Healthy Blue

Medical Policy

Subject:	Growth Factors, Silver-based Products and Autologous Tissues for Wound Treatment, Soft Tissue Grafting, and Regenerative Therapy		
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Description/Scope

This document addresses the use of the following:

- Recombinant human platelet-derived growth factor (becaplermin [Regranex®])
- Antimicrobial silver wound dressings, (for example, Acticoat, Actisorb™, and Silversorb®)
- Autologous blood-derived wound products, (for example, Aurix™ [formerly Autologel™], Vitagel®)
- Platelet rich plasma (PRP)
- Bone marrow aspirate concentrate
- Bioengineered autologous skin-derived products (for example, SkinTE™, MyOwn Skin™)
- Autologous adipose-derived regenerative cell therapy (for example, Lipogems)
- Autologous protein solution (APS, for example, nSTRIDE®)

Such products have been proposed for the treatment of skin wounds, various musculoskeletal injuries, and during various surgical procedures.

Note: For information regarding the use of other soft-tissue and bone grafting products, please see:

- SURG.00011 Allogeneic, Xenographic, Synthetic and Composite Products for Wound Healing and Soft Tissue Grafting
- TRANS.00035 Non-Hematopoietic Adult Stem Cell Therapy

Position Statement

Medically Necessary:

The use of recombinant human platelet-derived growth factor (becaplermin [Regranex]) is considered **medically necessary** when it is used as an adjunct to standard wound management for either of the indications (1 *or* 2) below:

A. When used according to the U.S. Food and Drug Administration (FDA) labeled indication for individuals with neuropathic diabetic ulcers extending into the subcutaneous tissue or beyond who 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; **and**
2. Full-thickness ulcer (Stage III or IV), extending through dermis into subcutaneous tissues; **and**
3. Participation in a wound management program, which includes sharp debridement, pressure relief (that is, non-weight-bearing), and infection control; **or**

B. As a treatment of pressure ulcers extending into the subcutaneous tissue who meet ALL of the following criteria:
1. Full-thickness ulcer (Stage III or IV), extending through dermis into subcutaneous tissues; **and**
2. Ulcer in an anatomic location that can be offloaded for the duration of treatment; **and**
3. Albumin concentration greater than 2.5 dL; **and**
4. Total lymphocyte count greater than 1,000; **and**
5. Normal values of vitamins A and C.

Note: Individuals are typically treated once daily for up to 20 weeks or until complete healing occurs with becaplermin.

Investigational and Not Medically Necessary:

The use of recombinant human platelet-derived growth factor (becaplermin [Regranex]) is considered **investigational and not medically necessary** for the above indications when criteria are not met and for all other applications not listed above as medically necessary, including, but not limited to, the following:
A. Ischemic ulcers; **or**
B. Venous stasis ulcers; **or**
C. Ulcers that do not extend through the dermis into subcutaneous tissue.

Antimicrobial silver wound dressings, (for example, Acticoat, Actisorb, and Silversorb) are considered **investigational and not medically necessary** for all applications.

Autologous blood-derived wound products, (for example, Aurix [formerly Autologel], Vitagel) are considered **investigational and not medically necessary** for all applications.

The use of platelet rich plasma (PRP), including autologous conditioned plasma (ACP), is considered **investigational and not medically necessary** for all indications, including the treatment of *any* of the following:
A. Cutaneous wounds; **or**
B. Soft tissue injuries (including epicondylitis and sinus surgery); **or**
C. Bone injuries (including surgically created wounds and non-unions).

The use of bone marrow aspirate concentrate (BMAC) is considered **investigational and not medically necessary** for all indications, including for the treatment of critical limb ischemia.

Bioengineered autologous skin-derived products (for example, SkinTE, MyOwn Skin) are considered **investigational and not medically necessary** for all indications.

Autologous adipose-derived regenerative cell therapy (for example, Lipogems) is considered **investigational and not medically necessary** for all indications.

Use of autologous protein solution (for example, nSTRIDE®), also known as autologous white blood cell concentrate, is considered **investigational and not medically necessary** for all indications.

Rationale

Becaplermin

Recombinant platelet-derived growth factor (PDGF, becaplermin gel [Regranex]) has been found to be efficacious as an adjunct to standard wound management for individuals with neuropathic diabetic ulcers and for the treatment of pressure ulcers. These conclusions are based on several well-designed randomized controlled studies. However, efficacy for other uses has not been demonstrated in the literature.

Sun and others (2017) conducted a meta-analysis of studies investigating the use of autogenous bone graft vs. PDGF in foot and ankle fusion procedures. A total of three prospective randomized controlled trials (RCTs) were included, involving 634 subjects (337 in the PDGF group and 297 in bone graft group). Results for mid-term CT fusion rates were similar for both groups (relative risk [RR], 1.13, p=0.31), as were mid-term radiographic union rates (RR=1.05, p=0.66) and long-term radiographic union rates (RR=1.11, p=0.33). Furthermore, no significant differences were reported between groups with regard to clinical healing status (p=0.76), clinical success rates (p=0.84), therapeutic failure rates (p=0.93), AOFAS scores (p=0.19), foot function index scores (p=0.12), weight-bearing pain (p=0.1), or adverse events (p=0.25). These results are promising, but the small number of studies limits the utility of this data. Additional study is warranted.

In 2016, the Society for Vascular Surgery, the American Podiatric Medical Association, and the Society for Vascular Medicine published their recommendations for the management of diabetic foot ulcers (DFUs) (Hingorani, 2016). These recommendations included the following statement supporting the use of becaplermin, "We suggest consideration of the use of PDGF (becaplermin) for the treatment of DFUs that are recalcitrant to standard therapy."

Silver

Antimicrobial silver wound dressings (e.g., Acticoat, Actisorb, AQUACEL® AG, Silversorb and Urgotul® Silver) have not been sufficiently evaluated in the peer-reviewed literature. It is not possible to determine their efficacy as a dressing to facilitate wound care because of the limited availability of clinical data. A nonrandomized, non-blinded non-inferiority study by Harding and colleagues published in 2011 compared AQUACEL AG (n=145) to Urgotul Silver (n=136). The results of the study indicate non-inferiority, within a pre-determined non-inferiority margin of -

15%. However, it should be noted that the use of either of these products is not well studied in comparison to standard treatment. A study by Biffi and others from 2012 did just that, comparing AQUACEL AG (n=58) in a blinded and randomized manner to standard care (n=54). The authors reported no significant differences between groups with regard to the overall rate of surgical site infections (experimental group, 15.5% vs. controls, 20.4%; p=0.451).

Another non-blinded, RCT involved 24 subjects with diabetic foot ulcers who received treatment with collagen/oxidized regenerated cellulose/silver (COS group) compared to 15 subjects who received standard treatment (Gottrup, 2013). The authors reported that more wounds in the COS group reached 50% wound closure by week 4 (79% [19/24]) compared to the control group (43% [6/14]), (p=0.035). At each time point recorded, there was a higher proportion of improved wounds in the COS group compared with the control group, and the differences were significant at week 4, week 8, and week 10 (p=0.035, p=0.018, p=0.046, respectively). At the end of the study, 91% of wounds in the collagen/ORC/silver treatment group were either healed or showed a reduction in wound size of at least 50% compared to 69% of wounds in the control group. However, this difference was not found to be significant. The number of subjects withdrawing from the study due to wound infection was significantly higher in the control group (31% [4/13]) vs. the COS group (0% [0/23]) (p=0.012). No adverse events were reported to be related to the use of COS. Given this data, further investigation with greater numbers of subjects in a larger number of centers and in different phases of wound care is needed.

In 2015, Ozaki and others published the results of a large RCT involving 500 subjects with lower extremity vascular surgery wounds assigned to post-operative treatment with standard gauze dressing or Acticoat dressing (n=250 per group). The intent-to-treat analysis indicated that there was no significant difference between groups with regard to wound complication rates. The authors concluded that the use of Acticoat provided no benefit with regard to wound complications.

In 2017, Li and colleagues published the findings of a meta-analysis involving nine RCTs including 2196 subjects with surgical wounds. They reported that silver-containing dressings did not effectively prevent the incidence of surgical site infections (RR=0.92), superficial surgical site infections (RR=0.67), or deep surgical site infections (RR=0.78). They also commented that the quality of the available evidence was "very low" and further high-quality studies are needed.

Struik and others (2018) reported the results of an RCT comparing AQUACEL Ag vs. standard care for post-operative wound care in 230 women who underwent breast cancer surgery. A total of 106 subjects received treatment with AQUACEL and 124 received standard care. The authors reported that 7 AQUACEL subjects (6.6%) developed surgical site infections vs. 16 control subjects (12.9%) (RR, 0.51; p=0.112; adjusted OR, 0.49; p=0.135). An ad hoc exploratory subgroup analysis of subjects undergoing breast conserving surgery resulted in surgical site infection rates of 1.8% in the AQUACEL group vs. 10.8% in controls (adjusted OR, 0.15; p=0.087). The AQUACEL group had fewer dressing changes within 48 hours (adjusted OR, 0.12; p<0.001) and fewer re-operations (0% vs. 3.2%, p=0.062). They concluded that the use of AQUACEL did not result in improvements in the primary outcome of the study, surgical site infections.

Connery and others reported the results of a blinded RCT of women undergoing cesarean delivery and treated with either standard gauze dressing (n=330) or Silver Nylon dressing (n=330). They reported that there were no significant differences between groups with regard to the primary outcome, superficial surgical site infection, at 1 and 6 weeks post-op (p=0.096). They concluded that silver nylon dressing was not more effective than gauze for the treatment of post-cesarean delivery wound recovery.

Autologous Blood-derived Products

At this time, there are no published peer-reviewed articles addressing the use of autologous blood-derived wound products, (e.g., Aurix [formerly Autologel], or Vitagel). Therefore, conclusions regarding the efficacy of these preparations cannot be reached.

Platelet Rich Plasma

Platelet rich plasma (PRP) has been available for several decades and its use has been proposed for a wide variety of medical conditions. The medical literature currently lists dozens of studies addressing the use of PRP for a wide variety of indications including chronic skin wounds, maxillofacial and sinus surgery, various musculoskeletal injuries and surgical procedures, endovascular surgery, plastic surgery, and thoracic and cardiac surgery. Unfortunately, most available studies are small, uncontrolled, retrospective, and/or have short follow-up periods, constituting significant methodological flaws which limit the utility of the studies in evaluating the benefits of PRP use.

Chronic lateral epicondylitis (LE)

There are several RCTs published addressing the use of PRP to treat chronic lateral epicondylitis (LE), also known as tennis elbow. The largest RCT available to date involved 230 subjects with chronic LE randomized in a double-blind fashion to receive PRP (n=116) or active controls who received needling only (n=114) (Mishra, 2013). After receiving a local anesthetic, all subjects had their extensor tendons needled with or without PRP. Subjects were followed for up to 24 weeks. No significant differences were noted between groups at 12 weeks (n=192, 83.5%). At 24 weeks (n=119, 51.8%), the PRP-treated subjects reported an improvement of 71.5% in their pain scores compared with 56.1% in the control group (p=0.019). Additionally, 29.1% of the PRP-treated group reported significant elbow tenderness versus 54.0% in the control group (p=0.009). Success rates for the subjects completing the 24-week follow-up period were 83.9% in the PRP group vs. 68.3% in the control group (p=0.037). No significant complications occurred in either group. The authors concluded that at 24 weeks clinically meaningful improvements were found in subjects treated with leukocyte-enriched PRP compared with an active control group. However, these results must be viewed with care, since the loss to follow-up was so large at 24 weeks (48.2%). Peerbooms and others (2010) published an RCT describing the use of PRP in 100 subjects with LE randomly assigned to receive a single injection of PRP (n=51) or corticosteroids (n=49). After 1 year, 25 of the 49 subjects (51%) in the corticosteroid group and 37 of the 51 (73%) in the PRP group were deemed "successful" with greater than 25% reduction in DASH Outcome Measure scores (p=0.005). The authors note that further study of the use of PRP is warranted. Krogh (2013) described a study that involved 60 subjects assigned to receive treatment with a

single injection of either PRP, saline, or glucocorticoid. Pain reduction at 3 months was observed in all 3 groups, with no statistically significant difference between the groups (p=0.717). At 1 month, however, glucocorticoid reduced pain more effectively than did both saline and PRP. At 3 months, glucocorticoid was more effective than PRP and saline in reducing color Doppler activity (p=0.0001) and tendon thickness (p=0.002). The authors concluded that a single injection with either PRP or glucocorticoid was not significantly superior to a saline injection for reducing pain and disability over a 3-month period in individuals with LE. Two other RCTs compared PRP to autologous blood injection (ABI). A study by Creaney (2011) involved 150 subjects (n=80 PRP group, n=70 ABI Group). The follow-up for this study was 6 months, and the authors noted that at 6 months the success rate in the PRP group was 66% vs. 72% in the ABI group (p=not significant), and there was a higher rate of conversion to surgery in the ABI group (20%) versus the PRP group (10%). Montalvan (2016) described the results of a double-blind placebo-controlled RCT involving 50 subjects assigned to receive either conditioned plasma (n=25) or saline solution (n=25). Subjects were monitored at baseline and 1, 3, 6 and 12 months. The primary outcome was relative improvement from baseline to 6 months in pain score on visual analog scale. The secondary outcome was Roles-Maudsley score and the assessment of pain on isometric contraction of extensor carpi radialis brevis and extensor digitorum communis. Three subjects dropped out from each study group before the 6 month time period. In the PRP group, the pain score decreased significantly from a mean of 6.8 at baseline to 2.5 at 6 months and 1.6 at 12 months. In the saline group the results changed from 7 at baseline to 2.1 and 1.8, respectively. At 6 months, no statistically significant difference was found between groups for relative improvement in pain score (p=0.24). The authors also reported no significant difference between groups with regard to secondary criteria. They concluded that PRP injections, for epicondylitis of recent evolution, were not more efficacious than saline injections. Thanasas (2011) reported on a smaller RCT involving 28 subjects assigned to receive a single injection of either autologous blood or PRP, with 14 subjects in each group. The results indicated that the visual analog pain scale was only significantly different at 6 months, in favor of the PRP group (p<0.5). No statistically significant differences were noted on the pain scale or the Liverpool elbow score. These studies present a mixed picture regarding the possible benefits to PRP therapy for LE.

A systematic review published in 2014 by de Vos and Weir evaluated the available literature on PRP treatment for epicondylar tendinopathy. The authors included six studies that met inclusion criteria, of which four were considered to be of high quality. Of these studies, three high-quality and two low-quality studies showed no significant benefit at the final follow-up measurement or in predefined primary outcome score when compared with a control group. Only one high-quality study showed a beneficial effect of a PRP injection when compared with a corticosteroid injection (corticosteroid injections are harmful in tendinopathy). The conclusion of this analysis was that there is strong evidence that PRP injections are not efficacious in chronic LE.

Mi et al. (2017) reported the results of a meta-analysis including eight RCTs involving 511 subjects comparing PRP to steroids in reducing pain and improving function in the treatment of epicondylar tendinopathy. Their results demonstrated no significant differences between groups with regard to pain relief in the short-term (2 to 4 weeks, p=0.03 and 6 to 8, p=0.24) or in the intermediate-term (12 weeks, p=0.35). They did find significant benefits to steroid treatment vs. PRP for function in the short-term (2 to 4 weeks, p<0.001; 6 to 8 weeks, p<0.001). In contrast, their findings indicated that PRP was superior to steroids for pain relief in the long-term (half year, p<0.001; 1 year, p<0.001) and for functional improvement in the intermediate-term (12 weeks, p<0.001) and the long-term (half

year, p<0.001; 1 year, p<0.001). They concluded that "PRP appears to be more effective in relieving pain and improving function in the intermediate-term (12 weeks) and long-term (half year and one year)."

In 2016, Tsikopoulos and colleagues published the results of a meta-analysis evaluating RCTs involving the use of PRP for tendinopathies vs. either placebo or dry needling. The primary condition treated was epicondylitis in two studies, rotator cuff tendinopathy in two studies, and patellar tendinopathy in the last. The authors identified five studies involving 190 subjects that met inclusion criteria. The buffy coat method of PRP preparation was used in 80% of the studies, and did not involve the use of activated platelets. There was a statistically significant difference in favor of PRP for pain intensity at 2 or 3, and 6 months after intervention (p=0.01) and for functional disability at 3 months after treatment (p=0.01).

A new PRP-containing product, Vergenix Soft Tissue Repair (STR) Matrix, was evaluated in a case series study of 40 subjects with LE (Farkash, 2018). STR is an injectable gel composed of cross-linked bioengineered recombinant human type I collagen combined with autologous platelet-rich plasma. The authors reported a 59% reduction at 6 months in the mean Patient-Rated Tennis Elbow Evaluation (PRTEE) score (p<0.001). Results in the 12-Item Short-Form Health Survey questionnaire (SF-12) demonstrated improvement from a mean score of 30.7 to 37.7 at 6 months. Grip strength increased from 28.8 kg at baseline to 36.8 kg at 6 months. The lack of a control group and other methodological weaknesses impair the reliability and generalizability of these results.

Shoulder conditions

The use of PRP for arthroscopic repair of the shoulder has been addressed in several moderately sized RCTs (Carr, 2015; Castricini, 2011; Gumina, 2012; Rodeo, 2012; Ruiz-Moneo, 2013; Walsh, 2018; Weber, 2013). Of these studies, three were double-blind studies (Carr, Ruiz-Moneo, and Weber). All of these trials found no significant benefit to the use of PRP with regard to perioperative morbidity, clinical outcomes, or structural integrity. A meta-analysis conducted by Zhao and colleagues in 2015 involved these studies, except the study by Carr, in addition to several smaller RCTs. Their findings showed that the available evidence does not support the use of PRP for full-thickness rotator cuff repair, and that the majority of studies reported no significant benefit to the addition of PRP to standard surgical repair.

A study by Battaglia (2014) investigated the difference in outcomes between PRP and hyaluronic acid (HA) for the treatment of hip osteoarthritis. This study involved 100 subjects evenly distributed between groups. The authors state that at no time point (1, 3, 6, 12, or 24 months) were significant differences noted between groups with regard to Harris Hip Score or visual analog pain scale ratings. They concluded that PRP was not superior to HA for the treatment of osteoarthritis (OA) of the hip. Another study by Dallari (2016) reported the results of an RCT involving 111 subjects with hip osteoarthritis assigned to treatment with 3 weekly injections of either PRP (n=44), PRP+HA (n=31), or HA alone (n=36). Subjects were followed for 12 months post treatment with no withdrawals or loss to follow-up. At all time points, the PRP group had the lowest VAS pain scores. The authors pointed out that at the 6 month follow-up in particular, the mean VAS score was 21 in the PRP group, 35 in the PRP+HA group, and 44 in the HA group (p<0.0005 for PRP vs. HA and p=0.007 for PRP vs PRP+HA). The McMaster Universities Osteoarthritis Index (WOMAC) score of the PRP group was significantly better at 2 month and 6 month follow-up

vs. the other groups, but not at the 12-month follow-up (at 2 months: p<0.009 for PRP vs. HA and p=0.026 for PRP vs PRP+HA; at 6 months: p<0.009 for PRP vs. HA and p=0.0005 for PRP vs PRP+HA; at 12 months: p<0.005 for PRP vs. HA and p=0.007 for PRP vs PRP+HA). Positive response at 12 months was reported for participants in all groups with regard to WOMAC scores (p=0.04), but not with VAS or Harris Hip scores (p=NS).

Anterior cruciate ligament (ACL) reconstruction surgery

Two RCTs have investigated the use of PRP for the prevention of tunnel widening following anterior cruciate ligament (ACL) reconstruction surgery (Mirzatolooei, 2013; Vadalà, 2013). These small studies (n=50 and 40, respectively) both reported no significant benefit to the use of PRP to prevent tunnel widening. It is unclear if further studies into this use of PRP would provide data demonstrating any benefit to PRP for this indication.

Seijas (2013) reported the results of an RCT involving 98 subjects evaluating the use of PRP in tendon graft remodeling following ACL reconstruction. The findings, based on MRI studies, indicated that PRP had a significant impact on remodeling, with more subjects in the PRP group vs. controls attaining higher stages of remodeling at 4 months (p=0.003), 6 months (p=0.0001), and 12 months (p=0.354). However, no clinical data is presented, and it is not clear if the level of improved tendon remodeling reported provides any significant clinical outcome benefits. Further investigation is warranted. Another RCT, conducted by Nin et al (2009) involved 100 subjects, 50 receiving standard surgical treatment and 50 undergoing ACL reconstruction with the addition of PRP. There were no significant differences between groups reported with regard to MRI appearance of the graft, inflammatory markers, clinical evaluation scores (visual analog scale, International Knee Documentation Committee), or KT-1000 arthrometer testing. Finally, Vogrin (2010) reported the results of a single-blinded RCT involving 50 subjects receiving similar group placement as used in the Nin study (25 in each group). The authors reported finding a significantly higher level of vascularization in the osteoligamentous interface vs. control group (p<0.001), but no evidence of revascularization in the intra-articular part of the graft. Further investigation into this treatment method is warranted.

Total knee arthroplasty

An RCT investigating the use of PRP for the treatment of postoperative pain and blood loss following total knee arthroplasty was done by Aggarwal and others (2014). This study randomized 40 subjects (59 knees) who were randomized to receive treatment with PRP (n=17, 27 knees) or without PRP (n=23, 32 knees). In the immediate postoperative period, the PRP group had a significantly lower reduction in hemoglobin and need for blood transfusion (p=0.00 and p=0.001, respectively), experienced less pain (p=0.00), and required fewer narcotics than the control group (p=0.00). At 3 months there was a significant difference in range of motion (p=0.01), no significant difference in wound scores (p=0.311), and a significant difference in Knee Society Score (KSS) and WOMAC scores at 12 weeks (p=0.00, p=0.00 respectively). No significant difference was found at 6 months. These findings warrant further investigation.

A meta-analysis of studies investigating the use of PRP vs. placebo following TKA procedures published by Li (2017) involved 11 trials and 1316 subjects. The pooled results indicated that PRP significantly increased range of

motion (ROM) on the third day (p=0.000) and at 3 months postoperatively (p=0.000). However no statistical differences between groups were noted in WOMAC questionnaire scores at 3 months (p=0.190), pain intensity at 24 hours, 48 hours or 7 days (p=0.77, p=0.76, and p=0.99, respectively), or infection rates (RR=0.64, p=0.464).

Osteoarthritis of the knee

PRP for the treatment of osteoarthritis of the knee (OA) has been the subject of several RCTs. The largest of these studies involved 176 subjects treated with either PRP or with hyaluronic acid (HA) (Sánchez, 2012). Response was judged based upon 50% decrease in knee pain from baseline to 24 weeks. The authors reported that the rate of response to PRP was 14.1% higher than that seen in the HA group (p=0.044). However, there were no significant differences between groups reported on the pain, stiffness, and physical function scales on the Western Ontario and WOMAC. The next largest RCT involved 120 subjects assigned to undergo unblinded treatment with either PRP (n=60) or with HA (n=60) (Cerza, 2012). At week 4, both groups showed a significant reduction in overall WOMAC score compared with baseline. The difference recorded between the PRP and the HA group was statistically significant (p<0.001) at this time point, with PRP providing significant improvement vs. HA. At weeks 12 and 24, continuous improvement in the subjects treated with PRP was noted, and a slight worsening was reported in subjects treated with HA (p<0.001). Both groups were still significantly better at week 24 compared to baseline. Another RCT, a double-blind study, included 78 subjects randomized to receive one of three treatments: Group A received a single injection of PRP (n=52 knees), Group B received two injections of PRP 3 weeks apart (n=50 knees), and Group C received a single injection of normal saline (n=46 knees) (Patel, 2013). Statistically significant improvement in all WOMAC parameters was noted in groups A and B within 2 to 3 weeks, lasting until the final follow-up at 6 months. A slight, but statistically insignificant, worsening was reported at the 6-month follow-up. The three groups were compared with each other and no improvement was noted in group C as compared with the other two groups (p<0001). No differences were noted between groups A and B, indicating that a single injection of PRP was sufficient to provide benefit. A third non-blinded RCT involved 120 OA subjects assigned to undergo treatment with either PRP (n=60) or HA (n=60). Both the PRP and HA groups demonstrated statistically significant improvement in both clinical evaluation schemes of the WOMAC at the 3- and 6-month follow-up periods with respect to baseline. The PRP group was reported to have had significantly better WOMAC scores at both the 3- and 6-month follow-up times (p<0.01 for both). A small RCT involving 30 subjects with osteoarthritis of the knee was published by Smith (2016). Subjects were assigned treatment with either autologous conditioned plasma or placebo (n=15 each group). The WOMAC scores in the plasma group at 1 week were significantly decreased compared with baseline scores, and the scores for this group remained significantly lower throughout the study duration. At 12 months post-treatment, subjects in the plasma group were reported to have improved their overall WOMAC scores by 78% from their baseline score vs. 7% in the placebo group.

A meta-analysis of 14 studies involving 1423 subjects receiving PRP for treatment of knee osteoarthritis (OA) was published by Shen (2017). The use of controls was reported to be homogeneous, involving saline placebo, HA, ozone, and corticosteroids. They reported that the risk of bias assessment showed that 4 studies were considered as moderate risk of bias and 10 as high risk of bias. The findings reported that compared with controls, PRP significantly reduced WOMAC pain subscores at 3, 6, and 12 months follow-up (p=0.02, p=0.004, and p<0.001, respectively), improved WOMAC physical function subscores at 3, 6, and 12 months (p=0.002, p=0.01 and

p<0.001, respectively), improved total WOMAC scores at 3, 6 and 12 months (all p<0.001). PRP was not found to increase the risk of post-injection adverse events (RR=1.40, p=0.24).

These studies point to promising benefits of PRP therapy for individuals with OA. However, evidence from larger double-blind RCTs is needed to properly evaluate this treatment method.

In 2013, the American Academy of Orthopaedic Surgeons (AAOS) released their guideline addressing treatment of osteoarthritis of the knee. This document addressed the use of PRP, and their recommendation stated: "We are unable to recommend for or against growth factor injections and/or platelet rich plasma for patients with symptomatic osteoarthritis of the knee." Their rationale for this conclusion was provided:

> There was a paucity of articles on the use of platelet concentrates in the treatment of osteoarthritis. Sanchez et al. used activated platelet aggregates in a fibrin matrix and Spakova et al. used a platelet concentrate. None of the studies controlled for platelet volume. All studies used hyaluronic acid as the control group.
>
> The studies showed decreased levels of pain in the post injection period but they were not constructed to allow for a comparative analysis of clinical effectiveness. The lack of controlled prospective blinded randomized clinical trials with a placebo control prevent the work group from making any recommendation on the use of platelets or platelet derived growth factor concentrates in the treatment of osteoarthritis of the knee.

Sternal wound infections

The treatment of sternal wound infections (SWI) with PRP has been described in a small number of studies. A large RCT involving 196 subjects who underwent cardiopulmonary bypass at risk of deep SWI (DSWI) were assigned to either application of autologous PRP before sternal wiring (n=97) or no PRP (n=99) (Dörge, 2013). The authors reported no significant differences between groups with regard to the incidence of DSWI (6.2% vs. 3.0%, p=NS). Serraino (2015) reported on the results of an RCT involving 1093 subjects who underwent cardiac surgery through median sternotomy. Subjects were assigned to receive care either with or without PRP applied inside the sternotomy wound prior to closure. The authors reported that the incidence of DSWI was significantly higher in the control group vs. the PRP group (1.5% vs. 0.20%, p=0.043). Superficial sternal wound infections (SSWIs) were reported to also have been significantly higher in the control group vs. the PRP group (2.8% vs. 0.5%, p=0.006).

Other Conditions

PRP has been investigated for the treatment of a large number of other conditions, including aortic arch repair (Zhou, 2015), burn wounds (Brown, 2016), carpal tunnel (Raeissdat, 2018; Wu, 2018), chronic skin wounds (de Leon, 2011; Frykberg, 2010; Guthrie, 2016; Moneib, 2017; Sakata, 2012), degenerative disk disease (Tuakli-Wosornu, 2016), diaphyseal fractures (Singh, 2017), distal radius fracture (Namazi, 2016), frozen shoulder (Lin, 2018), lasik eye surgery (Javaloy, 2013), long bone non-unions (Calori, 2008; Mariconda, 2008), pilonidal sinus

repair (Mostafaei, 2018), plantar fasciitis (Jain, 2018; Johnson-Lynn, 2018; Mahindra, 2016), postoperative chylothorax patching (Alamdari, 2018), refractory thin endometrium (Kim, 2019), rotator cuff calcification (Verhaegen, 2016), temporomandibular disorders (Nitecka-Buchta, 2019), total knee replacement (TKR) surgery (Berghoff, 2006; Everts, 2007; Gardner, 2007), and others. As stated above, these studies have small sample sizes and other serious design flaws which prevent the conclusions from being more widely generalized to clinical practice. Additionally, many of these studies concluded that there is little, if any, benefit to the use of PRP. One exception to this is the use of PRP during TKR, where the majority of studies reported significant benefits with regard to improving post-operative blood loss, length of stay and pain ratings. However, most of these small studies recommended the performance of larger studies to verify and confirm these findings.

PRP has also been extensively studied in neurosurgery, especially spinal fusion. Several small RCTs have been published investigating the use of PRP for improving fusion rates (Carreon, 2005; Feiz-Erfan, 2007; Hee, 2003; Weiner, 2003), none of which reported any significant benefit from PRP use.

In 2012, Hua and others reported the results of a randomized, non-blinded study of PRP vs. Nd-YAG laser treatment for benign cervical ectopy (n=60 in each group). The authors reported complete cure rates of 93.7% for the PRP group and 92.4% for the laser group ($p>0.05$). Mean time to re-epithelialization was significantly shorter in the PRP group (6.41 ± 2.05 weeks) than in the laser group (8.28 ± 1.72 weeks) ($p<0.01$). They also noted that the rate of adverse treatment effects (i.e. vaginal discharge or vaginal bleeding) was much lower in the PRP group than in the laser group ($p<0.01$) and the effects were milder. Eleven subjects in the PRP group had mild or moderate vaginal bleeding after treatment but none had heavy bleeding and of the 25 subjects with vaginal bleeding in the laser group, 2 had heavy bleeding necessitating tamponade. The results of this study are interesting; however, this is the first report in the literature of PRP used for this indication. Further study is warranted.

Overall, the body of data regarding potentially beneficial use of PRP for any condition is of poor quality and of limited use. Large well-designed trials are needed to effectively evaluate the use of PRP in the clinical setting.

Bone Marrow Aspirate Concentrate

The use of bone marrow aspirate concentrate (BMAC) has been proposed for several conditions, including for the treatment of critical limb ischemia (CLI). At this time, the only available evidence in the peer-reviewed published literature addressing BMAC involves a few small RCTs (de Girolamo, 2019; Iafrati, 2013) and several other small studies addressing CLI (Kolvenback, 2010), osteoarthritis (Rodriguez-Fontan, 2018), and treatment of chondral defects (Wang, 2019).

The RCT reported by Iafrati (2013) was double-blind and involved 48 subjects assigned to undergo treatment with BMAC (n=34) or sham (n=14). The authors noted that this pilot study was not powered to demonstrate statistical significance. However, they did note favorable trends for BMAC vs. control in major amputations (17.6% vs. 28.6%), improved pain (44% vs. 25%), improved ankle brachial index (32.4% vs. 7.1%), improved Rutherford classification (35.3% vs. 14.3%), and quality-of-life scoring better for BMAC in 6 of 8 domains. No adverse events were attributed to the injections and renal function was not reported to have been affected.

Further studies are needed to fully assess the safety and efficacy of BMAC therapy for any condition.

Bioengineered autologous skin-derived products

Bioengineered autologous skin-derived products have become available on the market. These products involve the harvesting of skin from an individual which is then processed in a lab, where it is altered in a manner that has been proposed to enhance it as a healing vector.

One such product, SkinTE, involves the use of a full-thickness skin sample which is then processed to create a paste of live autologous cells. This paste is then applied to the wound bed and covered, with the objective of creating a new, fully differentiated layer of skin. At this time there are no studies demonstrating the safety or efficacy of this product in the published peer-reviewed medical literature.

Another bioengineered autologous skin-derived product, named MyOwn Skin, is similar to SkinTE. This product is produced by culturing an individual's full-thickness skin sample in a laboratory to create several 4 inch by 4 inch patches that can be used for autografting. At this time there are no studies demonstrating the safety or efficacy of this product in the published peer-reviewed medical literature.

Autologous adipose-derived regenerative cell therapy

The use of autologous adipose-derived regenerative cell therapy, also referred to as autologous cellular implant derived from adipose tissue, has been proposed for a wide range of indications. However, at this time there are only a small number of published peer-reviewed studies describing the safety and efficacy of this treatment in the clinical setting. Haahr (2018) reported the results of a case series study involving 21 subjects with post-prostatectomy erectile dysfunction who received a single intracavernous injection of autologous adipose-derived regenerative cells. Pre-operative continence was reported in 15 subjects and the remaining 6 were incontinent at baseline. At 12 months, 8 of the 15 continent subjects reported erectile function sufficient for intercourse. No benefits were reported in the incontinent group. Another study by Gotoh (2019) reported the results of a case series study involving 13 subjects with persistent stress urinary incontinence after prostate surgery who underwent periurethral injection of adipose-derived regenerative cells. Urinary incontinence progressively improved up to 12 months after treatment in 10 of the 13 participants, and 1 participant with moderate incontinence achieved total continence at 14 weeks after injection. In the 10 participants who showed improvement at the final assessment, the mean daily leakage volume improved from 281.5 g to 119.0 g (reduction rate 57.7%)**.** These results persisted 4-5 years of follow-up.

Several small studies have described the use of "microfragmented" or "microfractured" adipose tissue therapy, marketed under the name Lipogems. Panchal (2018) reported the results of a case series study involving 17 subjects with refractory knee osteoarthritis. A total of 26 knees were treated with Lipogems-created microfractured autologous adipose tissue and followed for 12 months post-treatment. Knee Society Score (KSS) measures improved from 79.6 at baseline to 81.6 at 12 months (p=0.014). Similar findings were reported for the KSS

subscale for function, but not for the subscale for activity (p=0.014 and p=0.087, respectively). No significant adverse events were reported. A small RCT is currently underway to investigate the use of Lipogems-produced microfractured autologous adipose tissue for osteoarthritis of the knee (Jones, 2018). The results of this study will provide additional insight into the value of this proposed therapeutic option.

The use of Lipogems-produced microfractured autologous adipose tissue has also been investigated for gastrointestinal conditions, including for refractory complex fistulizing perianal Crohn's disease (Laureti, 2019). This small case series study involved 15 subjects who were all treated with microfractured autologous adipose tissue. All subjects were followed for 24 weeks, at which time 10 were reported to have both clinical and radiographic remission, 4 demonstrated improvements, and 1 failed treatment. These results were confirmed in all subjects by pelvic MRI. The authors reported no relevant postoperative complications or adverse events. They concluded that this therapy is a promising potential rescue therapy for individuals with refractory complex fistulizing perianal Crohn's disease. Naldini (2018) reported on a similar population of 19 subjects, 12 of whom received treatment with Lipogems-produced microfractured autologous adipose tissue as a first line therapy and 7 who had prior sphincter-saving procedures. Reported adverse events included 3 cases of minor abdominal wall hematoma that did not require any treatment and 1 case of perianal abscess. Mean follow-up was 9 ± 3.1 months (range 3-12 months), with the overall healing rate reported to be 73.7%. The first-line therapy group's healing rate was reported to be 83.3%, and the group with prior treatment had a 57.1% healing rate.

At this time, the available evidence addressing the safety and efficacy of autologous adipose-derived regenerative cell therapy are promising but weak. Additional trials with rigorous methodology are needed.

Autologous protein solution

APS, also known as autologous white blood cell concentrate, is a product produced from an individual's blood to create a solution of concentrated anti-inflammatory cytokines and anabolic growth factors. The nStride APS kit (Biomet Biologics, Warsaw, IN) has been proposed as a tool to create APS for intra-articular treatment of osteoarthritis of the knee. There are currently a limited number of published peer-reviewed studies describing clinical outcomes related to the administration of APS produced with the nStride kit. The first study, by van Drumpt (2016), was a case series study involving 11 subjects with early to moderate osteoarthritis of the knee who were treated with APS and followed for 6 months. No serious adverse events or adverse events related to APS treatment were reported. The mean WOMAC composite scores and pain, stiffness, and function subscale scores all showed significant improvement compared to baseline by 2 weeks post-injection ($p<0.001$). Continued improvement was reported through 3 months ($p<0.05$) and stable through 6 months. A second study, reported by Hix and colleagues (2017), was another case series study involving 11 subjects with early to moderate osteoarthritis of the knee who were treated with APS and followed for 12 months. Only mild adverse events were reported, with three cases of arthralgia and one case of musculoskeletal discomfort. All cases resolved within 6 days. At 1 year, WOMAC pain scores were reported to be significantly improved, with a 72.5% improvement in pain on average ($p<0.0001$). Similarly, WOMAC stiffness, function, and total scores were also significantly improved ($p<0.037$, $p<0.0064$, and $p<0.0064$, respectively). At all time points, Knee Injury and Osteoarthritis Outcome Score (KOOS) measures were significantly improved, including measurement scales for pain ($p<0.0029$), symptoms ($p<0.0269$),

stiffness (p<0.0420), function (p<0.0050), and sport function (p<0.0231). The most recent and largest study reported was an RCT published by Kon (2018) involving 46 subjects with moderate osteoarthritis of the knee randomized to receive a single ultrasound-guided injection of APS (n=31) or saline (n=15). Subjects were followed for 12 months, where improvement in WOMAC pain score was reported to be 65% in the APS group vs. 41% in the saline group (p=0.02). No significant differences between groups with regard to VAS pain scales were noted. At 12 months, the APS group showed improved SF-36 Bodily Pain subscale (p=0.0085) and Role Emotional Health subscale (p=0.0410), as well as CGI-C values (p=0.01) compared with saline controls. Significant differences between groups were also detected in change from baseline to 12 months in bone marrow lesion size as assessed on MRI and osteophytes in the central zone of the lateral femoral condyle, both in favor of the APS group (p=0.041 and p=0.032, respectively).

These study results are promising, but additional data is needed to fully assess the safety and efficacy of the use of APS for any condition including knee osteoarthritis.

Background/Overview

The skin is the largest organ of the body. It is composed of two layers, the epidermis and the dermis, and provides functions critical to survival. The skin acts as a protective barrier to fluid losses and dehydration and it protects against infection and injury by providing a barrier to repel bacteria and other organisms. The skin provides sensory contact with our environment that tells us whether we are feeling light touch, pressure, pain, heat, or cold. Damage to the skin that is extensive or prolonged may interfere with these functions or with those of other body systems and may become life threatening in some circumstances.

The treatment of burns and wounds that have failed to heal despite conservative measures, referred to as chronic wounds, pose a significant burden on the population in terms of pain, disability, and decreased quality of life. Chronic wounds may be due to the effects of diabetes, venous insufficiency to the extremities, pressure due to prolonged periods in the same body position, and other types of skin injuries. They can be difficult to treat and may require treatment with various coverings, such as skin graft or other materials to prevent infection, maintain an environment conducive to healing, or provide a medium for re-growth of new skin. Such coverings come in a wide array of types, from synthetic materials, tissues from the individuals themselves (autologous), human donors (allogeneic), or from animals such as cows and pigs (xenographic), or any combination of these materials (composites).

Human platelet-derived growth factors (PDGF, becaplermin [Regranex]), are produced from genetically-engineered yeast cells, into which the recombinant human form of the gene for the B-chain of PDGF has been inserted. The yeast cells read the inserted genes, as if they were their own and produce PGDF as a product of their metabolism. The PGDF is then collected and purified for use in clinical care. On June 6, 2008 the FDA required the following black box warning be placed on the label of Regranex:

> An increased rate of mortality secondary to malignancy was observed in patients treated with 3 or more tubes of REGRANEX Gel in a post-marketing retrospective cohort study. REGRANEX Gel should only

be used when the benefits can be expected to outweigh the risks. REGRANEX Gel should be used with caution in patients with known malignancy.

Antimicrobial silver wound dressings (e.g., Acticoat, Actisorb, Silversorb) involve a synthetic layer of nylon, rayon etc. coated with silver nanocrystals. It has been proposed that such coatings act as a barrier to infectious agents and kill bacteria before they are able to reach the wound.

Autologous wound care treatment may include a skin graft, which is a piece of skin from another site on the individual's body moved to the wound site. This method is frequently the preferred treatment, however, this method actually creates a new wound at the site where the graft was harvested, adding to the risk of infection and other complications.

Platelet rich plasma (PRP) is a substance derived from an individual's own blood, after high-speed centrifugation. It functions by re-creating the final phase in normal blood coagulation that produces a fibrin clot, adhering to the application site and providing wound coverage and stabilization. Additionally, PRP may increase the concentrations of beneficial healing factors within the application site, also potentially augmenting the healing effect. PRP's other proposed benefits include the fact that it is autologous and thus not immunoreactive, it is absorbable, and it is fairly simple to produce. Research of potential uses for PRP has been ongoing, including wound care, burns, orthopedics, maxillofacial surgery, plastic surgery, and others.

Another autologous method involves products derived from the individual's own blood growth factors, which are collected from the blood (e.g., Aurix or Vitagel). To make these types of products, blood is drawn from the individual and is centrifuged at high speeds to separate the blood components from one another. The platelet rich plasma portion of the blood is activated with various reagents to convert the blood protein fibrinogen into fibrin, one of the major components required to form a blood clot. This fibrin-rich gel-like substance is then immediately applied to the wound to form a wound covering.

Vitagel is a product that uses an individual's own blood mixed with microfibrillar collagen and thrombin to create an artificial scab on wounds. It has been proposed that this product may assist in controlling bleeding during operative procedures and other circumstances where bleeding may be of concern.

BMAC is an autologous substance that has been proposed as an adjunct to several medical therapies, including for critical limb ischemia. It is collected via needle aspiration of bone marrow which is then processed and re-injected into the individual being treated.

Bioengineered autologous skin-derived products involve the harvesting of skin from an individual which is then processed in a lab where it is altered in a manner that has been proposed to enhance its healing properties, and is then applied to the individual's wound.

Autologous adipose-derived regenerative cell therapy involves the injection of fat-derived tissue, either unprocessed or minimally processed, from one part of a person to another part of the same person. This treatment

method has been proposed as a treatment of a wide variety of indications, including orthopedic injuries. One commercially available device used to produce this type of therapeutic product is named Lipogems (Lipogems International, Norcross, GA), which is used to produce "microfractionated minimally manipulated adipose tissue". This device was cleared in 2016 by the U.S. FDA with these indications:

> "The Lipogems System is a sterile medical device intended for the closed-loop processing of lipoaspirate tissue in medical procedures involving the harvesting, concentrating and transferring of autologous adipose tissue harvested with a legally marketed lipoplasty system. The device is intended for use in the following surgical specialties when the transfer of harvested adipose tissue is desired: orthopedic surgery, arthroscopic surgery, neurosurgery, gastrointestinal and affiliated organ surgery, urological surgery, general surgery, gynecological surgery, thoracic surgery, laparoscopic surgery, and plastic and reconstructive surgery when aesthetic body contouring is desired. Only legally marketed accessory items, such as syringes, should be used with the system. If harvested fat is to be transferred, the harvested fat is only to be used without any additional manipulation."

Autologous protein solution, also referred to as autologous white blood cell concentrate, is a fluid created from an individual's blood and contains high concentrations of anti-inflammatory and anabolic proteins. It has been proposed that autologous protein solution may be helpful for a variety of conditions.

Definitions

Antimicrobial silver wound dressing (e.g., Acticoat, Actisorb, and Silversorb): A technology proposed to prevent wound adhesion, limit nosocomial (hospital) infections, control bacterial growth, and facilitate burn wound care through a silver-coated dressing material. It consists of layers of a silver-coated synthetic mesh.

Autologous: A product derived from the individual's own body or body products.

Autologous adipose-derived regenerative cell therapy: A medical therapy proposed to treat a wide array of conditions using fat cells from an individual which are extracted from one part of the body and then injected into another. In some cases the fat cells are processed in some fashion prior to reinjection.

Autologous conditioned plasma (ACP): A type of PRP, which is distinguished from other PRP products by a low concentration of white blood cells that may be detrimental to the healing process when present in high concentrations.

Autologous protein solution: A fluid created from an individual's blood that contains high concentrations of anti-inflammatory and anabolic proteins.

Growth factors: Products that play important roles in the regulation of cell division and tissue propagation.

Human-derived autologous wound factor gel (e.g., Aurix, Vitagel): A product that is derived from blood taken from an individual to create a platelet-rich plasma preparation for the treatment of wounds.

Platelet rich plasma (PRP): A preparation made of concentrated platelets from autologous blood; this substance has been suggested for use to improve healing for a wide variety of medical conditions.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

HCPCS

S0157	Becaplermin gel 0.01%, 0.5 gram [Regranex®]

ICD-10 Diagnosis

E08.40-E08.49	Diabetes mellitus due to underlying condition with neurological complications
E08.621-E08.622	Diabetes mellitus due to underlying condition with foot ulcer, other skin ulcer
E09.40-E09.49	Drug or chemical induced diabetes mellitus with neurological complications
E09.621-E09.622	Drug or chemical induced diabetes mellitus with foot ulcer, other skin ulcer
E10.40-E10.49	Type 1 diabetes mellitus with neurological complications
E10.621-E10.622	Type 1 diabetes mellitus with foot ulcer, other skin ulcer
E11.40-E11.49	Type 2 diabetes mellitus with neurological complications
E11.621-E11.622	Type 2 diabetes mellitus with foot ulcer, other skin ulcer
E13.40-E13.49	Other specified diabetes mellitus with neurological complications
E13.621-E13.622	Other specified diabetes mellitus with foot ulcer, other skin ulcer
L89.000-L89.95	Pressure ulcer
L97.101-L97.929	Non-pressure chronic ulcer of lower limb, not elsewhere classified
L98.411-L98.499	Non-pressure chronic ulcer of skin, not elsewhere classified

When services are Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

When services are also Investigational and Not Medically Necessary:
For the following procedure codes or when the code describes a procedure or product indicated in the Position Statement section as investigational and not medically necessary.

CPT	
20999	Unlisted procedure, musculoskeletal system, general [when specified as harvesting and injection of bone marrow aspirate concentrate or harvesting or injection of an autologous cellular implant from adipose tissue]
0232T	Injection(s), platelet rich plasma, any tissue, including image guidance, harvesting and preparation when performed
0481T	Injection(s), autologous white blood cell concentrate (autologous protein solution), any site, including image guidance, harvesting and preparation, when performed
0489T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; adipose tissue harvesting, isolation and preparation of harvested cells including incubation with cell dissociation enzymes, removal of non-viable cells and debris, determination of concentration and dilution of regenerative cells
0490T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; multiple injections in one or both hands
0565T	Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; tissue harvesting and cellular implant creation [Note: code effective 01/01/2020]
0566T	Autologous cellular implant derived from adipose tissue for the treatment of osteoarthritis of the knees; injection of cellular implant into knee joint including ultrasound guidance, unilateral [Note: code effective 01/01/2020]
	Note: CPT procedure code 20926 Tissue grafts, other (eg, paratenon, fat, dermis) is not an appropriate code for injection or application of PRP; or for harvesting or injection of adipose-derived cellular implants; this code represents harvesting of a tissue graft which is not addressed in this document
HCPCS	
A4649	Surgical supply, miscellaneous [no specific code for antimicrobial silver wound dressings (e.g., Acticoat, Actisorb, AQUACEL Ag, Promogran Prisma, Silversorb, Urgotul Silver)]
G0460	Autologous platelet rich plasma for chronic wounds/ulcers, including phlebotomy, centrifugation, and all other preparatory procedures, administration and dressings, per treatment [for example, Aurix]
Q4200	Skin TE, per square centimeter
Q4226	MyOwn Skin, includes harvesting and preparation procedures, per square centimeter
S9055	Procuren or other growth factor preparation to promote wound healing
	Note: HCPCS code P9020 Platelet rich plasma, each unit is not specific to autologous PRP; if used to describe autologous PRP it would be considered investigational and not medically necessary
ICD-10 Diagnosis	
	All diagnoses

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	08/22/2019	Medical Policy & Technology Assessment Committee (MPTAC) review. Revised document title. Revised INV and NMN statement regarding Bioengineered autologous skin-derived products. Added new INV and NMN statements addressing Autologous adipose-derived regenerative cell therapy and Use of autologous protein solution. Updated Description, Rationale, Definitions, References, and Index sections. Updated Coding section with 10/01/2019 HCPCS changes to add Q4226, 01/01/2020 CPT changes to add 0565T and 0566T, also added CPT 0481T, 0489T, 0490T.
Revised	01/24/2019	MPTAC review. Added new INV and NMN statement addressing bioengineered autologous skin-derived products. Updated Description,

		Rationale, and References sections. Updated Coding section; added HCPCS code Q4200.
Reviewed	01/25/2018	MPTAC review. The document header wording updated from "Current Effective Date" to "Publish Date." Updated Rationale, References, and Index sections.
Reviewed	02/02/2017	MPTAC review. Updated formatting in Position Statement section. Updated Rationale, References, and Index sections.
Revised	02/04/2016	MPTAC review. Added Aurix to Investigational and Not Medically Necessary statement. Removed Safeblood from document. Updated Rationale, Coding and References sections. Removed ICD-9 codes from Coding section.
Reviewed	02/05/2015	MPTAC review. Added clarification that 'autologous conditioned plasma' is a type of PRP. Updated Rationale and References sections.
Revised	02/13/2014	MPTAC review. Added investigational and not medically necessary statement addressing bone marrow aspirate concentrate. Updated Rationale, Coding and References sections.
Reviewed	05/09/2013	MPTAC review. No change to position statement. Updated Rationale and References sections. Updated Coding section with 07/01/2013 HCPCS changes.
New	05/10/2012	MPTAC initial document development.