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

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

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Contains Public Information
### Populations

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### Description

The use of blood-derived growth factors, including recombinant platelet-derived growth factors (PDGFs) and platelet-rich plasma (PRP), as a treatment of wounds or other miscellaneous non-orthopedic conditions, including but not limited to treatment of diabetic ulcers, pressure ulcers, ulcers related to venous stasis, 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 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 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 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 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 platelet-derived growth factor 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 (CFR) title 21, parts 1270 and 1271. Blood products such as platelet-rich plasma (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, FDA has not attempted to regulate activated PRP.²

Numerous PRP preparation systems 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.
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 November 13, 2017.

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
Diabetic Lower-Extremity Ulcers
The portion of this evidence review on the use of recombinant platelet-derived growth factor (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. 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. 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. A propensity score method with covariates to statistically model treatment selection was used to adjust for selection bias; results were stratified by 5 propensity score groups. Overall, the rate of healing was 26.5% in the control group and 33.5% in patients treated with recombinant PDGF. The relative risk (RR), controlling for the propensity to receive PDGF, was 1.32 (95% CI, 1.22 to 1.38) for healing and 0.65 (95% CI, 0.54 to 0.78) for amputation (6.4% in controls vs 4.9% in the PDGF group). The analysis also indicated that 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.

Section Summary: Diabetic Lower-Extremity Ulcers
Results from RCTs have shown improved rates of healing with use of recombinant PDGF for diabetic lower-extremity ulcers. The increase in the rate of healing must be balanced with the potential for increased risk from cancer. Overall the evidence is sufficient that use of recombinant PDGF improves health outcomes.

Pressure Ulcers
Rees et al (1999) conducted an RCT focusing on the use of becaplermin gel as a treatment for pressure ulcers. Patient selection criteria included full-thickness ulcers and an anatomic location where pressure could be offloaded during treatment. This latter patient selection criterion might have limited the number of patients with pressure ulcers who would have been considered candidates for becaplermin therapy. Patients were randomized to 1 of 4 parallel treatment groups and received either a placebo or 1 of 3 dosages of becaplermin. All patients received a standardized program of good wound care. In the 2 groups treated with the oncedaily 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 received becaplermin 0.01% twice daily. That group did not report improved outcomes compared with placebo, a finding that is unexplained.

Section Summary: Pressure Ulcers
Results from RCTs have shown improved rates of healing with use of recombinant PDGF for diabetic pressure ulcers. The increase in the rate of healing must be balanced with the potential for increased risk from cancer. Overall the evidence is sufficient that use of recombinant PDGF improves health outcomes.
Venous Leg Ulcers
In 2011, Senet et al in France published a multicenter, double-blind RCT of becaplermin gel for venous leg ulcers.\(^7\) 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: Venous Leg Ulcers**
The evidence is insufficient to determine whether becaplermin gel improves health outcomes when used to treat venous leg ulcers.

Acute Surgical or Traumatic Wounds
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).\(^8\) Statistical analysis showed that baseline characteristics of the 2 groups were similar for patient age, wound area (2.2-2.4 cm), and distribution of fingertip injuries across the digits. Assessment by an independent physician showed that, compared with the surgical intervention, treatment with recombinant PDGF resulted in faster return to work (10 days vs 38 days) and wound healing (25 days vs 35 days), less functional impairment (10% vs 22%), and less need for physical therapy (20% vs 56%), respectively. Fingertips treated with PDGF were also reported to have satisfactory aesthetic results, while surgically treated fingertips were shorter and often unsightly. These results, if confirmed in additional RCTs, could lead to improvement in health outcomes for patients with fingertip injuries. However, this trial was limited by its small sample size, method of randomization, and potential for investigator bias (although examining physicians were blinded to treatment allocation, actual treatment might have been obvious).

**Section Summary: Acute Surgical or Traumatic Wounds**
The evidence is insufficient to determine whether becaplermin gel improves health outcomes when used to treat acute or traumatic wounds.

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

**Platelet-Rich Plasma (IE, Autologous Blood-Derived Preparations)**
The portion of this evidence review on platelet-derived wound healing formulae was informed by a 1992 TEC Assessment that primarily focused on the Procuren process. 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.

**Mixed Wound Types (Chronic and Surgical)**

**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. 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 diabetic foot ulcers. Only 1 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 diabetic foot ulcers, venous leg ulcers, or mixed chronic wounds. There was no significant difference in the area epithelialized in 3 RCTs of mixed chronic wounds. In 2 RCTs of mixed chronic wounds, there was a significant difference favoring PRP in the wound area that was healed. Reviewers concluded that 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). 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. The 20 RCTs comprised 11 trials on oral and maxillofacial surgery, 7 on chronic skin ulcers, and 2 on surgery wounds. An industry-funded systematic review from 2011 included 21 studies of PRP gel for cutaneous wound healing, 12 of which were RCTs. There were 3 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 3 studies rated as high-quality and 6 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 diabetic foot ulcers identified 6 small RCTs.
published between 1992 and 2011. Although five of the studies reported positive results with PRP, the studies were small, and the possibility of selective publication bias was not assessed.

**Chronic Wounds**

Since the publication of the 2015 update to the Cochrane review on PRP for wounds, Escamilla Cardenosa et al (2017) reported on an unblinded RCT comparing PRP and saline for venous ulcer treatment. 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: Chronic Wounds**

The evidence for autologous PRP for a variety of chronic wounds includes RCTs, which have been summarized in a systematic review. For chronic wounds, including diabetic ulcers, pressure ulcers, and vascular ulcers, the systematic review of RCTs did not find that PRP was associated with improved outcomes.

**Acute Surgical or Traumatic Wounds**

**Surgical Wounds**

**Aortic Arch Repair**

In 2015, Zhou et al 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. An anesthesiologist prepared the PRP so that the surgeon was unaware of the treatment group. The volume of PRP transfused was 726 mL and led to a reduction in transfusion rates for red blood cells, frozen plasma, cryoprecipitate, and platelets by 34% to 70% (p<0.02). Hospital length of stay was also reduced (9.4 days vs 12.7 days). There was no difference in mortality between the 2 groups (1 patient in each group) and no significant differences in postoperative complications or other outcome measures. Corroboration of the effect of PRP on perioperative blood transfusion is needed.

**Sternotomy Wounds**

In 2015, Serraino et al 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. 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 these results is limited by likely differences in treatments over time. RCTs are needed to evaluate this potential use of PRP.

**Otolaryngology**

In 2016, El-Anwar et al reported on an RCT that evaluated PRP in 44 children (age range, 12-23 months) undergoing repair of a complete cleft palate. Speech and velopharyngeal valve movement on follow-up were evaluated by 3 judges who “usually assessed every patient blindly,” physical examination, video nasoendoscopy, and audio recording of audio perceptual assessment. At 6 months, PRP-treated patients had better nasality grade on audio perceptual assessment (p=0.024) and better velopharyngeal closure on endoscopy (p=0.016).
A 2008 double-blind RCT assessed the efficacy of PRP following tonsillectomy in 70 children (age range, 4-15 years). PRP was placed into the tonsil beds of half of the children, where it was directly visible. To compare pain symptoms and recovery, a daily diary was completed by the patient or a family member for 10 days after surgery. A FACES Pain Scale was used for children ages 4 to 7 years, while a numeric pain rating scale was used for children older than 7 years. Diaries from 83% of patients showed no differences in pain, medication doses, activity, and days eating solid foods between the 2 conditions.

**Other 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.

**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). 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 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.

In 2016, Marck et al 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. 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.

**Section Summary: Acute Surgical or Traumatic Wounds**

The evidence for autologous PRP for a variety of acute and traumatic wounds includes RCTs, which have been summarized in several systematic reviews. For a variety of 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 or pressure ulcers who receive recombinant PDGF, the evidence includes randomized controlled trials 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 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 randomized controlled trials. 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 or 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 the effects of the technology on health outcomes.

**Practice Guidelines and Position Statements**

**American College of Physicians**

In 2015, the American College of Physicians (ACP) published guidelines on treatment of pressure ulcers. 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):

- 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**

In 2016, the National Institute for Health and Care Excellence updated its guidance on the prevention and management of diabetic foot problems. The guidance stated that neither autologous platelet-rich plasma (PRP) 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 1.
Table 1. Summary of Key Trials

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<td>A Prospective Randomized Controlled Blinded Study to Evaluate the Safety and Efficacy of rhPDGF-BB Saturated Collagen Wound Dressings on Diabetic Foot Ulcers</td>
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<td>NCT02213952</td>
<td>Efficacy of Autologous Platelet-Rich Plasma in the Treatment of Vascular Ulcers in Primary Care: Clinical Trial Phase III</td>
<td>150</td>
<td>Dec 2017 (ongoing)</td>
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<tr>
<td>NCT02312596a</td>
<td>A Prospective, Randomized Clinical Trial of ECLIPSE PRP™ Wound Biomatrix in Non-Healing Diabetic Foot Ulcers</td>
<td>250</td>
<td>Jul 2018</td>
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<td>NCT02312570a</td>
<td>Clinical Trial of ECLIPSE PRP™ Wound Biomatrix in Chronic Non-Healing Pressure Ulcers</td>
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<td>NCT02402374a</td>
<td>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</td>
<td>192</td>
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<tr>
<td>NCT02071979a</td>
<td>Registry Trial of the Effectiveness of Platelet Rich Plasma for Chronic Non-Healing Wounds (CMS)</td>
<td>1500</td>
<td>Dec 2021</td>
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<tr>
<td><strong>Unpublished</strong></td>
<td></td>
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<tr>
<td>NCT02209662a</td>
<td>A Multi-Center, Randomized Trial Comparing the Effectiveness of API-PRP to Control, When Added to Standard of Care in the Treatment of Non-healing Diabetic Foot Ulcers</td>
<td>274</td>
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<td>Effectiveness of Autologous Platelet Rich Plasma in the Treatment of Chronic Non-Healing Wounds</td>
<td>1500</td>
<td>Mar 2016 (unknown)</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>E10.41</td>
<td>Type 1 diabetes mellitus with diabetic mononeuropathy</td>
</tr>
<tr>
<td>E10.42</td>
<td>Type 1 diabetes mellitus with diabetic polyneuropathy</td>
</tr>
<tr>
<td>E10.43</td>
<td>Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy</td>
</tr>
<tr>
<td>E10.44</td>
<td>Type 1 diabetes mellitus with diabetic amyotrophy</td>
</tr>
<tr>
<td>E10.49</td>
<td>Type 1 diabetes mellitus with other diabetic neurological complication</td>
</tr>
<tr>
<td>E10.621</td>
<td>Type 1 diabetes mellitus with foot ulcer</td>
</tr>
<tr>
<td>E10.622</td>
<td>Type 1 diabetes mellitus with other skin ulcer</td>
</tr>
<tr>
<td>E10.628</td>
<td>Type 1 diabetes mellitus with other skin complications</td>
</tr>
<tr>
<td>E11.41</td>
<td>Type 2 diabetes mellitus with diabetic mononeuropathy</td>
</tr>
<tr>
<td>E11.42</td>
<td>Type 2 diabetes mellitus with diabetic polyneuropathy</td>
</tr>
<tr>
<td>E11.43</td>
<td>Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy</td>
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</tr>
<tr>
<td>E11.628</td>
<td>Type 2 diabetes mellitus with other skin complications</td>
</tr>
<tr>
<td>I70.231</td>
<td>Atherosclerosis of native arteries of right leg with ulceration of thigh</td>
</tr>
<tr>
<td>I70.232</td>
<td>Atherosclerosis of native arteries of right leg with ulceration of calf</td>
</tr>
<tr>
<td>I70.233</td>
<td>Atherosclerosis of native arteries of right leg with ulceration of ankle</td>
</tr>
<tr>
<td>I70.234</td>
<td>Atherosclerosis of native arteries of right leg with ulceration of heel and midfoot</td>
</tr>
<tr>
<td>I70.235</td>
<td>Atherosclerosis of native arteries of right leg with ulceration of other part of foot</td>
</tr>
<tr>
<td>I70.238</td>
<td>Atherosclerosis of native arteries of right leg with ulceration of other part of lower right leg</td>
</tr>
<tr>
<td>I70.241</td>
<td>Atherosclerosis of native arteries of left leg with ulceration of thigh</td>
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<tr>
<td>I70.242</td>
<td>Atherosclerosis of native arteries of left leg with ulceration of calf</td>
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<tr>
<td>I70.243</td>
<td>Atherosclerosis of native arteries of left leg with ulceration of ankle</td>
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<tr>
<td>I70.244</td>
<td>Atherosclerosis of native arteries of left leg with ulceration of heel and midfoot</td>
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<tr>
<td>I70.245</td>
<td>Atherosclerosis of native arteries of left leg with ulceration of other part of foot</td>
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<td>I70.248</td>
<td>Atherosclerosis of native arteries of left leg with ulceration of other part of lower left leg</td>
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<td>I70.25</td>
<td>Atherosclerosis of native arteries of other extremities with ulceration</td>
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<tr>
<td>I70.431</td>
<td>Atherosclerosis of autologous vein bypass graft(s) of the right leg with ulceration of thigh</td>
</tr>
<tr>
<td>I70.432</td>
<td>Atherosclerosis of autologous vein bypass graft(s) of the right leg with ulceration of calf</td>
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<tr>
<td>I70.433</td>
<td>Atherosclerosis of autologous vein bypass graft(s) of the right leg with ulceration of ankle</td>
</tr>
<tr>
<td>I70.434</td>
<td>Atherosclerosis of autologous vein bypass graft(s) of the right leg with ulceration of heel and midfoot</td>
</tr>
<tr>
<td>I70.435</td>
<td>Atherosclerosis of autologous vein bypass graft(s) of the right leg with ulceration of other part of foot</td>
</tr>
</tbody>
</table>
170.438  Atherosclerosis of autologous vein bypass graft(s) of the right leg with ulceration of other part of lower leg
170.441  Atherosclerosis of autologous vein bypass graft(s) of the left leg with ulceration of thigh
170.442  Atherosclerosis of autologous vein bypass graft(s) of the left leg with ulceration of calf
170.443  Atherosclerosis of autologous vein bypass graft(s) of the left leg with ulceration of ankle
170.444  Atherosclerosis of autologous vein bypass graft(s) of the left leg with ulceration of heel and midfoot
170.445  Atherosclerosis of autologous vein bypass graft(s) of the left leg with ulceration of other part of foot
170.448  Atherosclerosis of autologous vein bypass graft(s) of the left leg with ulceration of other part of lower leg
170.45  Atherosclerosis of autologous vein bypass graft(s) of other extremity with ulceration
170.531  Atherosclerosis of nonautologous biological bypass graft(s) of the right leg with ulceration of thigh
170.532  Atherosclerosis of nonautologous biological bypass graft(s) of the right leg with ulceration of calf
170.533  Atherosclerosis of nonautologous biological bypass graft(s) of the right leg with ulceration of ankle
170.534  Atherosclerosis of nonautologous biological bypass graft(s) of the right leg with ulceration of heel and midfoot
170.535  Atherosclerosis of nonautologous biological bypass graft(s) of the right leg with ulceration of other part of foot
170.538  Atherosclerosis of nonautologous biological bypass graft(s) of the right leg with ulceration of other part of lower leg
170.541  Atherosclerosis of nonautologous biological bypass graft(s) of the left leg with ulceration of thigh
170.542  Atherosclerosis of nonautologous biological bypass graft(s) of the left leg with ulceration of calf
170.543  Atherosclerosis of nonautologous biological bypass graft(s) of the left leg with ulceration of ankle
170.544  Atherosclerosis of nonautologous biological bypass graft(s) of the left leg with ulceration of heel and midfoot
170.545  Atherosclerosis of nonautologous biological bypass graft(s) of the left leg with ulceration of other part of foot
170.548  Atherosclerosis of nonautologous biological bypass graft(s) of the left leg with ulceration of other part of lower leg
170.55  Atherosclerosis of nonautologous biological bypass graft(s) of other extremity with ulceration
170.631  Atherosclerosis of nonbiological bypass graft(s) of the right leg with ulceration of thigh
170.632  Atherosclerosis of nonbiological bypass graft(s) of the right leg with ulceration of calf
170.633  Atherosclerosis of nonbiological bypass graft(s) of the right leg with ulceration of ankle
170.634  Atherosclerosis of nonbiological bypass graft(s) of the right leg with ulceration of heel and midfoot
170.635  Atherosclerosis of nonbiological bypass graft(s) of the right leg with ulceration of other part of foot
170.638  Atherosclerosis of nonbiological bypass graft(s) of the right leg with ulceration of other part of lower leg
170.641  Atherosclerosis of nonbiological bypass graft(s) of the left leg with ulceration of thigh
170.642  Atherosclerosis of nonbiological bypass graft(s) of the left leg with ulceration of calf
170.643  Atherosclerosis of nonbiological bypass graft(s) of the left leg with ulceration of ankle
170.644  Atherosclerosis of nonbiological bypass graft(s) of the left leg with ulceration of heel and midfoot
170.645  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

<table>
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<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>06-05-2012</td>
<td>Policy added to the bcbksks.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.</td>
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<tr>
<td></td>
<td>In Policy section:</td>
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<tr>
<td></td>
<td>• The new stand-alone policy adds the following:</td>
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<tr>
<td></td>
<td>&quot;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:</td>
</tr>
<tr>
<td></td>
<td>1. Treatment of acute or chronic wounds including nonhealing ulcers</td>
</tr>
<tr>
<td></td>
<td>2. Adjunctive use in surgical procedures</td>
</tr>
<tr>
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<td>3. Primary use (injection) for other conditions such as epicondylitis (i.e., tennis elbow), plantar fasciitis, or Dupuytren’s contracture&quot;</td>
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<tr>
<td>02-05-2014</td>
<td>Description section updated</td>
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<tr>
<td></td>
<td>Policy section reformatted – no policy statement changes made.</td>
</tr>
<tr>
<td></td>
<td>Rationale section updated</td>
</tr>
<tr>
<td></td>
<td>In Coding section:</td>
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Contains Public Information
<table>
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<tr>
<th>Date</th>
<th>Updates</th>
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<tr>
<td>10-29-2015</td>
<td><strong>Description section updated</strong></td>
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<tr>
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<td>In Policy section:</td>
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</table>
|            | - 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 Dupuyten's contracture" to read, "Use of autologous blood-derived preparations (ie,
  platelet-rich plasma) is considered experimental/investigational for the treatment of
  acute or chronic wounds, including surgical wounds and nonhealing ulcers." |
|            | **Rationale section updated**                                            |
|            | In Coding section:                                                      |
|            | - Updated coding notations.                                              |
| 04-25-2016 | **Description section updated**                                          |
|            | **Rationale section updated**                                            |
|            | In Coding section:                                                      |
|            | - Coding notations updated                                               |
| 03-01-2017 | **Title changed to** "Recombinant and Autologous Platelet-Derived Growth Factors for
  Wound Healing and Other Non–Orthopedic Conditions" from "Recombinant and
  Autologous Platelet-Derived Growth Factors as a Treatment of Wound Healing and Other
  Non–Orthopedic Conditions"**                                             |
|            | **Description section updated**                                          |
|            | In Policy section:                                                      |
|            | - In Item A 2 d added "/uL" to correctly read "Total lymphocyte count >1000/uL" – no
  change in policy intent.                                                |
|            | **Rationale section updated**                                            |
|            | In Coding section:                                                      |
|            | - Removed ICD-10 Codes: E10.610, E10.618, E10.69, E11.610, E11.618, E11.69,
  I70.331, I70.332, I70.333, I70.334, I70.335, I70.338, I70.341, I70.342, I70.343, I70.344,
  I70.345, I70.348, I70.35, I70.731, I70.732, I70.733, I70.734, I70.735, I70.738, I70.741,
  I70.742, I70.743, I70.744, I70.745, I70.748, I70.75                      |
|            | - Added ICD-10 Codes: L97.121, L97.122, L97.123, L97.124, L97.211, L97.212, L97.213,
  L97.214, L97.221, L97.222, L97.223, L97.224, L97.311, L97.312, L97.313, L97.314,
  L97.321, L97.322, L97.323, L97.324, L97.411, L97.412, L97.413, L97.414, L97.421,
  L97.422, L97.423, L97.424, L97.511, L97.512, L97.513, L97.514, L97.521, L97.522,
  L97.523, L97.524, L97.811, L97.812, L97.813, L97.814, L97.821, L97.822, L97.823,
  L97.824, L98.491, L98.492, L98.493, L98.494                                |
| 03-01-2018 | **Description section updated**                                          |
|            | In Policy section:                                                      |
|            | - In Item B added "recombinant platelet-derived growth factor" to read "Other
  applications of recombinant platelet-derived growth factor (ie, becaplermin) are
  considered experimental/investigational, including, but not limited to:"    |
|            | - Updated Policy Guidelines                                              |
|            | **Rationale section updated**                                            |
|            | References updated                                                        |
REFERENCES


