Platelet-Rich Plasma for Wound Healing and the Treatment of Other Non-Orthopedic Indications

Medical Policy #: 02.01.61
Original Effective Date: November 2019
Reviewed: November 2022
Revised: November 2022

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

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), surgical and traumatic

wounds, and various musculoskeletal (orthopedic) conditions, as an adjunctive procedure in orthopedic surgeries. It is also being investigated 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, and vitiligo.

Wound Healing Treatment

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

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

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

Wound Closure Outcomes

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

- 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.

Recombinant Platelet-Derived Growth Factor for Diabetic Lower-Extremity Ulcers

Clinical Context and Therapy Purpose
The purpose of recombinant platelet-derived growth factor (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.

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

Interventions
The therapy being considered is recombinant platelet-derived growth factor (PDGF).

Comparators
Comparators of interest include standard wound care.

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

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

Review of Evidence
The portion of this evidence review on the use of recombinant PDGF (becaplermin gel) was informed by a 1999 BCBS Association TEC Assessment, which found that the evidence supported the conclusion that becaplermin gel, in conjunction with good wound care, improves the health outcomes of patients with chronic neuropathic diabetic ulcers that met the patient selection criteria defined therein. Becaplermin gel plus good wound care resulted in a 43% complete wound closure rate, compared with 28% for patients treated with good wound care alone. Becaplermin gel also appeared to reduce the average time to complete wound closure.

Systematic Reviews
A 2014 systematic review identified 6 RCTs (N=992 patients) that compared recombinant PDGFs with placebo or standard care. There was a combined odds ratio of 1.53 (95% confidence interval [CI], 1.14 to 2.04; p=.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 odds ratio 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 those who received PDGF were more likely to be younger, male, and have older wounds-factors not known to affect wound healing. These results support the clinical utility of recombinant PDGF for treatment of diabetic neuropathic foot ulcers in actual clinical practice.

Section Summary
Published evidence includes an industry-sponsored study and 2 systematic reviews that showed an improvement in treatment over control for tested outcome measures.

Recombinant Platelet-Derived Growth Factor for Pressure Ulcers

Clinical Context and Therapy Purpose
The purpose of recombinant platelet-derived growth factor (PDGF) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with pressure ulcers.

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

Interventions
The therapy being considered is recombinant platelet-derived growth factor (PDGF).

Comparators
Comparators of interest include standard wound care.

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

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

Review of Evidence
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
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 Stasis Leg Ulcers

Clinical Context and Therapy Purpose
The purpose of recombinant platelet-derived growth factor (PDGF) is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with venous stasis ulcers.

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

Interventions
The therapy being considered is recombinant platelet-derived growth factor (PDGF).

Comparators
Comparators of interest include standard wound care.

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

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

Review of Evidence
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
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 platelet-derived growth factor (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.

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

Interventions
The therapy being considered is recombinant platelet-derived growth factor (PDGF).

Comparators
Comparators of interest include standard wound care.

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

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

Review of Evidence
Topical recombinant PDGF has also been investigated for repair of work-related fingertip injuries. A 2005 prospective controlled trial alternately assigned 50 patients (fingertip wound area ≥1.5 cm, with or without phalangeal exposure) to daily treatment with PDGF (n=25) or surgical reconstruction (n=25). 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
Published evidence includes nonrandomized controlled trials reporting satisfactory aesthetic results. Larger RCTs are required to confirm and expound on these results.

Platelet-Rich Plasma for Chronic Wounds

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

The blood contains small solid components (red cells, white cells, and platelets). The platelets are best known for their importance in clotting blood. However, platelets also contain an abundance of proteins called growth factors (GFs) and cytokines which are suggested to promote healing and/or tissue growth enhancing the body's inherent capacity to repair and regenerate. Platelet-rich plasma (PRP) is extracted from a small quantity of blood collected from the patient using a standard peripheral vein puncture procedure followed by simple centrifuge to remove most of the larger cells (white and red blood cells) and the majority of the fluid and concentrate the platelets in a small volume of plasma (the liquid component of the blood) that is platelet-rich. The concentration of platelets and, thereby, the concentration of growth factors (GFs) can be 5 to 10 times greater or richer than usual. Although it is not exactly clear how PRP works, it is suggested that the increased concentration of growth factors in PRP stimulate the healing and growth of new structures.

Populations

The relevant population of interest is individuals with chronic wounds.

Interventions
The therapy being considered is platelet-rich plasma (PRP).

Comparators
Comparators of interest include standard wound care.

Outcomes

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

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

Review of Evidence

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.

Diabetic Foot Ulcers

Three 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)	Del Pino-Sedeno 2018[21,]	Li 2019[22,]	Qu 2020[23,]
Ahmed 2017[24,]	●	●	●
Chen 2008[a25,]		●	
Driver 2006[26,]	●	●	●
Elsaid 2020[27,]			●
Friese 2007 (conference proceeding)[28,]		●	
Game 2018[29,]			●
Gude 2019[30,]			●
Kakagia 2007[31,]	●	●	●
Karimi 2016[32,]	●		●
Li 2015[33,]	●	●	●
Liu 2016[a34,]		●	
Ma 2014[a35,]		●	

Milek 2017[36,]			●
Qi 2014[a37,]		●	
Saad Setta 2011[38,]	●	●	●
Saldalamacchia 2004[39,]	●	●	●
Serra 2013[40,]		●	●
Singh 2018[41,]			●
Steed 1992[42,]	●		
Steed 1996[43,]	●		
Xie 2020[44,]			●
Yang 2017[45,]			●
Zhang 2016[a46,]		●	
Zhou 2015[a47,]		●	
Zhu 2012[a48,]		●	

[a] In Chinese

Tables 3 and 4 summarize the characteristics and results of the 3 systematic reviews that have evaluated studies of PRP for individuals with diabetic foot ulcer

A meta-analysis by del Pino-Sedeno et al (2018) assessed 8 RCTs and 2 longitudinal-observational studies (N=525) to determine the safety and efficacy of PRP to treat diabetic foot ulcers. Results indicated PRP significantly increased chronic wound healing compared with standard treatment (RR=1.41; 95% CI: 1.08 to 1.84; p=.01; I^2=51%). Subgroup analysis showed that PRP source affected the proportion of completely healed diabetic foot ulcers (autologous RR=1.21; 95% CI: 1.04 to 1.42; p=.02; allogenic RR=3.20; 95% CI: 1.14 to 9.03; p=.03). PRP preparation method also influenced healing (homemade RR=1.22; 95% CI: 1.04 to 1.44; p=.02; commercial protocol RR=1.13; 95% CI: 0.58 to 2.20; p=.71; blood bank RR=3.20; 95% CI: 1.14 to 9.03; p=.03). The 2 trials that reported mean time for complete wound healing showed that PRP resulted in quicker healing (mean difference=-11.18 days; 95% CI: -20.69 to -1.68; p=.02; I^2=53%). Overall, the studies reported no significant differences in rates of wound complications or dermatitis, and rates of recurrences were similar between PRP and standard treatment. The authors noted, however, that results of their analysis should be interpreted cautiously because no statistical differences were found in the epithelialized area before and after wound treatment (mean difference=0.70 cm2; 95% CI: -0.96 to 2.35; p=.41; I^2=70%). This study was limited by the low number and quality of studies available on PRP for diabetic foot ulcers.

In their meta-analysis, Li et al (2019) assessed the efficacy and safety of autologous platelet-rich gel for topical treatment of diabetic chronic cutaneous ulcers. Their analysis included 15 RCTs with 829 patients. Results indicated that autologous platelet-rich gel had a significant positive effect on healing rate, shorter healing time, and lower risk of

infection than conventional treatment. Autologous platelet-rich gel also had a significantly lower incidence of infection when compared with conventional treatment (odds ratio=0.34; 95% CI: 0.15 to 0.77; p=.009). This meta-analysis was limited by a high or unclear risk of bias among the trials, which may indicate the trials were underpowered. Also, some studies had small sample sizes and limited outcome information. Further, 7 of the included trials are available only in the Chinese language. Finally, most of the trials were 8 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."

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

Study	Dates	Trials	Participants	N (Range)	Design	Duration
del Pino-Sedeno (2018)[21,]	Inception-2017	10	Patients with diabetic foot ulcers	N=525 (13-117)	RCTs, longitudinal observational studies	3 wk to 128.57 wk
Li (2019)[22,]	2004-2017	15	Patients with diabetic chronic cutaneous wounds/ulcers that do not show signs of healing in 4 weeks	N=829 (14-117)	RCTs	NR

Qu (2021)[23,]	Inception-2020	14	Adults with lower extremity diabetic ulcers, lower extremity venous ulcers, or pressure ulcers in any location, or a mix of these 3 etiologies	N=1,096 (range NR)	RCTs	Median = 6 wk (range, none to 11 months)

NR: not reported; 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
del Pino-Sedeno (2018)[21,]							
RR			1.41		0.57		2.76
MD		-11.18					
95% CI		-20.69 to -1.68	1.08 to 1.84		0.25 to 1.28		0.23 to 33.36
P-value		.02	.01		.17		.43
Li (2019)[22,]							
RR	1.39						
MD		-9.18					
OR				0.34			
95% CI	1.29 to 1.50	-11.32 to -7.05		0.15 to 0.77			
P-value	<.001	<.001		.009			
Qu (2021)[23,]							
RR			1.20	0.77			2.09
WMD						-1.10[a]	
95% CI			1.09 to 1.32	0.54 to 1.11		-1.81 to -0.39	0.31 to 13.93
P-value							

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

Other Chronic Wound Types

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

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.[51,] 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 to limitations in the randomization process and outcome measurement, deviations from intended interventions, and selective outcome reporting. Although both studies found that PRP significantly reduced wound size (strength of evidence=insufficient), neither study evaluated other important outcomes, such as complete wound closure.

Randomized Controlled Trials

One RCT of PRP for chronic wounds (Saha et al [2020]) was identified as published subsequent to the AHRQ review (2020). Key characteristics and results of selected RCTs are reported in Tables 5 and 6 below.

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

One recent 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.

Table 5. 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)
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)

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

Table 6. Summary of Key RCT Results

Study	Complete Healing	Healing Time	Pain	Quality of Life	Infection	Recurrence
Saha et al (2020)[,]	22 (39.29%) vs 11 (21.15%); p NR	NR	NR	NR	0 vs 0; p=.773	NR
Gupta et al (2021)	85.98% vs 81.72%[a]; p NR	NR	NR	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 7 and 8 summarize the relevance and design and conduct limitations of selected RCTs.

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

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not

delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Saha et al (2020)[,]						
Gupta et al (2021)		1-3. Blinding not described			1. Power calculations not reported	3. Confidence intervals and/or p values not reported

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

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

Platelet-Rich Plasma for Acute Surgical or Traumatic Wounds

Clinical Context and Therapy Purpose

The purpose of platelet-rich plasma (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.

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, quality of life (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.

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.

Otolaryngology
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).

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.

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 *(ie,* "pain duration was inquired from participants"). All patients completed the study and were included in the outcome assessments. PRP

significantly shortened mean healing time (4.8 vs 8.7 weeks; p<.001), pain duration (1.3 vs 3.4 weeks; p<.001), and antibiotic consumption duration (0.57 vs 1.74 weeks; p<.001). This RCT also performed regression analyses to evaluate the correlation between different factors in wound healing activity. Significant negative associations were found between healing time and wound volume and pain duration and angiogenesis. Notable limitations of this study included unclearly defined wound dressing in the comparator group, unblinded and poorly defined outcome assessment, short-term follow-up and lack of assessment of other important health outcomes.

Slaninka et al (2020) published an RCT that evaluated PRP in 24 individuals in the Czech Republic who had undergone dermo-epidermal skin grafts taken from the thigh area. 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 de bridement and placement of the external fixation system. The time needed for preparation and application of the PRP gel was 52 minutes. After that, PRP gel was applied to the wounds once weekly in the outpatient clinic until there was adequate tissue regeneration (mean, 21 days) sufficient to undergo reconstructive plastic surgery. Control patients receiving conventional treatment required a mean of 41 days for adequate tissue regeneration. Pain scores were significantly lower in PRP-treated patients at 2 and 3 weeks (visual analog scale score, 58 PRP vs. 80 controls). Although these results are encouraging, additional study with a larger number of patients is needed.

Marck et al (2016) reported on a randomized, double-blind, within-patient-controlled study in patients with deep dermal to full-thickness burns undergoing split-skin graft, comparing PRP with usual care. 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 that 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 (odds ratio [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.

Section Summary
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.

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

For individuals who have pressure ulcers who receive recombinant PDGF, the evidence includes 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 PDGF for pressure ulcers. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

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

For individuals who have acute surgical or traumatic wounds who receive PRP, the evidence includes a 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 for Other Non-Orthopedic Indications

Clinical Context and Therapy Purpose
The purpose of platelet rich plasma (PRP) injections is to provide a treatment option that is an alternative to or an improvement on existing therapies for non-orthopedic indications including but not limited to, androgenetic alopecia, alopecia areata, cerebral palsy, Crohn’s disease related perianal fistula, urethral stricture, and vitiligo.

Populations
The relevant population are individuals with non-orthopedic indications such as, androgenetic alopecia, alopecia areata, cerebral palsy, Crohn's disease related perianal fistula, urethral stricture, and vitiligo.

Interventions
The therapy being considered is platelet rich plasma (PRP) injections.

The use of PRP injections has been proposed as a treatment of various non-orthopedic indications and 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 quality of life (QOL).

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

Androgenetic Alopecia
Androgenetic alopecia is a common form of hair loss in both men and women. In men, this condition is also known as male-pattern baldness. Hair is lost in a well-defined pattern, beginning above both temples. Over time, the hairline recedes to form a characteristic "M" shape. Hair also thins at the crown (near the top of the head), often progressing to partial or complete baldness.

The pattern of hair loss in women differs from male-pattern baldness. In women, the hair becomes thinner all over the head, and the hairline does not recede. Androgenetic alopecia in women rarely leads to total baldness.

Androgenetic alopecia in men has been associated with several other medical conditions including coronary heart disease and enlargement of the prostate. Additionally, prostate cancer, disorders of insulin resistance (such as diabetes and obesity), and high blood pressure (hypertension) have been related to androgenetic alopecia. In women, this form of hair loss is associated with an increased risk of polycystic ovary syndrome (PCOS). PCOS is characterized by a hormonal imbalance that can lead to irregular menstruation, acne, excess hair elsewhere on the body(hirsutism), and weight gain.

Androgenetic alopecia is a frequent cause of hair loss in both men and women. This form of hair loss affects an estimated 50 million men and 30 million women in the United States. Androgenetic alopecia can start as early as a person's teens and risk increases with

age; more than 50 percent of men over age 50 have some degree of hair loss. In women, hair loss is most likely after menopause.

A variety of genetic and environmental factors likely play a role in causing androgenetic alopecia. Although researchers are studying risk factors that may contribute to this condition, most of these factors remain unknown. Researchers have determined that this form of hair loss is related to hormones called androgens, particularly an androgen called dihydrotestosterone. Androgens also have other important functions in both males and females, such as regulating hair growth.

Hair growth begins under the skin in structures called follicles. Each strand of hair normally grows for 2 to 6 years, goes into a resting phase for several months, and then falls out. The cycle starts over when the follicle begins growing a new hair. Increased levels of androgens in hair follicles can lead to a shorter cycle of hair growth and the growth of shorter and thinner strands of hair. Additionally, there is a delay in the growth of new hair to replace strands that are shed.

The inheritance pattern of androgenetic alopecia is unclear because many genetic and environmental factors are likely to be involved. This condition tends to cluster in families, however, and having a close relative with patterned hair loss appears to be a risk factor for developing the condition.

Treatment for androgenetic alopecia is pharmacologic therapy using 5-alpha reductase inhibitor topical therapy such as minoxidil or systemic agents that inhibit androgen production or action such as oral finasteride. While topical and other pharmacologic therapies are effective, the response to treatment is variable. Treatment may result in no effect, the inhibition of further hair loss, or a variable degree of regrowth of hair. Pharmacologic therapy must be continued indefinitely to maintain the response. Platelet-rich plasma (PRP) injections has emerged as a new treatment modality in the treatment of androgenetic alopecia and is being further investigated due to preliminary evidence suggesting it might have a beneficial role in hair regrowth.

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

Alopecia areata is a common disorder that causes hair loss. "Alopecia" is a Latin term that means baldness, and "areata" refers to the patchy nature of the hair loss that is typically seen with this condition.

In most people with alopecia areata, hair falls out in small, round patches, leaving coin-sized areas of bare skin. This patchy hair loss occurs most often on the scalp but can affect other parts of the body as well. Uncommonly, the hair loss involves the entire scalp (in which case the condition is known as alopecia totalis) or the whole body (alopecia universalis). Other rare forms of alopecia areata, which have different patterns of hair loss, have also been reported.

Alopecia areata affects people of all ages, although it most commonly appears in adolescence or early adulthood. Hair loss occurs over a period of weeks. The hair usually grows back after several months, although it may fall out again. In some cases, unpredictable cycles of hair loss followed by regrowth can last for years. In addition to hair loss, some affected individuals have fingernail and toenail abnormalities, such as pits on the surface of the nails.

The hair loss associated with alopecia areata is not painful or disabling. However, it causes changes in a person's appearance that can profoundly affect quality of life and self-esteem. In some people, the condition can lead to depression, anxiety, and other emotional or psychological issues.

Alopecia areata affects 1 in every 500 to 1,000 people in the United States. It is one of many recognized forms of alopecia; alopecia areata is the second most common form after androgenetic alopecia (male-pattern baldness in men and female-pattern baldness in women). Alopecia areata affects men and women equally, and it can occur in people of any ethnic background.

Alopecia areata is one of a large group of immune system diseases classified as autoimmune disorders. Normally, the immune system protects the body from foreign invaders, such as bacteria and viruses, by recognizing and attacking these invaders and clearing them from the body. In autoimmune disorders, the immune system malfunctions and attacks the body's own tissues instead. For reasons that are unclear, in alopecia areata the immune system targets hair follicles, stopping hair growth. However, the condition does not permanently damage the follicles, which is why hair may later regrow.

Many of the genes that have been associated with alopecia areata participate in the body's immune response. These include several genes belonging to a gene family called the human leukocyte antigen (HLA) complex. The HLA complex helps the immune system distinguish the body's own proteins from proteins made by foreign invaders. Each HLA gene has many different variations, allowing each person's immune system to react to a wide range of foreign proteins. Certain variations in HLA genes likely contribute to the inappropriate immune response targeting hair follicles that leads to alopecia areata. Immune system genes outside the HLA complex, such as several genes involved in inflammation, have also been associated with alopecia areata.

Some of the genetic variations associated with alopecia areata have been identified in people with other autoimmune disorders, which suggests that this group of diseases may share some genetic risk factors. People with alopecia areata have an increased risk of developing other autoimmune disorders, including vitiligo, systemic lupus erythematosus, atopic dermatitis, allergic asthma, and autoimmune thyroid diseases (such as Hashimoto thyroiditis and Graves' disease). Similarly, people with those autoimmune disorders have an increased risk of developing alopecia areata.

In many cases, it is unknown what triggers hair loss in people with alopecia areata. It is possible that environmental factors, such as emotional stress, physical injury, or illness, provoke an abnormal immune response in people who are at risk. However, in most affected people, the onset of hair loss has no clear explanation.

The inheritance pattern of alopecia areata is unclear because multiple genetic and environmental factors appear to be involved. Overall, the risk of developing the condition is greater for first-degree relatives (such as siblings or children) of affected individuals than it is in the general population. People with alopecia areata are also more likely to have family members with other autoimmune disorders.

Treatment success depends on the age of onset and the extent of hair loss. The prognosis tends to be worse in more extensive cases (alopecia totalis or universalis), or when alopecia areata begins in early childhood. The most common treatment for mild cases of alopecia areata (involving less than 50% of loss of scalp hair) is direct intradermal injections of corticosteroids into patches of hair loss. Multiple injections are administered monthly to the skin in and around the bare patches; an average of 4 to 6 monthly injections are usually required for significant improvement. Therapy for extensive alopecia areata (involving more than 50% loss of scalp hair) may be prolonged and difficult but consists of topical immunotherapy. Systematic corticosteroids may be required depending on the severity of the condition and the adequacy of the response to topical therapy. Platelet-rich plasma (PRP) injections has emerged as a new treatment modality in the treatment of alopecia areata and is being further investigated due to preliminary evidence suggesting it might have a beneficial role in hair regrowth.

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.

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 showing the role of platelet rich plasma (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 alopecias, 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.

In 2020, Almohanna et. al. performed a review of platelet-rich plasma (PRP) in the treatment of alopecia areata. The authors concluded a few studies and case reports support the use of PRP for the treatment of alopecia areata (AA), however, further large-scale studies are needed to evaluate the efficacy of PRP as monotherapy or in association with other therapeutic modalities for AA. Although PRP is relatively safe and potentially effective, there is no standardized protocol or recommendations for the number of PRP sessions required to treat and maintain hair growth.

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 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, and ustekinumab. 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.

Summary of Evidence
Despite the growing interest in regenerative medicine, few trials investigating platelet-rich plasma (PRP) efficacy on hair growth has 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 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.

Platelet-Rich Plasma Injection for the Treatment of Vitiligo
Vitiligo is a disease that causes the loss of skin color in blotches. Usually, the discoloration first shows on sun-exposed areas, such as the hands, feet, arms, face and lips. The extent and rate of color loss from vitiligo is unpredictable. It can affect the skin on any part of the body. Normally the color of hair and skin is determined by melanin. Vitiligo occurs when the cells that produce melanin die or stop functioning. Vitiligo affects people of all skin types, but it may be noticeable in people with darker skin. Vitiligo can start at any age, but often appears before the age of 20. Treatment for vitiligo may restore color to the affected skin, but it does not prevent continued loss of skin color or recurrence. The use of platelet-rich plasma (PRP) is receiving interest as potential treatment of several dermatological diseases, including 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 search was conducted in the PubMed database for “platelet-rich plasma," "platelet releasate," "platelet gel," "platelet-rich fibrin" or "PRP" and "dermatology," "skin," "cutaneous," "wound," or "ulcer." In total, 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 that 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.

In 2020, Merucri et. al. conducted a 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.

Summary of Evidence
Based on review of the peer reviewed medical literature, there is limited evidence regarding the use of platelet-rich plasma (PRP) injections in the treatment of vitiligo. While these studies may have shown promise, to date, no standard protocols regarding PRP preparation 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 vitiligo warrants further investigation in well-designed randomized comparative studies with longer time of observation to determine its efficacy. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Platelet-Rich Plasma Injection for the Treatment of Cerebral Palsy
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.

Summary of Evidence
Based on review of the peer reviewed medical literature, there is little evidence (one case study) regarding the use of platelet-rich plasma (PRP) injections in the treatment of cerebral palsy (CP). While this study may have shown some promise, to date, no standard protocols regarding PRP preparation 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 cerebral palsy (CP) warrants further investigation in well-designed randomized comparative studies to determine its efficacy. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Platelet-Rich Plasma Injection for the Treatment of Crohn's Disease-Related Perianal Fistula

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.

In 2020, Portilla et.a l. 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.

Summary of Evidence

Based on review of the peer reviewed medical literature, there is little evidence (one prospective pilot study) on combining the well-known mucosal advancement flap with platelet-rich plasma (PRP) in the treatment of Crohn's disease-related high perianal fistulas. While this study may have shown some promise, to date, no standard protocols regarding PRP preparation 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 in the treatment of Crohn's disease-related high perianal fistulas warrants further investigation in well-designed randomized comparative studies to determine its efficacy. The evidence is insufficient to determine the effects of the technology on net health outcomes.

Platelet-Rich Plasma Injection for the Treatment of Urethral Stricture

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 that 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.

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.

Summary of Evidence
Based on review of the peer reviewed medical literature further investigation in well-designed randomized comparative studies is needed regarding the use of platelet-rich plasma injections for the treatment of urethral stricture disease (USD) to determine its efficacy. To date, no standard protocols regarding PRP preparation 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 evidence is insufficient to determine the effects of the technology on net health outcomes.

Practice Guideline and Position Statements

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.

Platelet-Rich Plasma for Non-Orthopedic Indications Other than Wounds
There is no evidence based clinical practice guidelines that recommend the use of platelet-rich plasma (PRP) injections in the treatment of non-orthopedic indications to include the use in dermatological diseases.

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

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

Platelet-Rich Plasma

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.

A number of PRP preparation systems are available, many of which were cleared for marketing by FDA through the 510(k) process for producing platelet-rich preparations intended to be mixed with bone graft materials to enhance the bone grafting properties in orthopedic practices. The use of PRP outside of this setting (e.g., an office injection) would be considered off-label.

Examples of approved devices include:

- Aurix™ System (Nuo Therapeutics, Inc. Gaithersburg, MD)
- AutoloGel (Cytomedix, Inc., Rockville, MD)
- Autologous Platelet Grafting™ (SafeBlood® Technologies, Inc., Little Rock, AR)
- Cascade® Autologous Platelet System (Musculoskeletal Transplant Foundation [MTF], Edison, NJ)
- Fibrinet® Autologous PRP System (Cascade Medical Enterprises, Wayne, NJ)
- Gravitational Platelet Separation System (GPS®II) (Biomet Biologics, Inc., Warsaw, IN)
- Mini GPSII (Biomet Biologics, Inc., Warsaw, IN)
- Elmd-500 Autotransfusion System (Medtronic Electomedics)
- SmartPReP® 2 APC+ system (Harvest Technologies Corporation, Plymouth, MA)

The use of different devices and procedures can lead to variable concentrations of activated platelets and associated proteins, increasing variability between studies of clinical efficacy.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policies

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

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 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
- 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 (ie, stage III or IV), extending through dermis into subcutaneous tissues
3. Participation in a wound management program, which includes sharp debridement, pressure relief (ie, 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 (ie, 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.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 0232T Injection(s), platelet rich plasma, any tissue, including image guidance, harvesting and preparation when performed
- G0460 Autologous platelet rich plasma for non-diabetic chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment
- G0465 Autologous platelet rich plasma (prp) for diabetic chronic wounds/ulcers, using an fda-cleared device (includes administration, dressings, phlebotomy, centrifugation, and all other preparatory procedures, per treatment)
- 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

SELECTED REFERENCES

- UpToDate: Alopecia Areata: Management. Andrew G. Messenger M.D., FRCP. Topic last updated September 29, 2022. Also available at https://www.uptodate.com
- UpToDate. Female Pattern Hair Loss (Androgenetic Alopecia in Women): Treatment and Prognosis. Amy McMichael M.D., Topic last updated December 21, 2021. Also available at https://www.uptodate.com
- UpToDate. Treatment of Androgenetic Alopecia in Men. Jeff Donovan M.D., PhD, Beth G. Goldstein M.D., Adam O. Goldstein M.D., MPH. Topic last updated February 23, 2021. Also available at https://www.uptodate.com
- Delamere FM, Sladden MMN, Dobbins HM, et. al. Interventions for alopecia areata. Cochrane Database Syst Rev. 2008 Apr 16 (2): CD004413. PMID 18425901
- Garg S, Messenger AG. Alopecia areata: evidence- based treatments. Semin Cutan Med Surg 2009 Mar;28(1):15-8. PMID 19341938
- Hordinsky M, Donati A. Alopecia areata: an evidence- based treatment update. Am J Clin Dermatol 2014 Jul 15(3):231-46. PMID 25000998
- Trink A, Sorbellini E, Bezzola P, et. al. A randomized, double-blind, placebo and active controlled, half-head study to evaluate the effects of platelet-rich plasma on alopecia areata. Br J Dermatol 2013 Sep 169(3):690-4. PMID 23607773

- Maria-Angeliki G, Alexandros-Efstratios K, Dimitris R, et. al. Platelet-rich plasma as a potential treatment for noncicatricial alopecias. Int J Trichnology 2015 Apr-Jun;7(2):54-63. PMID 26180449
- Ayatollahi A, Hosseini H, Gholami J, et. al. Platelet rich plasma for treatment of non-scarring hair loss: a systematic review of literature. J Dermatology Treat 2017 Nov;28(7):574-581. PMID 28271918
- Cervantes J, Perper M, Wong LL, et. al. Effectiveness of platelet-rich plasma for androgenetic alopecia. A review of the literature. Skin Appendage Disord 2018 Jan;4(1):1-11. PMID 29457005
- Giordana S, Romeo M, di Summa P, et. al. A meta-analysis on evidence of platelet rich plasma for androgenetic alopecia. Int J Trichology 2018 Jan-Feb;10(1):1-10. PMID 29440850
- Atanaskova Mesinkovska N. Emerging unconventional therapies for alopecia areata. J Investig Demertol Symp Proc 2018 Jan;19(1):S32-S33. PMID 29273103
- Mao G, Zhang G, Fan W. Platelet-rich plasma for treating androgenetic alopecia: a systematic review. Aesthetic Plast Surg 2019 Oct;43(5):1326-1336. PMID 31187167
- Gupta AK, Carviel JL. Meta-analyses of efficacy of platelet-rich plasma therapy for androgenetic alopecia. J Dermatolog Treat 2017 Feb;28(1):55-58. PMID 27152474
- Gkini MA, Kouskoukis AE, Trissianis G, et. al. Study of platelet-rich plasma injections in the treatment of androgenetic alopecia through an one-year period. J Cutan Aesthet Surg 2014 Oct-Dec;7(4):213-9. PMID 25722600
- Messenger AG, McKillop P, Farrant AJ, et. al. British Association of Dermatologists guidelines for the management of alopecia areata 2012. British Association of Dermatologists 2012 166 pp 916-926
- Alcaraz J, Oliver A, Sanchez JM. Platelet-rich plasma in a patient with cerebral palsy. Am J Case Rep 2015 Jul 17;16:469-72. PMID 26185982
- Gottgens KW, Smeets RR, Stassen LP, et. al. Treatment of Crohn's disease related perianal fistulas combining the mucosa advancement flap with platelet-rich plasma: a pilot study. Tech Coloproctol 2015 Aug;19(8):455-9. PMID 25975971
- Hessler MJ, Shyam N. Platelet-rich plasma and its utility in medical dermatology: a systematic review. J Am Acad Dermatol 2019 Sep 81(3):834-846. PMID 31009668
- Gul M. Modified platelet-rich plasma with transforming growth factor B1 neutralization antibody injection may reduce recurrence rate of urethral stricture. Med Hypotheses 2016 Dec;97:1-3 PMID 27876114
- Mercuri SR, Vollono L, and Paolino G. The usefulness of platelet – rich plasma (PRP) for the treatment of Vitiligo: State of the art and review. Drug Des DeVel Ther 2020: 14: 1749-1755. PMID 32440100
- Barton VR, Toussi A, Awasthi S, Kiuru M. Treatment of pediatric alopecia areata: A systematic review. J Am Acad Dermatol. 2021 Apr 30
- Gupta V, Parihar AS, Sharma VK, et al. Evaluation of platelet-rich plasma on hair regrowth and lesional T-cell cytokine expression in alopecia areata: A randomized

observer-blinded, placebo-controlled, split-head pilot study. J Am Acad Dermatol. 2021;84(5):1321-1328
- de la Portilla F, Jimenez-Salido A, Araujo-Miguez A, et. al. Autologous platelet-rich plasma in the treatment of perianal fistula in Crohn's disease J Gastrointest Surg 2020 Dec;24(12):2814-2821
- Hayes Inc. Health Technology Assessment February 10, 2022 Platelet-Rich Plasma for Wound Treatment in Diabetic Foot Ulcers
- Hayes Inc. Health Technology Assessment October 26, 2021 Platelet-Rich Plasma for Wound Treatment in Venous Leg Ulcers
- U.S. Food and Drug Administration. Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds -- Developing Products for Treatment. Rockville, MD: Food and Drug Administration; 2006 June.
- U.S. Food and Drug Administration (FDA). Tissue and Tissue Products. 2016; http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/. Accessed December 1, 2021.
- Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Becaplermin for wound healing. TEC Assessments. 1999;Volume 14:Tab 5.
- Crovetti G, Martinelli G, Issi M, et al. Platelet gel for healing cutaneous chronic wounds. Transfus Apher Sci. Apr 2004; 30(2): 145-51. PMID 15062754
- Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. Plast Reconstr Surg. Nov 2004; 114(6): 1502-8. PMID 15509939
- Kevy SV, Jacobson MS. Comparison of methods for point of care preparation of autologous platelet gel. J Extra Corpor Technol. Mar 2004; 36(1): 28-35. PMID 15095838
- Castillo TN, Pouliot MA, Kim HJ, et al. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. Am J Sports Med. Feb 2011; 39(2): 266-71. PMID 21051428
- Mazzucco L, Balbo V, Cattana E, et al. Not every PRP-gel is born equal. Evaluation of growth factor availability for tissues through four PRP-gel preparations: Fibrinet, RegenPRP-Kit, Plateltex and one manual procedure. Vox Sang. Aug 2009; 97(2): 110-8. PMID 19392780
- Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Growth factors for wound healing. TEC Evaluations. 1992;7:352-377.
- Zhao XH, Gu HF, Xu ZR, et al. Efficacy of topical recombinant human platelet-derived growth factor for treatment of diabetic lower-extremity ulcers: Systematic review and meta-analysis. Metabolism. Oct 2014; 63(10): 1304-13. PMID 25060693
- Sridharan K, Sivaramakrishnan G. Growth factors for diabetic foot ulcers: mixed treatment comparison analysis of randomized clinical trials. Br J Clin Pharmacol. Mar 2018; 84(3): 434-444. PMID 29148070
- Margolis DJ, Bartus C, Hoffstad O, et al. Effectiveness of recombinant human platelet-derived growth factor for the treatment of diabetic neuropathic foot ulcers. Wound Repair Regen. Nov-Dec 2005; 13(6): 531-6. PMID 16283867

- Rees RS, Robson MC, Smiell JM, et al. Becaplermin gel in the treatment of pressure ulcers: a phase II randomized, double-blind, placebo-controlled study. Wound Repair Regen. May-Jun 1999; 7(3): 141-7. PMID 10417749
- Senet P, Vicaut E, Beneton N, et al. Topical treatment of hypertensive leg ulcers with platelet-derived growth factor-BB: a randomized controlled trial. Arch Dermatol. Aug 2011; 147(8): 926-30. PMID 21482863
- Freedman BM, Oplinger EH, Freedman IS. Topical becaplermin improves outcomes in work related fingertip injuries. J Trauma. Oct 2005; 59(4): 965-8. PMID 16374289
- Martinez-Zapata MJ, Marti-Carvajal A, Sola I, et al. Efficacy and safety of the use of autologous plasma rich in platelets for tissue regeneration: a systematic review. Transfusion. Jan 2009; 49(1): 44-56. PMID 18954394
- Martinez-Zapata MJ, Marti-Carvajal AJ, Sola I, et al. Autologous platelet-rich plasma for treating chronic wounds. Cochrane Database Syst Rev. May 25 2016; (5): CD006899. PMID 27223580
- Martinez-Zapata MJ, Marti-Carvajal AJ, Sola I, et al. Autologous platelet-rich plasma for treating chronic wounds. Cochrane Database Syst Rev. Oct 17 2012; 10: CD006899. PMID 23076929
- Carter MJ, Fylling CP, Parnell LK. Use of platelet rich plasma gel on wound healing: a systematic review and meta-analysis. Eplasty. 2011; 11: e38. PMID 22028946
- Picard F, Hersant B, Bosc R, et al. The growing evidence for the use of platelet-rich plasma on diabetic chronic wounds: A review and a proposal for a new standard care. Wound Repair Regen. Sep 2015; 23(5): 638-43. PMID 26019054
- Del Pino-Sedeno T, Trujillo-Martin MM, Andia I, et al. Platelet-rich plasma for the treatment of diabetic foot ulcers: A meta-analysis. Wound Repair Regen. Mar 2019; 27(2): 170-182. PMID 30575212
- Li Y, Gao Y, Gao Y, et al. Autologous platelet-rich gel treatment for diabetic chronic cutaneous ulcers: A meta-analysis of randomized controlled trials. J Diabetes. May 2019; 11(5): 359-369. PMID 30182534
- Qu W, Wang Z, Hunt C, Morrow AS, Urtecho M, Amin M, Shah S, Hasan B, Abd-Rabu R, Ashmore Z, Kubrova E, Prokop LJ, Murad MH. Platelet-Rich Plasma for Wound Care in the Medicare Population. Technology Assessment Program Project ID 040-353-492. (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. HHSA290201500013I.) Rockville, MD: Agency for Healthcare Research and Quality. https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/prp/prp-wound-care.pdf. Accessed December 13, 2021.
- Ahmed M, Reffat SA, Hassan A, et al. Platelet-Rich Plasma for the Treatment of Clean Diabetic Foot Ulcers. Ann Vasc Surg. Jan 2017; 38: 206-211. PMID 27522981
- Chen HY, Chen CX, Liang Y, Wang J. Efficacy of autologous platelet rich gel in the treatment of refractory diabetic foot. Chin J New Clin Med. 2008; 17:1-2.

- Driver VR, Hanft J, Fylling CP, et al. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy Wound Manage. Jun 2006; 52(6): 68-70, 72, 74 passim. PMID 16799184
- Elsaid A, El-Said M, Emile S, et al. Randomized Controlled Trial on Autologous Platelet-Rich Plasma Versus Saline Dressing in Treatment of Non-healing Diabetic Foot Ulcers. World J Surg. Apr 2020; 44(4): 1294-1301. PMID 31811339
- Friese G, Herten M, Scherbaum WA. The use of autologous platelet concentrate activated by autologous thrombin (APC+) is effective and safe in the treatment of chronic diabetic foot ulcers-a randomized controlled trial. In: eds. Proceedings of the Fifth International Symposium on the Diabetic Foot, May September 12, 2007, Noordwijkerhout, The Netherlands. 2007.
- Game F, Jeffcoate W, Tarnow L, et al. LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden: an observer-masked, randomised controlled trial. Lancet Diabetes Endocrinol. Nov 2018; 6(11): 870-878. PMID 30243803
- Gude W, Hagan D, Abood F, et al. Aurix Gel Is an Effective Intervention for Chronic Diabetic Foot Ulcers: A Pragmatic Randomized Controlled Trial. Adv Skin Wound Care. Sep 2019; 32(9): 416-426. PMID 31436621
- Kakagia DD, Kazakos KJ, Xarchas KC, et al. Synergistic action of protease-modulating matrix and autologous growth factors in healing of diabetic foot ulcers. A prospective randomized trial. J Diabetes Complications. Nov-Dec 2007; 21(6): 387-91. PMID 17967712
- Karimi R, Afshar M, Salimian M, et al. The effect of platelet rich plasma dressing on healing diabetic foot ulcers. Nurs Midwifery Stud. 2016;5(3):e30314.
- Li L, Chen D, Wang C, et al. Autologous platelet-rich gel for treatment of diabetic chronic refractory cutaneous ulcers: A prospective, randomized clinical trial. Wound Repair Regen. Jul-Aug 2015; 23(4): 495-505. PMID 25847503
- Liu GY, Deng XL, Sun Y, Wang MZ, Gao J, Gou J. Effect of autologous platelet-rich gel on the treatment of diabetic foot ulcers. J Xi'an Jiaotong Univ (Med Sci). 2016;37:264-267.
- Ma L. Clinical efficacy of autologous platelet rich gel in the treatment of diabetic foot and diabetic chronic cutaneous ulcer. Chin J Mod Drug Appl.2014;8:86-88
- Milek T, Baranowski K, Zydlewski P, et al. Role of plasma growth factor in the healing of chronic ulcers of the lower legs and foot due to ischaemia in diabetic patients. Postepy Dermatol Alergol. Dec 2017; 34(6): 601-606. PMID 29422826
- Qi KQ, ChenTJ PJL, Shang XL. The application of autologous platelet-rich gel in the treatment of diabetic foot ulcers. Chin J Diabetes. 2014;22: 1102-1105.
- Saad Setta H, Elshahat A, Elsherbiny K, et al. Platelet-rich plasma versus platelet-poor plasma in the management of chronic diabetic foot ulcers: a comparative study. Int Wound J. Jun 2011; 8(3): 307-12. PMID 21470370
- Saldalamacchia G, Lapice E, Cuomo V, et al. A controlled study of the use of autologous platelet gel for the treatment of diabetic foot ulcers. Nutr Metab Cardiovasc Dis. Dec 2004; 14(6): 395-6. PMID 15853123

- Serra R, Grande R, Butrico L, et al. Skin grafting and topical application of platelet gel in the treatment of vascular lower extremity ulcers. Acta Phlebologica. 2014 01 Dec;15(3):129-36.
- Singh SP, Kumar V, Pandey A, et al. Role of platelet-rich plasma in healing diabetic foot ulcers: a prospective study. J Wound Care. Sep 02 2018; 27(9): 550-556. PMID 30204574
- Steed DL, Goslen JB, Holloway GA, et al. Randomized prospective double-blind trial in healing chronic diabetic foot ulcers. CT-102 activated platelet supernatant, topical versus placebo. Diabetes Care. Nov 1992; 15(11): 1598-604. PMID 1468291
- Steed DL, Edington HD, Webster MW. Recurrence rate of diabetic neurotrophic foot ulcers healed using topical application of growth factors released from platelets. Wound Repair Regen. Apr-Jun 1996; 4(2): 230-3. PMID 17177818
- Xie J, Fang Y, Zhao Y, et al. Autologous Platelet-Rich Gel for the Treatment of Diabetic Sinus Tract Wounds: A Clinical Study. J Surg Res. Mar 2020; 247: 271-279. PMID 31706541
- Yang L, Gao L, Lv Y, et al. Autologous platelet-rich gel for lower-extremity ischemic ulcers in patients with type 2 diabetes. International Journal of Clinical and Experimental Medicine. 2017 30 Sep;10(9):13796-801.
- Zhang L Qiang D, Sun YH. Clinical observation of autologous platelet rich gel in the treatment of diabetic foot ulcers. Ningxia Med J. 2016;38:809-811.
- Zhou XP, Gong YX, Yang ZD, Wang W. Application value analysis of autologous platelet gel in refractory skin ulcer of diabetic patients. World Lat Med Inform. 2015;15:19-20
- Zhu SF, Liu H, Li L, Wang XF. Preliminary application of autologous platelet rich gel in diabetic neuropathic ulcers. Med Innov China. 2012;9:18-19.
- Centers for Medicare & Medicaid Services. National Coverage Analysis (NCA) Tracking Sheet for Autologous Blood-Derived Products for Chronic Non-Healing Wounds (CAG-00190R4). 2020; https://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx?NCAId=300&NCDId=217&ncdver=5&IsPopup=y&bc=AAAAAAAACAQA&. Accessed December 12, 2021.
- Qu W, Wang Z, Hunt C, et al. The Effectiveness and Safety of Platelet-Rich Plasma for Chronic Wounds: A Systematic Review and Meta-analysis. Mayo Clin Proc. Sep 2021; 96(9): 2407-2417. PMID 34226023
- Oliveira BGRB, Carvalho MR, Ribeiro APL. Cost and effectiveness of Platelet Rich Plasma in the healing of varicose ulcer: Meta-analysis. Rev Bras Enferm. 2020; 73(4): e20180981. PMID 32609173
- Saha S, Patra AC, Gowda SP, et al. Effectiveness and safety of autologous platelet-rich plasma therapy with total contact casting versus total contact casting alone in treatment of trophic ulcer in leprosy: An observer-blind, randomized controlled trial. Indian J Dermatol Venereol Leprol. May-Jun 2020; 86(3): 262-271. PMID 31997794

- Gupta A, Channaveera C, Sethi S, et al. Efficacy of Intralesional Platelet-Rich Plasma in Diabetic Foot Ulcer. J Am Podiatr Med Assoc. May 01 2021; 111(3). PMID 33231614
- Zhou SF, Estrera AL, Loubser P, et al. Autologous platelet-rich plasma reduces transfusions during ascending aortic arch repair: a prospective, randomized, controlled trial. Ann Thorac Surg. Apr 2015; 99(4): 1282-90. PMID 25661906
- Serraino GF, Dominijanni A, Jiritano F, et al. Platelet-rich plasma inside the sternotomy wound reduces the incidence of sternal wound infections. Int Wound J. Jun 2015; 12(3): 260-4. PMID 23692143
- El-Anwar MW, Nofal AA, Khalifa M, et al. Use of autologous platelet-rich plasma in complete cleft palate repair. Laryngoscope. Jul 2016; 126(7): 1524-8. PMID 27075516
- Sidman JD, Lander TA, Finkelstein M. Platelet-rich plasma for pediatric tonsillectomy patients. Laryngoscope. Oct 2008; 118(10): 1765-7. PMID 18622315
- Almdahl SM, Veel T, Halvorsen P, et al. Randomized prospective trial of saphenous vein harvest site infection after wound closure with and without topical application of autologous platelet-rich plasma. Eur J Cardiothorac Surg. Jan 2011; 39(1): 44-8. PMID 20634084
- Alamdari DH, Asadi M, Rahim AN, et al. Efficacy and Safety of Pleurodesis Using Platelet-Rich Plasma and Fibrin Glue in Management of Postoperative Chylothorax After Esophagectomy. World J Surg. Apr 2018; 42(4): 1046-1055. PMID 28986682
- Mohamadi S, Norooznezhad AH, Mostafaei S, et al. A randomized controlled trial of effectiveness of platelet-rich plasma gel and regular dressing on wound healing time in pilonidal sinus surgery: Role of different affecting factors. Biomed J. Dec 2019; 42(6): 403-410. PMID 31948604
- Slaninka I, Fibir A, Kaska M, et al. Use of autologous platelet-rich plasma in healing skin graft donor sites. J Wound Care. Jan 02 2020; 29(1): 36-41. PMID 31930949
- Kazakos K, Lyras DN, Verettas D, et al. The use of autologous PRP gel as an aid in the management of acute trauma wounds. Injury. Aug 2009; 40(8): 801-5. PMID 18703188
- Marck RE, Gardien KL, Stekelenburg CM, et al. The application of platelet-rich plasma in the treatment of deep dermal burns: A randomized, double-blind, intra-patient controlled study. Wound Repair Regen. Jul 2016; 24(4): 712-20. PMID 27169627
- Yeung CY, Hsieh PS, Wei LG, et al. Efficacy of Lyophilised Platelet-Rich Plasma Powder on Healing Rate in Patients With Deep Second Degree Burn Injury: A Prospective Double-Blind Randomized Clinical Trial. Ann Plast Surg. Feb 2018; 80(2S Suppl 1): S66-S69. PMID 29369904
- Huang H, Sun X, Zhao Y. Platelet-rich plasma for the treatment of burn wounds: A meta-analysis of randomized controlled trials. Transfus Apher Sci. Feb 2021; 60(1): 102964. PMID 33127309

- Qaseem A, Humphrey LL, Forciea MA, et al. Treatment of pressure ulcers: a clinical practice guideline from the American College of Physicians. Ann Intern Med. Mar 03 2015; 162(5): 370-9. PMID 25732279
- Association for the Advancement of Wound Care (AAWC). Guideline of Pressure Ulcer Guidelines. Malvern, PA: AAWC; 2010.
- Association for the Advancement of Wound Care (AAWC). International Consolidated Venous Ulcer Guideline (ICVUG). 2015; https://aawconline.memberclicks.net/assets/appendix%20c%20guideline%20icvug-textformatrecommendations-final%20v42%20changessaved18aug17.pdf. Accessed December 1, 2021.
- National Institute for Health and Clinical Excellence (NICE). Diabetic foot problems: prevention and management [NG19]. 2019; https://www.nice.org.uk/guidance/ng19/resources/diabetic-foot-problems-prevention-and-management-pdf-1837279828933 . Accessed December 13, 2021.

POLICY HISTORY

Date	Reason	Action
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

*CPT® is a registered trademark of the American Medical Association.