio; RR: risk ratio; 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; I²=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 AHRQ review in finding no significant difference in complete wound closure (RR=2.54; 95% CI, 0.42 to 15.30; 4 studies, n=156; I²=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

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saha et al (2020)[6]</td>
<td>Iran</td>
<td>1</td>
<td>2016 to 2018</td>
<td>Individuals with clinically diagnosed trophic ulcers due to leprosy</td>
<td>Autologous PRP therapy with total contact casting (N=59)</td>
<td>Only total contact casting (N=59)</td>
</tr>
</tbody>
</table>

PRP: Platelet-rich plasma

Table 6. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Complete Healing</th>
<th>Healing Time</th>
<th>Pain</th>
<th>Quality of Life</th>
<th>Infection</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saha et al (2020)[6]</td>
<td>22 (39.29%) vs 11 (21.15%); p NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0 vs 0; p=.773</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: Not reported

Table 7. Study Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparator</th>
<th>Outcomesd</th>
<th>Duration of Follow-upf</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Data Completenessd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saha et al (2020)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
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 populations of interest are 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 wound specialists and primary care providers 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, quality of life, 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 principles described in the first indication.
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 difference 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 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 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 this study 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 audiorecording of audioperceptual assessment (APA). At 6 months, PRP-treated patients had better nasality grade on APA (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 to 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 either the patient or 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 the 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 a 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, 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.(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 one 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 a prospective RCT that evaluated treatment of acute traumatic wounds (open fractures, closed fractures with skin necrosis, and 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 with 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 debridement and
placement of the external fixation system. The time needed for preparation and application of
the PRP gel was 52 minutes. Thereafter, 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 randomized controlled trial 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 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 x 107 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 2 and 3. 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 for 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 Platelet-Derived Growth Factors
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, 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 qualitatively 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. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, 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. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, 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 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, quality of life, 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 the effects of the technology on health outcomes.

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, quality of life, 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 found that this 2015 guideline is listed an 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 on 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

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
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</tr>
<tr>
<td>NCT02312596a</td>
<td>A Prospective, Randomized Clinical Trial of PRP Concepts Fibrin Bio-</td>
<td>250</td>
<td>Jul 2021</td>
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<td>Matrix in Chronic Non-Healing Pressure Ulcers</td>
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</tr>
<tr>
<td>NCT02312570a</td>
<td>A Prospective, Randomized Clinical Trial of PRP Concepts Fibrin Bio-</td>
<td>250</td>
<td>Jul 2021</td>
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<tr>
<td>NCT02307448a</td>
<td>Effectiveness of Autologous Platelet Rich Plasma in the Treatment of</td>
<td>80</td>
<td>Dec 2022</td>
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<td>Chronic Non-Healing Wounds</td>
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<tr>
<td>NCT02402374a</td>
<td>Randomized, Placebo-controlled, Blind-assessor Study to Evaluate the</td>
<td>192</td>
<td>Dec 2020</td>
</tr>
<tr>
<td></td>
<td>Safety and Efficacy of Autologous Platelet Rich Plasma Gel Prepared</td>
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<tr>
<td></td>
<td>With the RegenKit-BCT Plus Family of Kits for the Treatment of</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Diabetic Foot Ulcer</td>
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**Government Regulations**

**National/Local:**
**National Coverage Determination (NCD) for Blood-Derived Products for Chronic Non-Healing Wounds (270.3)**
**Effective Date of this Version: 8/2/2012**
**Implementation Date: 7/1/2013**

**Indications and Limitations of Coverage**

**B. Nationally Covered Indications**

Effective August 2, 2012, upon reconsideration, The Centers for Medicare and Medicaid Services (CMS) has determined that platelet-rich plasma (PRP) – an autologous blood-derived product, will be covered only for the treatment of chronic non-healing diabetic, venous and/or pressure wounds and only when the following conditions are met:

The patient is enrolled in a clinical trial that addresses the following questions using validated and reliable methods of evaluation. Clinical study applications for coverage pursuant to this National coverage Determination (NCD) must be received by August 2, 2014.

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

Prospectively, do Medicare beneficiaries that have chronic non-healing diabetic, venous and/or pressure 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, venous and/or pressure 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?

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?

[See NCD for clinical trial standards]

**C. Nationally Noncovered Indications**

Effective April 27, 2006, coverage for treatments utilizing becaplermin, a non-autologous growth factor for chronic, non-healing subcutaneous wounds, remains nationally non-covered under Part B based on section 1861 (s)(2)(A) and (B) of the Social Security Act because this product is usually administered by the patient.
Proposed Decision Memo for Autologous Blood-Derived Products for Chronic Non-Healing Wounds (CAG-00190R4); December 21, 2020

Decision Summary
The Centers for Medicare & Medicaid Services (CMS) proposes to cover autologous platelet-rich plasma (PRP) for the treatment of chronic non-healing diabetic wounds under section 1862(a)(1)(A) of the Social Security Act (the Act).

CMS proposes that coverage of autologous PRP for the treatment of all other chronic non-healing wounds will be determined by local Medicare Administrative Contractors (MACs) under section 1862(a)(1)(A) of the Act.

History of Medicare Coverage
In 1992, CMS issued a national coverage determination non-covering platelet-derived wound healing formulas intended to treat patients with chronic, non-healing wounds. CMS conducted reconsiderations in 2003, 2006, and 2008. For those reconsiderations, national non-coverage was upheld, except that as part of the 2006 reconsideration, CMS noted coverage for routine costs when used in accordance with the clinical trial policy defined in section 310.1 of the National Coverage Determinations Manual.

As a result of the 2012 reconsideration, CMS issued a national coverage determination covering the use of autologous platelet-rich plasma (PRP) for the treatment of chronic wounds under Coverage with Evidence Development (CED) only for patients who have chronic non-healing diabetic, pressure, and/or venous wounds and when specific conditions were met. The current policy is codified in 270.3 of the Medicare National Coverage Determinations manual. Section 270.3 of the NCD Manual has been included at Appendix C.

A. Current Request
On May 9, 2019, CMS received a complete, formal request from Nuo Therapeutics to reconsider the national coverage determination for Autologous Blood-Derived Products for Chronic Non-Healing Wounds. The requester stated that autologous Platelet-Rich Plasma (PRP) is the prevalent blood-derived therapeutic product used for treating chronic non-healing wounds and asked that CMS re-evaluate the coverage of Aurix (the proprietary formulation of autologous PRP manufactured by Nuo Therapeutics, Inc.) for the treatment of chronic, non-healing diabetic foot ulcers. CMS broadened the scope of this reconsideration to include autologous PRP for the treatment of chronic non-healing diabetic, venous, and pressure wounds. The request letter can be found here: https://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx?NCAId=300.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicaid Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)
Related Policies

Orthopedic Applications of Platelet-Rich Plasma
Orthopedic Applications of Stem Cell Therapy
Prolotherapy
Wound Therapy (BCN Only)

References


55. Sidman JD, Lander TA, Finkelstein M. Platelet-rich plasma for pediatric tonsillectomy patients. Laryngoscope 2008; 118(10):1765-7. PMID 18622315


The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 1/20/21, the date the research was completed.
### Joint BCBSM/BCN Medical Policy History

<table>
<thead>
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<th>Policy Effective Date</th>
<th>BCBSM Signature Date</th>
<th>BCN Signature Date</th>
<th>Comments</th>
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Next Review Date: 1st Qtr, 2022
BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: RECOMBINANT AND AUTOLOGOUS PLATELET-DERIVED GROWTH FACTORS AS A TREATMENT OF WOUND HEALING AND OTHER NON-ORTHOPEDIC CONDITIONS

I. Coverage Determination:

<table>
<thead>
<tr>
<th>Plan Type</th>
<th>Description</th>
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<tr>
<td>Commercial HMO (includes Self-Funded groups unless otherwise specified)</td>
<td>Recombinant platelet derived growth factor covered; criteria apply. Autologous platelet derived growth factors not covered.</td>
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<tr>
<td>BCNA (Medicare Advantage)</td>
<td>See the Government Regulations section of this policy.</td>
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<tr>
<td>BCN65 (Medicare Complementary)</td>
<td>Coinsurance covered if primary Medicare covers the service.</td>
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</tbody>
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II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member’s certificate and is not guaranteed. Please consult the individual member’s certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.