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

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Related Policies:

- 02.01.32 Platelet-Rich Plasma and Autologous Protein Solution for Orthopedic Applications
- 02.01.18 Prolotherapy
- 08.01.22 Stem Cell Therapy for Orthopedic Indications (Including Allograft Bone Products used with Stem Cells)

Summary

Description

***Note**: This medical policy will address the use of platelet-rich plasma (PRP) for wound healing and the treatment of other non-orthopedic indications. For platelet-rich plasma (PRP) in the treatment of*

*orthopedic indications refer to medical policy 02.01.32 and for the use of platelet-rich plasma in combination with mesenchymal stem cells refer to medical policy 08.01.22 Stem Cell Therapy for Orthopedic Indications (Including Allograft Bone Products used with Stem Cells) **

*Stem cell transplantation using hematopoietic stem cells for treatment of blood cancer, non-cancer conditions and solid tumors are not in scope of this policy. Refer to medical policy 07.03.11 Hematopoietic Stem Cell Transplantation (Bone Marrow Transplant) Autologous and Allogeneic**

The use of blood-derived growth factors, including recombinant platelet-derived growth factors (PDGFs) and platelet-rich plasma (PRP) has been suggested as a treatment for wounds (diabetic ulcers, pressure ulcers, venous stasis ulcers) or other miscellaneous non-orthopedic indications, including but not limited to, androgenetic alopecia, alopecia areata, cerebral palsy, Crohn's disease related perianal fistula, urethral stricture, and vitiligo.

Summary of Evidence

Recombinant Platelet-Derived Growth Factors for Wound Healing Treatment

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

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

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

Platelet-Rich Plasma Treatment for Wound Healing Treatment

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

evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

Platelet-Rich Plasma Treatment for Other Miscellaneous Non-Orthopedic Indications

For individuals who have alopecia areata/androgenetic alopecia who receive PRP, the evidence includes systematic reviews and RCTs investigating the efficacy of PRP on hair growth. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. Most of the reviewed studies have important methodological deficiencies. Main flaws include lack of a reference protocol regarding the frequency of applications as well as the injected amount of PRP, heterogeneity in application modes, lack of controls, small sample size, lack of detailed reports in patients' characteristics and used statistical methods. Furthermore, few studies referred to the safety profile of PRP. In addition, currently there is no evidence that PRP is more effective than minoxidil or finasteride treatments. Additional large scale double-blind, randomized controlled studies treating both men and women, with standardized PRP preparation methods and administration protocols, repeated treatments, standardized objective data documentation and evaluation, physician, and subject assessment, isolating the effects of PRP in different grades of androgenetic alopecia and alopecia areata, and performing long-term follow-up. The evidence is insufficient to determine the effects of the technology on net health outcomes.

For individuals who have one of the following miscellaneous conditions: vitiligo, cerebral palsy (CP), Crohn's disease (CD) related to high perianal fistula, urethral stricture disease or thin endometrium (TE) related to infertility treatment who receive PRP, the evidence includes systematic reviews, meta-analyses and case studies. Relevant outcomes are symptoms, change in disease status, morbid events, QOL, and treatment-related morbidity. While some of these studies may show promise, studies using standard PRP preparation protocols are still needed to more conclusively determine treatment effectiveness. Published studies report variations in processing, such as the number of centrifugations or compounds added, which make it difficult to compare results from different clinical studies. The use of PRP for the treatment of these indications warrant further investigation in well-designed randomized comparative studies with longer time of observation to determine safety and efficacy. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Additional Information

Not applicable.

OBJECTIVE

The objective of this 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, surgical and traumatic wounds, and other miscellaneous non-orthopedic indications, including but not limited to, androgenetic alopecia, alopecia areata, cerebral

palsy, Crohn's disease related perianal fistula, urethral stricture, vitiligo and thin endometrium (TE) related to infertility.

PRIOR APPROVAL

Not applicable.

POLICY

Recombinant Platelet – Derived Growth Factor (PDGF) and Platelet-Rich Plasma for Wound Management

Recombinant platelet-derived growth factor (PDGF) (i.e., becaplermin) may be considered **medically necessary** when used as an adjunct to standard wound management for the following indications (*for further information on patient selection criteria, see Policy Guidelines next*):

- Neuropathic diabetic ulcers extending into the subcutaneous tissue
- Pressure ulcers extending into the subcutaneous tissue.

Other applications of recombinant platelet-derived growth factor (PDGF) (i.e., becaplermin) are considered **investigational**, including, but not limited to the following because evidence is insufficient to determine that the technology results in an improvement in net health outcomes:

- Ischemic ulcers
- Venous stasis ulcers, and ulcers not extending through the dermis into the subcutaneous tissue.

Use of platelet-rich plasma (PRP) (i.e., autologous blood-derived preparations) is considered **investigational** for the treatment of acute or chronic wounds, including surgical wounds and nonhealing ulcers because evidence is insufficient to determine that the technology results in an improvement in net health outcomes.

Platelet-Rich Plasma (PRP) for Non-Orthopedic Indications Other than Wound Care

The use of platelet-rich plasma (PRP) injections for the treatment of non-orthopedic indications including, but not limited to the following is considered investigational because the evidence is insufficient to determine that the technology results in an improvement in net health outcomes:

- Alopecia areata/androgenetic alopecia
- Cerebral palsy (CP)
- Crohn's disease-related perianal fistula
- Thin endometrium (TE)/endometrium related issues for infertility treatment
- Urethral stricture
- Vitiligo

POLICY GUIDELINES

Becaplermin

Appropriate candidates for becaplermin gel for treatment of neuropathic ulcers should meet **ALL** of the following criteria:

1. 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;
2. Full-thickness ulcer (i.e., stage III or IV), extending through dermis into subcutaneous tissues;
3. Participation in a wound management program, which includes sharp debridement, pressure relief (i.e., non-weight bearing), and infection control.

Appropriate candidates for becaplermin gel for the treatment of pressure ulcers should meet **ALL** of the following criteria:

1. Full-thickness ulcer (i.e., stage III or IV), extending through dermis into subcutaneous tissues;
2. Ulcer in an anatomic location that can be offloaded for the duration of treatment;
3. Albumin concentration >2.5 dL;
4. Total lymphocyte count >1000/µL;
5. Normal values of vitamins A and C.

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.

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 (i.e., 1.6 mm or the thickness of a dime). The amount of the gel used will depend on the size of the ulcer, measured in square centimeters. However, an average-sized ulcer, measuring 3 cm^2, treated for an average length of time of 85 days, will require a little more than one 15-g tube. If the ulcer is treated for the maximum length of time of 140 days, 1.75 of the 15-g tubes would be required.

Coding

See the Codes table for details.

BACKGROUND

Wound Healing Treatment

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

Autologous platelet concentrate suspended in plasma, also known as platelet-rich plasma (PRP), can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets, releasing various growth factors, and results in the polymerization of fibrin from fibrinogen, creating a platelet gel. The platelet gel can then be applied to wounds or may be used as an adjunct to surgery to promote hemostasis and accelerate healing. In the operating room setting, PRP has been investigated as an adjunct to a variety of periodontal, reconstructive, and orthopedic procedures. For example, bone morphogenetic proteins are a transforming growth factor, and thus PRP has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries.

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

Wound Closure Outcomes

This review addresses the use of recombinant PDGF products and PRP for non-orthopedic indications (alopecia areata/androgenetic alopecia, cerebral palsy (CP), Crohn's disease-related perianal fistula, urethral stricture, vitiligo), which also include a number of wound closure-related indications.

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

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

Regulatory Status

Becaplermin

In 1997, becaplermin gel (Regranex®; Smith & Nephew), a recombinant PDGF product, was approved by the FDA for the following labeled indication:

"Regranex Gel is indicated for the treatment of lower extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. When used as an adjunct to, and not a substitute for, good ulcer care practices including initial sharp debridement, pressure relief and infection control, Regranex Gel increases the complete healing of diabetic ulcers.

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

In 2008, the manufacturer added the following black box warning to the labeling for Regranex®: "An increased rate of mortality secondary to malignancy was observed in patients treated with 3 or more

tubes of Regranex Gel in a post marketing retrospective cohort study. Regranex Gel should only be used when the benefits can be expected to outweigh the risks. Regranex Gel should be used with caution in patients with known malignancy."

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

Platelet-Rich Plasma

Blood products such as platelet rich plasma (PRP) are regulated by the Center for Biologics Evaluation and Research (CBER). CBER is responsible for regulating human cells, tissues, and cellular and tissue-based products. The regulation process for these products is described in the U.S. Food and Drug Administration (FDA) 21 CFR 1271 of the Code of Federal 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.

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.

RATIONALE

This evidence review was created in November 2019 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through March 2026.

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The 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 individuals with diabetic lower-extremity 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.

Comparators

Comparators of interest include standard wound care.

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews

A 2014 systematic review identified 6 RCTs (N=992) that compared recombinant PDGFs with placebo or standard care. There was a combined odds ratio (OR) of 1.53 (95% confidence interval [CI], 1.14 to 2.04; p=.004) favoring recombinant PDGF for complete healing rate.

Sridharan et al (2018) conducted a systematic review and meta-analysis of RCTs on topical growth factors compared with standard of care in patients with diabetic foot ulcers (DFUs). The primary outcome of concern was complete healing, and the second outcome of concern was the existence of adverse events. Rankogram was generated based on the surface under the cumulative ranking curve. In total, 26 studies with 2088 participants and 1018 adverse events were included. The pooled OR estimates for recombinant human epidermal growth factor (rhEGF), autologous -PRP, and recombinant human platelet-derived growth factor were 5.7 [95% CI, 3. 34 to 10.37], 2.65 [95% CI, 1.65 to 4.54], and 1.97 [95% CI, 1.54 to 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 Trails Assessing Recombinant Platelet-Derived Growth Factor for Diabetic Lower Extremity Ulcers

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

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

Retrospective Studies

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

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 PDGF is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with 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.

Comparators

Comparators of interest include standard wound care.

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials

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 once-daily dosage (becaplermin 0.01% or 0.03%), the incidence of complete healing was significantly improved compared with the placebo group. There was no difference in outcome between the 0.01% and 0.03% groups, suggesting there is no clinical benefit in increasing the potency above 0.01%. A third group received becaplermin 0.01% twice daily. That group did not report improved outcomes compared with placebo, a finding that is unexplained.

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

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

Recombinant Platelet-Derived Growth Factor for Venous Statis 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 individuals with 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.

Comparators

Comparators of interest include standard wound care.

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Randomized Controlled Trials

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

Section Summary: Recombinant Platelet-Derived Growth Factor for Venous Statis 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 individuals with acute surgical or traumatic wounds.

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

Populations

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

Interventions

The therapy being considered is recombinant PDGF.

Comparators

Comparators of interest include standard wound care.

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

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

Adverse Events

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

Section Summary: Recombinant Platelet-Derived Growth Factor for Acute Surgical or Traumatic Wounds

Published evidence includes nonrandomized controlled trials reporting satisfactory aesthetic results. Larger RCTs are required to confirm and expound on these results.

Platelet-Rich Plasma for Chronic Wounds

Clinical Context and Therapy Purpose

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

The 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.

Comparators

Comparators of interest include standard wound care.

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Diabetic Foot Ulcers

Systematic Reviews

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

Six recent systematic reviews have evaluated studies of PRP for individuals with diabetic foot ulcers. Table 2 provides a crosswalk of the studies included in the systematic reviews.

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

Primary Study (Year)	Li 2019	Qu 2021	Deng 2023	Platini 2024	Hu 2025[b]	Tian 2025[b]
Abhirami 2023						●
Ahmed 2017	●	●	●	●	●	●
Alamdari 2021			●	●	●	
Chen 2008[a]	●					
Driver 2006	●	●	●		●	●

Primary Study (Year)	Li 2019	Qu 2021	Deng 2023	Platini 2024	Hu 2025[b]	Tian 2025[b]
Elsaid 2020		●	●		●	●
Friese 2007 (conference proceeding)	●		●			
Game 2018		●				
Gude 2019		●		●		●
Goda 2018						
Gowsick 2023					●	●
Gupta 2021					●	●
Habeeb 2020			●			●
Helmy 2021			●			
Hossam 2021			●		●	●
Jeong 2010			●			
Kamineni 2023						●
Kakagia 2007	●	●	●			
Karimi 2016		●	●			●
Li 2012[a]			●			
Li 2015	●	●	●	●	●	●
Liu 2016[a]	●		●			●
Liao 2020			●			
Malekpour 2021						●
Mandadap 2022						●
Meamar 2021			●			
Ma 2014[a]	●					
Milek 2017		●				
Orban 2022					●	
Qi 2014[a]	●					
Rainys 2019			●	●		●
Saad Setta 2011	●	●	●			
Satapathy 2023						●
Saldalamacchia 2004	●	●	●			●
Serra 2013	●	●		●		
Singh 2018		●	●		●	●
Steed 1992			●			●

Primary Study (Year)	Li 2019	Qu 2021	Deng 2023	Platini 2024	Hu 2025[b]	Tian 2025[b]
Steed 1996			●			
Tofign 2022			●			
Xie 2020		●		●	●	●
Yang 2017		●				●
Zhao 2025						●
Zhang 2016[a]	●					
Zhou 2015[a]	●					
Zhu 2012[a]	●					

[a] In Chinese
[b]Only noting studies with PRP.

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 ulcer.

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 to 12 weeks long and others only 2 to 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 1 observational study (100%). Strength of the body of evidence was rated based on the Evidence-based Practice Center methods guide. The findings of this Technology Assessment indicated that there is moderate-strength evidence that PRP modestly increases complete wound closure (see meta-analysis results in Table 4 below) and low-strength evidence that PRP may shorten time to wound closure (meta-analysis not feasible). However, due to risk of bias and severe imprecision, evidence is insufficient to draw conclusions about other important outcomes, including wound infection, amputation, pain reduction, and wound recurrence. Important limitations of the literature were described as "inadequate description of offloading and wound care procedures, wound characteristics, PRP formulation techniques, concentration and volume; inadequate length of follow-up, and lack of stratification by comorbidities and other patient characteristics, such as diabetes control, vascular perfusion, and under representation of older adults"

A meta-analysis by Deng et al (2023) assessed 22 RCTs (N=1559) to determine the safety and efficacy of PRP to treat diabetic foot ulcers. Results indicated PRP significantly increased the overall healing rate of diabetic foot ulcers compared with standard treatment (risk ratio [RR]=1.42; 95% CI: 1.30 to 1.56; p<.001; I^2=55%). PRP increased the complete wound healing time of diabetic foot ulcers compared to conventional treatment (mean difference [MD]=-3.13; 95% CI: -5.86 to -0.39; p<.001; I^2=97.5%) and resulted in a greater reduction in diabetic foot ulcer area (MD=1.02; 95% CI: 0.51 to 1.53; p<.001; I^2=36%). The rate of amputation, reported by 3 trials, significantly reduced risk for the autologous PRP group (RR=0.35; 95% CI, 0.15 to 0.83; p<.001; I^2=0%). Four studies reported adverse events, and pooled analysis revealed a similar rate of events between the PRP and control groups (RR=0.96; 95% CI, 0.57 to 1.61; p>0.05; 35%). The authors reported no significant publication bias was detected by funnel plot analysis; however, a sensitivity analysis suggested that the pooled outcome assessment for time to wound healing may be affected by considerable inter-study variability. The low number of high-quality of studies available on PRP for diabetic foot ulcers and the low number of studies reporting some outcomes of interest were limitations of this meta-analysis.

Platini et al. (2024) conducted a systematic review and meta-analysis to assess the efficacy and safety of autologous platelet-rich plasma gel for managing diabetic foot ulcers in older adults (N=598) across 8 RCTs. Compared with standard care, autologous PRP gel significantly improved wound healing rates (Relative Risk [RR]=1.32; 95% CI: 1.22 to 1.57; p<.0001; I^2=23%) and reduced the time to complete healing (MD= -16.97 days; 95% CI: -32.64 to -1.29; p<.0001; I^2=93%). PRP also shortened hospital stays (MD=-20.11 days; 95% CI: -38.02 to -2.20; p=.03) and decreased the amputation rate (RR=0.36; 95% CI: 0.16 to 0.84; p=.02; I^2=0%) when compared to conventional treatments. The authors also noted its infection prevention efficacy during early treatment was significant at one week (RR=0.56; 95% CI: 0.34 to 0.91; p=.02) and two weeks (p=.01), but when assessed from week 4 to 12, no significant differences were observed. No improvements in the reduction of wound surface area were noted in the included studies. Heterogeneity across outcomes varied but was particularly high in healing duration outcomes. Funnel plot analyses revealed minimal publication bias. Limitations included non-standardized dosages of PRP, high heterogeneity for some pooled estimates, and insufficient reporting of some clinical outcomes.

Hu et al (2025) published a network meta-analysis that evaluated 12 interventions for diabetic foot ulcer treatment across 99 RCTs involving 7356 patients. Platelet-rich plasma was evaluated in 11 RCTs. For wound healing time, PRP significantly reduced duration compared with standard care, with a mean difference of 21.65 days, and ranked second among interventions (SUCRA 74.6%). Regarding wound healing rate, PRP demonstrated significant improvement over standard care (OR, 2.63). For amputation risk and percentage area reduction, no statistically significant differences were observed between PRP and standard care groups. Limitations of the meta-analysis include the inclusion of relatively small trials with short durations. The dosages of PRP were also not described.

Tian et al (2025) published a network meta-analysis that included 51 RCTs involving 3401 patients with diabetic foot ulcers who received treatment with one of 7 interventions, including PRP in 22 studies. For wound healing time, PRP significantly reduced duration compared with standard care, with a mean difference of 16.92 days, ranking second among the interventions (SUCRA 66%). Regarding wound healing rate, PRP demonstrated a significant improvement over standard care (RR, 1.24). For ulcer area reduction, the difference between PRP and standard care was not statistically significant. However, PRP significantly reduced the risk of amputation compared with standard care (RR, 0.17; 95% CI, 0.01 to 0.61), ranking first among available therapies (SUCRA 80%). Limitations of the meta-analysis include the inclusion of relatively small trials with short durations. The dosages of PRP were also not described.

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

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Li (2019)	2004-2017	15	Patients with diabetic chronic cutaneous wounds/ulcers that do not show signs of healing in 4 weeks	N=829 (14-117)	RCTs	NR
Qu (2021)	Inception-2020	14	Adults with lower extremity diabetic ulcers, lower extremity venous ulcers, or pressure ulcers in any location, or a mix of these 3 etiologies	N=1,096 (range NR)	RCTs	Median = 6 wk (range, none to 11 months)
Deng (2023)	Inception-2023	22	Adult with diabetic foot ulcers	N=1559	RCTs	NR
Plantini (2024)	Inception-2024	8	Older adults with diabetic foot ulcers	N=598	RCTs	NR
Hu (2025)	1992-2023	99 total (11 focused on PRP)	Individuals with diabetic foot ulcer	N=848 (24-174) in studies investigating PRP	RCTs	6-20 weeks in studies investigating PRP
Tian (2025)	Inception-2025	51 (23 focused on PRP)	Individuals with diabetic foot ulcer	N=730 in studies investigating PRP	RCTs	4-20 weeks in studies investigating PRP

NR: not reported; PRP: platelet rich plasma; RCT: randomized controlled trial; wk: week(s); y: year(s).

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

Study	Healing Rate	Healing Time	Complete Wound Healing	Risk of Infection	Wound complications	Pain Reduction	Recurrence
Li (2019)							
RR	1.39						
MD		-9.18					
OR				0.34			
95% CI	1.29 to 1.50	-11.32 to -7.05		0.15 to 0.77			
P-value	<.001	<.001		.009			

Study	Healing Rate	Healing Time	Complete Wound Healing	Risk of Infection	Wound complications	Pain Reduction	Recurrence
Qu (2021)							
RR			1.20	0.77			2.09
WMD						-1.10[a]	
95% CI			1.09 to 1.32	0.54 to 1.11		-1.81 to -0.39	0.31 to 13.93
P-value							
Deng (2023)							
RR	1.42				.096		
MD		-3.13					
95% CI	1.30 to 1.56	-5.86 to -0.39			0.57 to 1.61		
P-value	<.001	<.001			.203		
Platini (2024)							
RR	1.32	-16.97		0.56			
MD							
95% CI	1.22 to 1.57	-32.64 to -1.29		0.34 to 0.91			
P-value	<.0001	<.0001		.02			
Hu (2025)							
OR	2.63						
MD		-21.65 days					
95% CI	1.57 to 4.41	-33.61 to -9.69					

Study	Healing Rate	Healing Time	Complete Wound Healing	Risk of Infection	Wound complications	Pain Reduction	Recurrence
Tian (2025)							
RR	1.24						
MD		-16.92					
95% CI	1.07 to 1.50	-26.15 to -7.09					

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

Randomized Controlled Trials

Key characteristics and results of several RCTs of diabetic foot ulcers published subsequent to the AHRQ review (2020) are summarized in Tables 5 and 6 below.

One RCT of PRP dressing with total-contact casting compared to standard saline dressing for diabetic foot ulcers (Gupta et al [2021]) did not find significant differences in rates of ulcer area reduction or absolute ulcer area reduction between groups over the 6-week study period. Another RCT of PRP versus standard wound care found accelerated rates of ulcer area reduction and decreased incidence of wound infections with PRP treatment; however, the difference in the percentage of healed surface between groups lost statistical significance at 6, 7, or 8 weeks of follow-up and it is unclear whether complete wound healing was achieved in either group.

Table 5. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Intervention	Control
Gupta et al (2021)	India	1	2016 to 2018	Individuals with diabetes mellitus with noninfected diabetic foot ulcers with total ulcer area of 20 cm^2 or less on the plantar surface	Autologous intralesional PRP therapy with total contact casting (n=30)	Saline dressing (n=30)
Hossam et al (2022)	Egypt	1	2018	Individuals with type 1 or 2 diabetes with non-ischemic revascularized chronic diabetic foot ulcers of more than 6 months duration with no clinical signs of infection, Wagner grade 1 or 2, and ASA physical status class 2	Autologous intralesional $CaCl_2$-activated PRP therapy (injection and/or gel) with saline gauze (n=40)	Standard wound care with moist dressing with or without collagenase ointment (n=40)

PRP: Platelet-rich plasma; RCT: randomized controlled trial.

Table 6. Summary of Key RCT Results

Study	Complete Healing	Percentage of Healed Surface Area[a]	Healing Time	Pain	Quality of Life	Infection	Recurrence
Gupta et al (2021)	85.98% vs 81.72%[a]; p NR	6 weeks: 85.98% vs 81.72%; p=NR	NR	NR	NR	NR	NR
Hossam et al (2022)	95% vs 77.8%[b]; p<.001	1 week: 23.1% vs 0%; p=.002 5 weeks: 89.2% vs 60.1%; p<.001 8 weeks: 96.7% vs 95.5%; p=.529	NR	NR	NR	PRP: 4 (10%) Control: 18 (45%) with 4 resulting in amputation p<.001	NR

NR: not reported; RCT: randomized controlled trial.
[a] Percentage of healed surface area in treatment vs. control groups.
[b] Proportion of patients with complete healing in treatment (n=38) vs. control groups (n=28) at 6 and 9 weeks, respectively.

Study relevance, design, and conduct limitations are summarized below in Tables 9 and 10.

Other Chronic Wounds

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.

For individuals with lower extremity venous ulcers, the evidence included 8 RCTs and 3 observational studies (total N=615). The majority compared PRP to management without PRP. Risk of bias was described as moderate due to randomization and outcome measurement limitations. There were no significant differences between PRP versus management without PRP in complete wound closure (RR=1.49; 95% CI: 0.72 to 3.06; 5 studies, N=250; I^2=29.4%), wound recurrence (RR=0.38; 95% CI: 0.09 to 1.57), wound infection (RR=0.79; 95% CI: 0.22 to 2.81), or quality of life as measured by the Chronic Lower Limb Venous Insufficiency Questionnaire (weighted mean difference [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. Based on fewer studies identified from searches only through July 2018, although their findings indicated greater reductions in wound area for PRP, findings were consistent with the ARHQ review in finding no significant difference in complete wound closure (RR=2.54; 95% CI, 0.42 to 15.30; 4 studies, N=156; I^2=69%).

For individuals with pressure ulcers, the AHRQ Technology Assessment (2020) 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.

A meta-analysis by Fang et al (2023) pooled data from 6 studies on patients treated for lower extremity venous ulcers with PRP.[7] A total of 294 patients were included, with 148 patients in the PRP group and 146 in the control group. PRP was found to have a greater reduction in elliptical area at the end of treatment compared to the control group (Mean difference [MD], -1.19; 95% CI, -1.8 to -.058; P=.0001) with a moderate quality of evidence. The healing rate also favored PRP over the control group (RR=5.73; 95% CI, 3.29 to 9.99; P<.00001) with a moderate quality to the evidence base. The authors suggest there may be publication bias in the calculation of these pooled estimates according to Egge's test.

Hu et al. (2024) conducted a systematic review and meta-analysis of 16 RCTs (N=699) to evaluate the efficacy and safety of PRP for venous ulcer treatment. PRP demonstrated a significant improvement in complete ulcer healing (Odds Ratio [OR]=5.06; 95% CI: 2.35 to 10.89; p<.01; I^2=58%) and a 47% greater reduction in ulcer size compared with standard therapy (MD=47%; 95% CI: 32% to 62%; p<.05; I^2=75%). PRP also significantly shortened healing time by an average of 3.25 months (MD=-3.25; 95% CI: -4.06 to -2.43; p<.05; I^2=49%). Recurrence rates were markedly reduced (OR=0.16; 95% CI: 0.05 to 0.50; I^2=18%), with no significant differences in infection (OR=0.89; 95% CI: 0.38 to 2.07; I^2=0%), VAS Pain scores (MD=1.19; 95% CI: -0.67 to 3.04; I^2=52%), or irritative dermatitis rates (OR=0.38; 95% CI: 0.08 to 1.90; I^2=0%). Funnel plot analysis and Egger’s test (p=.0079) suggested the potential for publication bias. Limitations included heterogeneity in PRP preparation, inconsistency in ulcer measurement methods, the potential for publication bias, moderate to high heterogeneity for some outcome estimates, and limited sample sizes.

Randomized Controlled Trials

Two RCTs of PRP for chronic wounds (Saha et al [2020]) were identified as published subsequent to the AHRQ review (2020).[1] Key characteristics and results of selected RCTs are reported in Tables 7 and 8 below.

Saha et al. 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.

Shehab et al (2023) conducted an RCT of adjunct PRP in addition to compression therapy in individuals with post-phlebitis venous ulcers. Forty patients were randomized 1:1 to either PRP and compression therapy or placebo. The median number of treatments was 6 (range 3 to 6). Both participants and outcome assessors were blinded to treatment allocation. The median ulcer surface area, the primary outcome, was significantly lower for the PRP group (4 cm^2 vs 10 cm^2; p=.036) as well as the median volume of ulcers (1 cm^3 vs 3 cm^3; p=.008). This translated to individuals in the PRP group experiencing a larger drop in ulcer area (74% vs 40%; p=.008) and volume (81% vs 48%; p=.013) compared to placebo. Differences in VAS pain scores were observed in favor of the PRP group at both the 3-month and 6-month follow-ups. Nine patients in the PRP group had complete wound healing, but the authors did not report the rate of complete healing in the control group, and healing time and recurrence were not reported.

Tables 7 Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Intervention	Control
Saha et al (2020)	Iran	1	2016 to 2018	Individuals with clinically diagnosed trophic ulcers due to leprosy	Autologous PRP therapy with total contact casting (n=59)	Only total contact casting (n=59)
Shehab et al (2023)	Egypt	1	2019 to 2020	Adults with chronic post-phlebitic lower limb venous ulcers	Autologous PRP therapy with compression therapy (n=20)	Placebo plus compression therapy (n=20)

PRP: platelet-rich plasma; RCT: randomized controlled trial.

Table 8. Summary of Key RCT Results

Study	Complete Healing	Healing Time	Pain	Quality of Life	Infection	Recurrence
Saha et al (2020)66,	22 (39.29%) vs 11 (21.15%); p NR	NR	NR	NR	0 vs 0; p=.773	NR
Shehab et al (2023)67,	9 (45%) vs NR	NR	BL: 6.5 vs 6.4; p=.43 3 mos: 1 vs 4.5; p<.0001 6 mos: 0.5 vs 2.2; p<.0001	NR	NR	NR

NR: not reported; RCT: randomized controlled trial.
[a] Percentage of healed surface area in study and control groups at 6 weeks.

Tables 9 and 10 summarize the relevance and design and conduct limitations of selected RCTs.

Table 9. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Saha et al (2020)	4. Single site in Iran	4. Short duration of treatment; 8 weeks		1. Recurrence, quality of life not addressed 5. Clinical significance of difference in wound surface area not prespecified	1. 4- weeks follow-up post-treatment insufficient to assess long-term efficacy
Gupta et al (2021)	4. Single site in India	4. Short duration of treatment; 6 weeks	3. Total-contact casting not used in control group	1. Complete wound healing, recurrence, quality of life not addressed 5. Clinical significance of difference in wound surface area not prespecified	1. 6- week study period insufficient to assess long-term efficacy
Hossam et al (2022)	4. Single site in Egypt	1. Frequency and type of PRP treatment (injection and/or gel)		1. Complete wound healing, recurrence, quality of life not	1. 8- week study period insufficient to

		not standardized 4. Short duration of treatment; 8 weeks		addressed 5. Primary outcome differences and timepoints were not prespecified	assess long-term efficacy
Shehab et al (2023)	4. Single site in Egypt	1. Frequency and type of PRP treatment (injection and/or gel) not standardized 4. Short duration of treatment; 6 weeks	1. Placebo treatment not clearly defined	1. Recurrence, quality of life not addressed	

PRP: platelet-rich plasma.
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 10. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Saha et al (2020)						
Gupta et al (2021)		1-3. Blinding not described			1. Power calculations not reported	3. Confidence intervals and/or p values not reported
Hossam et al (2022)		1-3. Blinding not described		1. High loss to follow-up or missing data; reasons for and extent of missingness unclear at all timepoints	1. Power calculations not reported	3. Confidence intervals not reported
Shehab et al (2023)					1. Power calculations not reported	4. Complete healing rate not reported for the control group

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

Section Summary: Platelet-Rich Plasma for Chronic Wounds

The evidence for autologous PRP for a variety of chronic wounds includes systematic reviews, RCTs, which have been summarized in several systematic reviews, and nonrandomized trials. In meta-analyses of individuals with lower extremity diabetic ulcers, PRP demonstrated an improvement over the control groups in complete wound closure, recurrence rate, 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 individuals with acute surgical or traumatic wounds.

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

Populations

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

Interventions

The therapy being considered is PRP.

Comparators

Comparators of interest include standard wound care.

Outcomes

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Surgical Wounds

Aortic Arch Repair

Zhou et al (2015) reported on a double-blind RCT with 80 patients that assessed the effect of PRP on the amount of blood transfused in the perioperative period for elective ascending and transverse aortic arch repair. 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<.02). Hospital length of stay was also reduced (9.4 days vs. 12.7 days). There was no difference in mortality between the 2 groups (1 patient in each group) and no significant differences in postoperative complications or other outcome measures. Corroboration of the effect of PRP on perioperative blood transfusion is needed.

Sternotomy Wounds

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

Zhu et al (2023) published a meta-analysis of the effect of PRP on sternal wound healing.[70,] Eleven studies with a total of 8961 cardiac surgery patients were included. Patients were either treated with PRP (n=3663) or control therapies (n=5298), with sample sizes ranging from 44 to 2000 participants. PRP was found to have a significantly lower rate of sternal wound infection (OR, 0.11; 95% CI, 0.03 to 0.34; p<.001; I^2, 0%), deep sternal wound infection (OR, 0.29; 95% CI, 0.16 to0.51; p<.001; I^2, 32%) and superficial sternal wound infection (OR, 0.20; 95% CI, 0.13 to 0.33; p<.001; I^2, 0%) compared to patients in the control cardiac surgery groups. All pooled estimates at no to low heterogeneity (0% to 32%). The poor quality of included studies, heterogeneous PRP preparations, and heterogeneous cardiac surgeries limit the interpretation of the results.

Otolaryngology

A 2008 double-blind RCT assessed the efficacy of PRP following tonsillectomy in 70 children (age range, 4 to 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.

El-Anwar et al (2016) reported on an RCT that evaluated PRP in 44 children (age range, 12 to 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=.024) and better velopharyngeal closure on endoscopy (p=.016).

Dinaki et al. (2024) conducted an RCT evaluating submucosal PRP injection on wound healing after endoscopic sinus surgery in 30 patients with chronic rhinosinusitis. Patients were randomized 1:1 to PRP (2.5 ml on each side) or control (no additional treatment with no placebo). PRP significantly reduced moderate crusting on endoscopy at 1 week (36.6% vs. 80%; p<.00001) through 12 weeks post-surgery (0% vs. 16.6%; p=.021). Bleeding was lower in the PRP group during the first 2 weeks (minimal bleeding: 33.3% vs. 66.6%; p=.004 at 1 week; 10% vs. 50%, p=.0003 at 2 weeks) but not significantly different between groups thereafter. Granulation tissue formation was reduced at 8 and 12 weeks in the PRP group (mild granulation: 30% vs. 60%; p=.021 at 8 weeks; 26.6% vs. 46.6%; p=.005 at 12 weeks). VAS scores improved significantly in the PRP group across all time points, with a median score of 0 (interquartile range [IQR]: 0 to 1) at 12 weeks compared to 2 (IQR: 1 to 2) in controls (p=.001). No significant differences were observed for adhesion or infection rates (p>.05). Limitations included the small sample size with an absence of power calculations, lack of double blinding, and absence of follow-up beyond 3 months.

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.

Alamdari et al (2018) published a clinical trial evaluating the efficacy of pleurodesis with a combination of PRP and fibrin glue compared with surgical intervention. The study population consisted of 52 esophageal cancer patients with postoperative chylothorax who did not respond to conservative management. Each member of the population was consecutively and randomly allocated to either a PRP fibrin glue pleurodesis arm or a surgical thoracic duct ligation arm. Twenty-six in each arm were treated with their respective interventions. The patients were distributed into the intervention arms in a way that made each group similar in terms of tumor size and patient demographics. This distribution procedure was not described. All patients (26) in the PRP treatment arm and 20 (76.9%) in the surgery arm were successfully treated (p=.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 <.001). The study was limited due to the fact the procedure for randomization was not described and, thus, its efficacy cannot be evaluated.

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. 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 *(i.e.,* “pain duration was inquired from participant"). 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. Indications for skin grafts were primarily hard-to-heal lower leg wounds. PRP was applied to 1 thigh and covered with Vaseline-impregnated, open-weave gauze and gauze. The control was the other thigh, which was also covered with open-weave gauze and gauze, but without PRP. Of the 24 included individuals, 3 (12.5%) were excluded after developing infections. The infections were described as first occurring on the non-PRP wound and only subsequently occurring on the PRP wound after several days. PRP significantly shortened median healing time (14 days vs 18 days; p=.026). No other outcomes were reported. Notable limitations of the RCT include its small sample size and that it did not address important health outcomes and harms.

Traumatic Wounds

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

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

Yeung et al (2018) performed a prospective RCT to test the efficacy of lyophilized platelet-rich plasma powder (LPRP) on the healing rate of wounds in patients with deep, second-degree burn injuries in comparison with a control group using a placebo. LPRP was dissolved in a solution and applied on deep second-degree burn wounds once per day for 4 consecutive days. Twenty-seven patients with deep second-degree burns were recruited and then those who met eligibility criteria were randomized into 2 groups. The LPRP group received the intervention (n=15) and the control group received a placebo application (n=12). A concentration of 1.0×10^7 platelets/cm^2 (wound area) was sprayed on the wound evenly. Function was assessed by the percentage of wound closure and bacteria picking out rate at weeks 2 and 3. The mean burn area of control for the LPRP was 75.65 ± 50.72 cm^2 and 99.73 ± 70.17 cm^2 (p=.0013), respectively. In the control group, the original wound area was 25.49 cm^2 at baseline, 23.79 cm^2 (6.67% healed) at week 2, and 4.34 cm^2 (86.40% healed) at week 3. In the LPRP group, the original wound area was 84.36 cm^2, followed by 23.96 cm^2 (71.59% healed) at week 2, and 0.63 cm^2 (99.24% healed) at week 3. The wound closure rate at week 2 in the LPRP group reached nearly 80% and was greater than 90% by week 3, showing a significant difference (p<.05). Alternatively, in the control group, the wound closure rates were 60% and 80% in 2 and 3 weeks, respectively. The postoperative infection rate in the LPRP (26.67%) was lower than the control group (33.33%). Neither was significant, statistically. One limitation of this study is that the powder is made by an independent lab

and dissolved in a specified amount of water. This provides an opportunity for accidental error-this may also be the case with some liquid PRP.

Huang et al (2021) published a meta-analysis of 8 RCTs representing 539 patients with burn wounds. The healing rate of burn wounds was improved with PRP (OR, 4.43; 95% CI, 2.13 to 9.22), yielding a significantly shorter wound healing time (OR, -4.23; 95% CI, -5.48 to -2.98) compared to conventional dressings for both superficial and deep burn groups. Incidence of adverse events, pain scores, and scar scores was also all improved in the PRP treatment group. Interpretation of results is limited by risks of bias arising from lack of blinding, small study size, heterogenous PRP preparations, and short follow-up durations.

Imam et al (2023) published a meta-analysis of 13 comparative studies, including 808 individuals with burn wounds who were treated with PRP (n=413) or standard wound therapy (n=395) with sample sizes ranging from 25 to 100 individuals. PRP had a shorter healing time than compared to standard therapy (MD, -5.80; 95% CI, -7.73 to -3.88; p<.001) as well as a higher healing rate (OR, 3.14; 95% CI, 2.05 to 4.8; p<.001) although these pooled estimates had substantial (I^2=93%) and moderate heterogeneity (I^2=42%), respectively. Individuals treated with PRP also had a higher percentage of graft take area (MD, 4.39; 95% CI, 1.51 to 7.26; p<.001) and higher percent of area healed (MD, 12.67; 95% CI, 9.79 to 15.55, p<.001) compared to standard therapy for burn wounds with a low level of heterogeneity. No differences were observed in the graft take ratio or infection rates which showed low heterogeneity.

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 systematic reviews and RCTs. For a variety of other conditions, studies have either not demonstrated a benefit or have demonstrated small benefits in studies with methodologic limitations.

Platelet-Rich Plasma for Other Miscellaneous Non-Orthopedic Indications

Clinical Context and Therapy Purpose

The purpose of PRP injections is to provide a treatment option that is an alternative to or an improvement on existing therapies for other miscellaneous non-orthopedic indications including but not limited to, androgenetic alopecia, alopecia areata, cerebral palsy, Crohn's disease related perianal fistula, urethral stricture, vitiligo, and thin endometrium (TE) related to infertility.

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

Populations

The relevant population are individuals with androgenetic alopecia, alopecia areata, cerebral palsy, Crohn's disease related perianal fistula, urethral stricture, vitiligo and thin endometrium (TE) related to infertility.

Interventions

The therapy being considered is PRP injections.

The use of PRP injections has received considerable interest due to the appeal of a minimally invasive method of applying growth factor for the potential benefit of healing and growth of new structures.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are symptoms, changes in disease status, adverse events, and QOL.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Platelet-Rich Plasma Injection for the Treatment for Androgenetic Alopecia and Alopecia Areata

Androgenetic Alopecia

Systematic Reviews

In 2018, Cervantes et. al. evaluated the effectiveness of platelet rich plasma treatment for androgenetic alopecia (AGA). A total of 12 studies conducted from 2011 to 2017 were evaluated and summarized by study characteristics, mode of preparation, and treatment protocols. A total of 295 subjects were given PRP or control treatment in studies, and evaluated for terminal hair density, hair quality, andagen/telogen hair ratio, keratinocyte proliferation, blood vessel density, etc. Some studies also provided subject self-assessment reports. Most of the studies reviewed showed effectiveness of PRP in increasing terminal hair density/diameter. However, the authors concluded several study design limitations need to be addressed before PRP is widely introduced as a treatment option in this clinical setting. The field would benefit from additional large scale double-blind, randomized controlled studies treating both men and women, with standardized PRP preparation methods and administration protocol, repeated treatment, standardized objective data documentation and evaluation, physician and subject assessment, isolating the effects of PRP in different grades of AGA, and performing long-term follow-up.

In 2018, Giordano et. al. completed a systemic review and meta-analysis on the evidence of platelet-rich plasma (PRP) for androgenetic alopecia (AGA), as there has been an increase in use by plastic surgeons for hair restoration. This meta-analysis compared local injection of PRP versus control to investigate the

efficacy of local PRP injections in AGA. The primary outcome was the difference in number of hairs per square centimeter. Secondary outcomes were hair cross-section increase, hair regrowth, and thickness percentage increase. Seven studies were included, five studies were randomized controlled trials (RCTs) and two were retrospective studies. There was a total of 194 patients, age ranged from 19 to 63 years, with a follow up from 3 to 24 months. A significantly locally increased hair number per cm^2 was observed after PRP injections versus control (mean difference [MD] 14.38, 95% confidence interval [CI] 6.38-22.38, $P < 0.001$). Similarly, a significantly increased hair thickness cross-section per 10^{-4} mm^2 (MD 0.22, 95% CI 0.07-0.38, $P = 0.005$) favoring PRP group. The pooled results did not show a significant percentage increase in hair number (MD 18.79%, 95% CI—- 8.50-46.08, $P = 0.18$), neither hair thickness (MD 32.63%, 95% CI—- 16.23-81.48, $P = 0.19$) among patients treated with PRP. The results of this meta-analysis should be viewed in light of a number of limitations and potential bias influencing these findings. The number of patients considered was extremely small and there were differences in patients' age, devices used, centrifugation methods, control, and areas of treatment, which might be a confounding factor for the results. Other major limitations of this pooled analyses include the fact that most of the included studies used internal controls, where the patient's contralateral side or other areas served as its own control, whereas in others, patients were randomized into groups where PRP was either used or not used. There were also differences in the treated scalp areas. The authors concluded, PRP injection for local hair restoration in patients with AGA seems to increase hairs number and thickness with minimal or no collateral effects. However, the current evidence does not support this treatment modality over other treatments due to the lack of clinical evidence, established protocols (i.e., number of sessions, centrifugation, zones to be injected, etc.), and long-term follow-up outcomes. The results of this meta-analysis should be interpreted with caution because it includes pooling many small studies and larger randomized studies should be performed to verify this perception. The medical literature does not confirm that the treatment is scientifically relevant. The addition of PRP might be useful in improving the outcomes of hair transplantation procedures, but there is no evidence whether PRP is more effective then minoxidil or finasteride treatments. Larger studies with long-term follow-up are warranted to validate this promising treatment modality.

Alopecia Areata

Systematic Reviews

In 2022, Barton et. al. performed a systematic review on the treatment of pediatric alopecia areata. Inclusion criteria were met by 122 total reports discussing 1032 patients. Reports consisted of 2 randomized controlled trials, 4 prospective comparative cohorts, 83 case series, 2 case-control studies, and 31 case reports. Included articles assessed the use of aloe, apremilast, anthralin, anti-interferon gamma antibodies, botulinum toxin, corticosteroids, contact immunotherapies, cryotherapy, hydroxychloroquine, hypnotherapy, imiquimod, Janus kinase inhibitors, laser and light therapy, methotrexate, minoxidil, phototherapy, psychotherapy, prostaglandin analogs, sulfasalazine, topical calcineurin inhibitors, topical nitrogen mustard, and32stekinumabb. The authors concluded "topical corticosteroids are the preferred first-line treatment for pediatric AA, as they hold the highest level of evidence, followed by contact immunotherapy. More clinical trials and comparative studies are needed to further guide management of pediatric AA and to promote the potential use of pre-existing, low-cost, and novel therapies, including Janus kinase inhibitors."

In 2017, Alyatollahi et. al. conducted a systematic review of the literature regarding the treatment of non-scarring hair loss with platelet-rich plasma (PRP) treatment. Although there are many studies regarding the role of PRP in bone grafts, teeth osteosynthesis, and wound healing, there have been little peer reviewed studies about the safety and efficacy of PRP application in the treatment of hair loss. Among 704 articles, 18 articles matched the inclusion criteria, 14 for androgenic alopecia and four for alopecia

areata. They included two case reports, eight case series, six controlled clinical trials and only two randomized controlled trials. The authors concluded “most of the available evidence has shown low quality and controversial results about the efficacy of PRP in treating non-cicatricial alopecia’s, including androgenetic alopecia and alopecia areata. Further randomized controlled studies with more sample size and standard protocols regarding the number and interval of treatment sessions, number of platelets, method of activation, etc., are required to investigate the efficacy and safety of PRP in treating hair loss.”

Randomized Controlled Trials

In 2021, Gupta et. al. evaluated platelet-rich plasma on hair regrowth and lesional T-cell cytokine expression in alopecia areata in a randomized observer-blinded, placebo controlled, split-head pilot study involving 27 patients with alopecia areata (Severity of Alopecia Tool score ≥25%). Alopecia patches on either side of the scalp were randomized to receive 3 intradermal injections of platelet-rich plasma or normal saline at monthly intervals and evaluated 3 months after the last session. Lesional T-cell cytokine messenger RNA expression was compared pre- and posttreatment in the platelet-rich plasma-treated sites. The mean Severity of Alopecia Tool score did not change significantly compared with baseline with either platelet-rich plasma or placebo injections at any visit; however, the mean percentage reduction in the score in the platelet-rich plasma arm was more than in the placebo arm (9.05% ± 36.48% vs 4.99% ± 33.88%; P = .049) at final assessment. The mean interferon gamma (P = .001) and interleukin 17 cytokine (P = .009) messenger RNA expression decreased, whereas the mean interleukin 10 (P = .049) and FOXP3 (P = .011) messenger RNA expression increased significantly after platelet-rich plasma treatment. Limitations of this study included small sample size and relatively short follow-up. The authors concluded “platelet-rich plasma was found to have limited efficacy in alopecia areata.”

In 2013, Trink et. al. performed a randomized, double-blind, placebo and active controlled, half-head study to evaluate the effects of platelet-rich plasma (PRP) on alopecia areata (AA). Alopecia areata (AA) is a common autoimmune condition, causing inflammation-induced hair loss. This disease has very limited treatment possibilities, and no treatment is either curative or preventive. Platelet-rich plasma (PRP) has emerged as a new treatment modality in dermatology, and preliminary evidence has suggested that it might have a beneficial role in hair growth. Forty-five patients with AA were randomized to receive intralesional injections of PRP, triamcinolone acetonide (TrA) or placebo on one half of their scalp. The other half was not treated. Three treatments were given for each patient, with intervals of 1 month. The endpoints were hair regrowth, hair dystrophy as measured by dermoscopy, burning or itching sensation, and cell proliferation as measured by Ki-67 evaluation. Patients were followed for 1 year. PRP was found to increase hair regrowth significantly and to decrease hair dystrophy and burning or itching sensation compared with TrA or placebo. Ki-67 levels, which served as markers for cell proliferation, were significantly higher with PRP. No side-effects were noted during treatment. The authors concluded “this pilot study, which is the first to investigate the effects of PRP on AA, suggests that PRP may serve as a safe and effective treatment option in AA, and calls for more extensive controlled studies with this method.”

Platelet-Rich Plasma Injection for the Treatment of Vitiligo

Systematic Review

Jafarzadeh et al (2024) conducted a systematic review to study the efficacy and safety of various regenerative treatments for vitiligo to include platelet-rich plasma (PRP). The authors searched the following data bases PubMed, Scopus, EMBASE and Web of Science (ISI). Forty-eight studies were included with 2186 patients (1056 [48.3%] women and 772 men [35.3%]) with an average age of 29.7 years. Among the 48 studies there were a total of 96 intervention groups out of which 76 were treated using regenerative medicine methods that included PRP (15 groups 19.7%) and the reviewers examined each regenerative medicine method individually. For PRP there was a total of 338 patients in 11 studies

with 15 intervention groups that included 169 women and 113 men with an average age of 25.55 years. PRP was also combined with fractional CO_2 laser and Psoralen + sunlight (PUVASOL). Repigmentation improvement was noted in 13 groups ($p \leq 0.05$), while two groups showed no significant difference to controls. Adverse events included injection site reactions such as pain, erythema, swelling, and bruising. Limitations included a high risk bias that complicated the ability to accurately assess the efficacy and safety due to many studies not using validated outcome measures related to quality of life, treatment burden and other patient-reported outcome measures. While results may be promising well-designed clinical trials with comparisons to traditional treatment methods with long term follow-up is needed to better inform clinical practice and treatment strategies for this condition.

In 2020, Merucri et. al. conducted a systematic review with the aim to identify studies that documented the use of platelet – rich plasma (PRP) for vitiligo. Six studies were identified with a total of 253 patients. The mean time of follow-up of treated patients was 6 months (ranging between 3 and 12 months). In all reports, all treated patients showed a stable vitiligo, and a significantly higher improvement in the PRP groups was always observed compared to control groups, regardless of the combined treatment associated with PRP. Regarding the side effects, PRP in vitiligo patients is safe, without important and specific side effects. Pain at the injection site was the main side effect, although it can be avoided applying 45–60 minutes before the injection of an anesthetic cream. In order to avoid local superinfection topical antibiotics can be used 3 days after injection. Ecchymosis in the site of injection may occur. Ejjiyar et. al. reported the onset of Koebner's phenomenon in a female patient phototype IV with the onset of facial non-segmental vitiligo after the third injection of PRP, for aesthetic purposes. The authors concluded PRP is a well-tolerated agent, recently receiving increasing attention by the medical community for its potential use in several dermatological conditions, including vitiligo. Literature confirms PRP as a safe and promising treatment for stable vitiligo lesions in different body sites, above all when PRP is combined with other physical procedures, such as fractional carbon dioxide laser. Four-six sessions, with 2–3-week interval are needed in order to obtain clinically significant results. However, the lack of consensus regarding preparation methods, makes it difficult to compare results from different clinical studies. Larger clinical trials with longer time of observation and the standardization of processing protocols represent a very fertile field for future research about the effectiveness of PRP for the treatment of vitiligo.

In 2019, Hesseler et. al. stated that the field of dermatology has seen numerous therapeutic innovations in the past 10 years with platelet-rich plasma (PRP), recently garnering interest in alopecia, acne scarring, and skin rejuvenation. In other conditions of dermatology, such as chronic wounds and vitiligo, PRP has been examined but has received less attention. A systematic review was conducted that focused on conditions of medical dermatology and consolidated the available evidence on PRP for the practicing dermatologist. They evaluated the literature up to October 31, 2018 and 14 articles met the inclusion criteria for this review. In studies representing Levels of Evidence 1b-4 according to the Center for Evidence-Based Medicine, Oxford, PRP significantly improved wound healing in chronic diabetic ulcers, venous ulcers, pressure ulcers, leprosy ulcers, acute traumatic wounds, and ulcers of multifactorial etiologies; two studies also documented benefits of adjunctive PRP in stable vitiligo. The authors concluded "in vitiligo as well as chronic wounds of multiple etiologies, PRP warrants further investigation because it represents a potential therapeutic adjunct or alternative with a favorable side effect profile."

Platelet-Rich Plasma Injection for the Treatment of Cerebral Palsy

Case Study

In 2015, Alcaraz et. al. reported on case of a cerebral palsy (CP) patient who received intravenous platelet-rich plasma (PRP). These investigators administered an intravenous injection of concentrated

PRP (25 cc) in a 6 -year- old boy with perinatal CP, cognitive impairment, and marked and severe generalized spasticity. They performed follow-up at 3 and 6 months after the injection. All serum samples for determination were obtained by ELISA technique. Cognitive scales (Bayley, Battelle, M.S.C.A, Kaufman ABC, and Stanford-Binet Intelligence scale) were used before and after treatment. The determination protocol that was applied before the analysis was performed manually and the autotransfusion was considered suitable for treatment. These researchers determined the plasma levels of factor similar to insulin-1 (IGF-1), platelet-derived growth factor (PDGF), vasculo-endothelial growth factor (VEGF), and transforming growth factor B (TGF-B) before and during treatment monitoring. No adverse effects were observed in the patient except for a small hematoma in the area channeling venous access. These investigators observed a clear improvement in the cognitive sphere (memory, ability to perform more complex tasks, and acquisition of new skills) and in language, maintaining stable levels of growth factor in plasma 3-5 times higher than average for his age group at both 3- and 6-month follow-up. Positron emission tomography (PET) images showed an evident increased demarcation in the cerebral cortex. The authors proposed that this therapy is useful in these patients to harness the neurostimulative and neuroregenerative power of endogenous growth factors derived from platelets. The findings of this single case study need to be validated in well-designed randomized studies.

Platelet-Rich Plasma Injections for the Treatment of Crohn’s Disease Related Perianal Fistula

Systematic Review

Mazzaro et. al. (2024) conducted a systematic review to evaluate the efficacy of regenerative therapies, particularly platelet-rich plasma (PRP) in the treatment of individuals with Crohn’s disease (CD). The reviewers searched the following databases PubMed, PubMed PMC, BVS-BIREME, Scopus, Web of Sciences, Embase, Cochrane, EBSCOhost, ProQuest, and EndNote for studies that investigated the use of regenerative therapies, using PRP alone or in combination with other treatments (i.e., adipose derived stem cells, stromal vascular fraction (SVF) and surgical approaches depending on location). The studies included were observational. Outcomes of this review focused on interventions aimed at regenerating tissues affected by the disease and reported relevant outcomes such as symptom improvement, lesion healing and reduction in inflammation using clinical examination, endoscopic findings (Crohn’s Disease Endoscopic Index of Severity [CDEIS]), Perianal Crohn’s Disease Activity Index (PCADI) and MRI Assche Score. Ten studies were included with a total of 143 patients with the focus of this study on patients with perianal CD (PCD) (138 patients), and 5 patients with refractory colonic CD. The typical procedure involved the injection of PRP or PRP and combination therapy near the internal openings and the fistula tracts. The local application of PRP injections demonstrated moderate efficacy but was less effective than the combination therapies, with a lower complete healing rate of 38.51% (95% CI [11.96; 68.77], chi^2 = 16.24, I^2 = 82%). Twelve adverse events were reported to include infection, postoperative pain and minor bleeding at injection site. Limitations included small sample sizes and single-center designs. While this study may show promise the authors concluded “more extensive randomized controlled trials will be necessary to confirm its effectiveness and standardize treatment protocols. Furthermore, contextualizing these findings within the broader landscape of existing evidence, including systematic reviews and meta-analyses, is imperative to garner a comprehensive understanding of the efficacy and safety profiles of these interventions.”

Case Studies

In 2020, Portilla et.al. conducted a pilot study at single center January 2013 and December 2015. Autologous platelet-rich plasma was prepared in platelet-rich and platelet-poor fractions for local intrafistular injection in patients with proven, established perianal Crohn's disease. Patients were

permitted biological therapies, and the Perianal Crohn's Disease Activity Index was recorded. Patients were followed for 48 weeks for clinical signs of healing (complete, partial or non-healing), monitoring fistula drainage, closure and epithelialization. The study included 29 patients (19 males; mean age 38 ± 12.8 years) with four exclusions in the operating room because surgery was not indicated and four lost to follow-up. Five adverse events were recorded, with two requiring the drainage of abscess collections. Of the 21 patients assessable at 24 weeks, there was complete healing, partial healing and non-healing in 7 (33.3%), 8 (38.1%) and 6 (28.6%) patients, respectively. By 48 weeks, there was complete healing, partial healing and non-healing in 6 (40%), 6 (40%) and 3 (20%) patients, respectively, with a reduction in the number of visible external fistula openings at both time points (P = 0.021). By the end of the study, there was a higher trend of healing if biological therapies were continued (85.7% with biologics vs. 75% without, P = 0.527), but there were no statistically significant differences and no differences in the Perianal Crohn's Disease Activity Index.

In 2015, Gottgens et. al. conducted a prospective pilot study in one tertiary referral center in the attempt to improve healing rates by combining the well-known mucosal advancement flap with platelet-rich plasma (PRP). Consecutive patients with primary or recurrent Crohn's disease-related high perianal fistulas, defined as involving the middle and/or upper third parts of the anal sphincter complex, were included. A staged procedure was performed with non-cutting seton treatment for 3 months first, followed by a mucosal advancement flap with injection of platelet-rich plasma into the fistula tract. Ten consecutive patients were operated on between 2009 and 2014. Half (50%) of the patients had undergone previous fistula surgery. Mean follow-up was 23.3 months (SD 13.0). Healing of the fistula was 70% (95% confidence interval, 33-89%) at 1 year. One patient (10%) had a recurrence, and in two patients (20%) the fistula was persistent after treatment. An abscess occurred in one patient (10%). The median post-operative Vaizey score was 8.0 (range 0-21), indicating a moderate to severe continence impairment. The authors concluded, the results of combining the mucosal advancement flap with platelet-rich plasma (PRP) in patients with Crohn's disease-related high perianal fistulas are moderate with a healing rate of 70%. Further investigation is needed to determine the benefits and risks on continence status for this technique in this patient population.

Platelet-Rich Plasma Injections for the Treatment of Urethral Stricture

Systematic Review

In 2021, Pang et. al. completed a systematic review and meta-analysis for adjuncts to minimally invasive treatment of urethral stricture disease (USD) in men. A total of 26 studies were included in the systematic review, from which 13 different adjuncts were identified, including intralesional injection (triamcinolone, *n* = 135; prednisolone, *n* = 58; mitomycin C, *n* = 142; steroid-mitomycin C-hyaluronidase, *n* = 103, triamcinolone-mitomycin C-*N*-acetyl cysteine, *n* = 50; platelet-rich plasma, *n* = 44), intraluminal instillation (mitomycin C, *n* = 20; hyaluronic acid and carboxymethylcellulose, *n* = 70; captopril, *n* = 37; 192-iridium brachytherapy, *n* = 10), application via a lubricated catheter (triamcinolone, *n* = 124), application via a coated balloon (paclitaxel, *n* = 106), and enteral application (tamoxifen, *n* = 30; deflazacort, *n* = 36). Overall, 13 randomized controlled trials were included in the meta-analysis. Use of any adjunct was associated with a lower rate of USD recurrence (odds ratio [OR] 0.37, 95% confidence interval [CI] 0.27–0.50; $p < 0.001$) compared to no adjunct use. Of all the adjuncts, mitomycin C was associated with the lowest rate of USD recurrence (intralesional injection: OR 0.23, 95% CI 0.11–0.48; $p < 0.001$; intraluminal injection: OR 0.11, 95% CI 0.02–0.61; $p = 0.01$). Urinary tract infection (2.9–14%), bleeding (8.8%), and extravasation (5.8%) were associated with steroid injection; pruritis of the urethra (61%) occurred after instillation of captopril; mild gynecomastia (6.7%) and gastrointestinal side effects (6.7%) were associated with oral tamoxifen. The authors

concluded adjuncts to minimally invasive treatment of USD appear to lower the recurrence rate and are associated with a low adjunct-specific complication rate. However, the studies included were at high risk of bias. Mitomycin C is the adjunct supported by the highest level of evidence.

Case Study

In 2016, Gul reported on the use of a modified platelet-rich plasma with a transforming growth factor B1 neutralization antibody injection that may reduce the recurrence rate of urethral stricture. Urethral stricture is one of the most bothersome urologic diseases among urologists and has a substantial impact on quality of life and healthcare costs. Although it can be cured with internal urethrotomy easily, post-surgery stricture recurrence is challenging. Several adjuvant therapies have been used in conjunction with internal urethrotomy but none of them are used routinely because the pathophysiology of the disease is still obscure. Fibrosis is the most accused hypothesis for the action. Platelet-rich plasma (PRP) is an autologous blood product containing a high concentration of platelets that is being used for a very wide range of clinical healing applications. It comprises a concentration of fundamental protein growth factors shown to be actively excreted by platelets to initiate accurate wound healing. Although PRP can play a critical role in wound healing and has been used in fibrotic diseases successfully, it has some deleterious cytokines such as transforming growth factor β1 (TGF β1) which can also cause fibrosis. The author concluded “the new hypothesis is that the subcutaneous injection of neutralized platelet-rich plasma with TGFβ1 antibody at the planned urethrotomy site may prevent recurrence and provide superior healing and long-term results. This theory needs to be validated in well-designed randomized studies.”

Platelet-Rich Plasma Intrauterine Injections of the Endometrium for the Treatment of Infertility

Meta-Analyses

Liu et al (2024) in a meta-analysis of randomized controlled trials (RCTs) addressed the safety and effectiveness of intrauterine platelet-rich plasma (PRP) injection therapy in women with thin endometrium (TE) compared to a control group (placebo or other treatment methods) in improving clinical outcomes post-assisted reproduction. Searches of PubMed, The Cochran Library, Embase, Web of Science and Medline were completed from inception through June 8, 2024. Eight RCTs (Eftekhar 2018, Chang 2019, Nazari 2019, Coksuer 2019, Abdujabbar 2022, Efendieva 2023, Pandey 2023, Yu 2024) that included 678 patients with TE were included. The participants were women aged over 18 years with thin endometrium, defined as endometrial thickness <7 mm on the day of ovulation after the peak of natural cycle luteinizing hormone, the day of gonadotropin-releasing hormone injection in controlled ovarian hyperstimulation cycles, or the day of progesterone initiation in frozen embryo transfer cycles. The experimental group received either pure PRP treatment, or a combination of PRP treatment with conventional hormone replacement therapy (HRT, which included estradiol valerate or suppository progesterone treatment). The control group received a placebo or HRT. All eight studies ensured the completeness of outcome data and had no selective reporting of results. Patients receiving PRP infusion demonstrated significantly superior outcomes compared to the control group in endometrial thickness (MD: 1.23, 95%CI: 0.87 to 1.59, P=0.000), clinical pregnancy rate (RR: 2.04, 95%CI: 1.52 to 2.76, P=0.000), live birth rate (RR: 2.46; 95%CI: 1.57 to 3.85, P=0.000), cycle cancellation rate (RR: 0.46, 95%CI: 0.23 to 0.93, P=0.000), and embryo implantation rate (RR: 2.71; 95%CI: 1.91 to 3.84, P=0.000). There was no statistical significance in spontaneous abortion rate (RR: 0.85, 95%CI: 0.40 to 1.78, P=0.659), chemical pregnancy rate (RR: 1.84, 95%CI: 0.72 to 4.72, P=0.204) and endometrial vascular improvement rate (RR: 1.10; 95%CI: 0.89 to 1.38, P=0.367) between the two groups. There were no reported complications or adverse events in any of the studies associated with the PRP injections. Limitations include the sample size and heterogeneity among the different studies regarding various factors related to PRP preparation methods,

concentration, dosage, timing of PRP and the number and quality of embryos transplanted per cycle. The authors concluded “further high-scale, high-quality, multicenter, and rigorously designed randomized controlled trials are required for validation.”

Section Summary: Platelet-Rich Plasma Injections for the Treatment of Other Miscellaneous Indications

Despite the growing interest in regenerative medicine, few trials investigating PRP efficacy on hair growth have been published. Most of the reviewed studies have important methodological deficiencies. Main flaws include lack of a reference protocol regarding the frequency of applications as well as the injected amount of PRP, heterogeneity in application modes, lack of controls, small sample size, lack of detailed reports in patients’ characteristics and used statistical methods. Furthermore, few studies referred to the safety profile of PRP. In addition, currently there is no evidence that PRP is more effective than standard of care treatment utilizing minoxidil or finasteride.

For individuals who have one of the following miscellaneous conditions vitiligo, cerebral palsy (CP), Crohn’s disease (CD) related to high perianal fistula, urethral stricture disease or thin endometrium (TE) who receive PRP, the evidence includes systematic review, meta-analyses and few case studies. While some of these studies may show promise, this limited evidence found, to date, there are no standard protocols regarding PRP preparation that exist. Published studies report variations in processing, such as the number of centrifugations or compounds added, which make it difficult to compare results from different clinical studies. The use of PRP for the treatment of these indications warrants further investigation in well-designed randomized comparative studies with longer time of observation to determine safety and efficacy.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.” A search of the ACP website on December 1, 2020 found that this 2015 guideline is now listed as inactive.

Association for the Advancement of Wound Care

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

- Pressure ulcer: “Growth factors are not indicated for PU [pressure ulcers] at this time.” (Level C evidence - no randomized controlled trials (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 (NICE)

In 2019, the National Institute for Health and Care Excellence (NICE) updated its guidance on the prevention and management of diabetic foot problems. 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.

Wound Health Society

The 2023 Wound Healing Society (WHS) guideline for the treatment of pressure ulcers makes the following recommendations:[,]

"Consider the use of growth factor therapy for pressure ulcers that are not responsive to initial comprehensive therapy and/or before surgical repair...Platelet rich plasma (PRP) gel consists of cytokines, growth factors, chemokines, and a fibrin scaffold derived from a patient’s blood. The mechanism of action of PRP gel is thought to be inducing and stimulating cellular and molecular processes enhancing wound healing."

The 2024 WHS guideline for the treatment of diabetic foot ulcers makes the following recommendations:[8,]

"Topical growth factors such as platelet-derived and recombinant human epidermal growth factor have been shown to increase the incidence of ulcer healing and reduce the time to heal."

"The evidence is uncertain for the efficacy of therapy with platelet-rich plasma as studies report mixed results regarding the benefits of this therapy."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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Codes

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	0232T	Injection(s). platelet rich plasma, any tissue, including image guidance, harvesting and preparation when performed

HCPCS		
	G0460	Autologous platelet rich plasma or other blood-derived product for non-diabetic chronic wounds/ulcers, including as applicable phlebotomy, centrifugation or mixing, and all other preparatory procedures, administration and dressings, per treatment
	G0465	Autologous platelet rich plasma (PRP) or other blood-derived product for diabetic chronic wounds/ulcers, using an FDA-cleared device for this indication, (includes as applicable administration, dressings, phlebotomy, centrifugation or mixing, and all other preparatory procedures, 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
Type of Service	Medical	
Place of Service	Inpatient, Outpatient, Home	

POLICY HISTORY

Date	Action	Action
March 2026	Annual Review	Policy Revised
March 2025	Annual Review	Policy Revised
March 2024	Annual Review	Policy Renewed
March 2023	Annual Review	Policy Revised
November 2022	Annual Review	Policy Revised
November 2021	Annual Review	Policy Renewed
November 2020	Annual Review	Policy Revised
November 2019		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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