Biologic Materials for Dental Indications

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Instructions for Use

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Related Dental Policies

- Dental Barrier Membrane Guided Tissue Regeneration
- Surgical and Partial Extractions of Erupted Teeth and Removal of Retained Roots
- Surgical Extraction of Impacted Teeth
- Non-Surgical Extractions

Coverage Rationale

Biologic Materials for Soft and Osseous Tissue Regeneration

The following Biological Materials may be indicated to aid regeneration:

- Enamel Matrix Derivative
- Bioactive Glass

Biological Materials to aid in soft and osseous tissue regeneration are not indicated for the following due to insufficient evidence of efficacy:

- In conjunction with Periradicular surgery
- For treating Mucogingival Deformities

All other Biological Materials, including but not limited to bone morphogenic protein, amniotic membranes, and stem cells, are not indicated for regeneration due to insufficient evidence of efficacy.

Collection and Application of Autologous Blood Concentrate Product

Collection and application of Autologous Blood Concentrate products are not indicated due to insufficient evidence of efficacy.

Placement of Intra-Socket Biological Dressing to Aid in Hemostasis or Clot Stabilization

The placement of intra-socket biological dressing to aid in hemostasis or clot stabilization may be indicated in individuals with a high risk of uncontrolled bleeding. These include but are not limited to:

- Individuals taking medications known to impact hemostasis (e.g., anticoagulants, interferon alpha)
- Individuals with bleeding disorders (e.g.,von Willebrand disease, hemophilia)
- Individuals with an underlying medical condition that is known to impact hemostasis (e.g., immune disorders, liver and kidney disease, lymphoproliferative disorders)

The placement of intra-socket biological dressing to aid in hemostasis or clot stabilization is not routinely indicated for all extractions.

Definitions

Autologous Blood Concentrates: Blood products made using the patient's own blood and include Platelet-rich fibrin (PRF) and platelet-rich plasma. (PRP)

Bioactive Glass: A group of biocompatible bioceramic materials that are similar to bone hydroxyapatite in terms of calcium and phosphate contents. They dissolve when they are exposed to body fluids, and by forming the apatite crystals on their surface, they gain the ability to chemically bond with the apatite crystals which are present in bone and tooth tissues. (Jafari, 2022)

Biologic Materials/Biologic Response Modifiers: Agents that alter wound healing or host-tumor interaction. Such materials can include cytokines, growth factor, or vaccines, but do not include any actual hard or soft tissue graft material. These agents are added to graft material or used alone to effect acceleration of healing or regeneration in hard and soft tissue surgical procedures. (ADA)

Enamel Matrix Derivative: A porcine-derived tooth enamel matrix product. (Fan, 2023)

Mucogingival Deformity: A departure from the normal dimension and morphology of, and/or interrelationship between gingiva and alveolar mucosa; the abnormality may be associated with a deformity of the underlying alveolar bone. (AAP)

Periradicular: Surrounding the root. (AAE)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CDT Code	Description
D4265	Biologic materials to aid in soft and osseous tissue regeneration, per site
D4999	Unspecified periodontal procedure, by report
D7921	Collection and application of autologous blood concentrate product
D7922	placement of intra-socket biological dressing to aid in hemostasis or clot stabilization, per site; This procedure can be performed at time and/or after extraction to aid in hemostasis. The socket is packed with a hemostatic agent to aid in hemostasis and or clot stabilization.

Description of Services

Regenerative materials seek to facilitate the regeneration of the periodontium (bone and soft tissue) lost due to disease, injury, or defect. Biomaterials may enhance cellular interactions, promote healing, and support tissue reconstruction. These materials are typically used in combination with each other, or surgical procedures which can make definitive determination of efficacy challenging. The role of these materials is evolving and the technologies outlined in this policy are not all inclusive (Pranathi, 2024).

The placement of intra-socket biological dressings following an extraction include products made of gelatin, collagen, and cellulose for soft tissue bleeding, and bone wax for cancellous bone bleeding. These products may be needed to aid in hemostasis or clot stabilization and are typically considered inclusive to the primary extraction procedure.

Clinical Evidence

Autologous Platelet Concentrates

While some studies are promising, the majority of evidence on platelet-derived blood or plasma therapies compared to other standard treatment is highly variable with regard to efficacy or improved health outcomes for a wide range of

conditions. Higher quality studies with longer follow up, larger numbers of participants as well as standardization of best practices are needed to determine the benefit of this technology.

In a 2024 double blind randomized controlled trial, Yari et al. compared the postoperative sequelae of three modifications of platelet-rich fibrin (PRF) on the clinical outcomes of impacted third molar (M3) removal. Sixty-four participants with vertical and mesioangular impactions classified as moderately difficult were randomly and equally assigned to four groups (16 each): leukocyte-PRF (L-PRF), advanced-PRF which claims to contain more leukocytes (A-PRF), and advanced-PRF plus in which centrifuge speed and time are decreased (A-PRF+) and a control group. Follow up occurred at one, two, three, and seven days, with 14 day follow up for soft tissue healing only. Outcomes assessed were soft tissue healing, pain, number of analgesics taken, incidence of alveolar osteitis, trismus, and facial swelling. The results showed that for soft tissue healing, all three treatment groups had a better healing index with no statistically significant differences between them. There was no statistically significant difference in the VAS pain scores between the groups before surgery and on day seven, however there were decreased pain scores on days one, two and three. On day two follow up, A-PRF and A-PRF+ showed significantly lower VAS score than the L-PRF. There was a statistically significant difference in the number of pain medication taken on days two and three, with all three platelet concentrates causing a statistically significant decrease in the number taken. No difference was found at days one and seven. A statistically significant difference in swelling was noted on days two and three. No participants had alveolar osteitis and there were no statistically significant differences in incidents of trismus. The authors concluded that the variations of PRF has positive impact on post-surgical outcomes in the short term. Further research should also evaluate bone healing and impact on the distal of the second molars This study is limited by a small number of participants and short-term follow-up and additional research with larger numbers are needed to validate these findings.

Alasqah (2024) conducted a randomized study to evaluate the efficacy of platelet rich plasma (PRP) in maintaining ridge dimension and discomfort in atraumatic extraction sites of the maxilla and mandible. Sixty patients were equally randomized to receive PRF, PRF+ collagen, and a control group. At baseline and three month follow up, CBCT was used to assess bone dimension, and postoperative pain was assessed at twenty-four hours, and three- and seven-day(s) post extraction. The results showed that there were no significant differences in bone dimensions among the three groups, but the PRF and PRF+ collagen groups experienced reduced short-term pain. The authors concluded that this study provides valuable information on short term results, but longer follow up is needed to assess long term impact on ridge morphology and the clinical outcomes such as implant success.

In a 2024 systematic review, Niemczyk et al. assessed the impact on clinical outcomes of using platelet-rich plasma (PRP) and injectable platelet-rich fibrin (i-PRF) in conjunction with scaling and root planing (SRP). Twelve randomized controlled trials, nine with a split mouth design and three double blinded. Out of the twelve studies, two investigated the use of PRP, one study used PRGF, eight involved i-PRF, and one did not specify type. Each of the studies considered different clinical parameters to be assessed, but all included probing pocket depth (PPD), and only one did not consider clinical attachment level (CAL). Follow-up periods ranged from six weeks to six months. The results showed for i-PRF studies, all reported PPD and CAL which showed improvement in these parameters. A statistically significant difference in PPD and disease burden was observed between baseline and one, two and three months in both the PRP and i-PRF groups. Two studies found no benefit to saline and one study had the presence of disease as an inclusion criteria. The findings also show that there are antibacterial properties of both PRP and i-PRP against Porphyromonas gingivalis, with i-PRP showing a wider inhibitory effect. The authors concluded that this systematic review shows that the use of PRP and i-PRF are beneficial in improving outcomes of SRP. The studies are limited by a lack of heterogeneity in evaluating results, mixed treatment protocols, and short follow up periods. Further research is needed to validate these findings.

In a 2023 systematic review, Malcangi et al. evaluated the potential of autologous platelet concentrates/concentrated growth factors (CGF) combined with bone graft for maxillary sinus augmentation. Twenty-two articles were included. The results showed histologically enhanced vascularization and new bone formation when using growth factors. The influence of PRF combined with bone grafting takes advantage of the body's natural ability to form new bone cells, and promote healing, and PRP provides statistically significant implant related primary stability. When compared, sinus elevation using CGF alone results in bony changes similar to a demineralized bovine bone matrix. This systematic review is limited by the heterogeneity of the included studies with regard to combinations of products, and more research is needed to validate these findings.

Csifó-Nagy et al. (2021) conducted a blinded, randomized clinical trial to evaluate the healing of intrabony periodontal defects after treatment with a new generation of platelet-rich fibrin (A-PRF+) which is a platelet rich fibrin concentration obtained by lower speed centrifugation, compared to enamel matrix derivative (EMD). Thirty intrabony defects in eighteen individuals that met the following criteria were selected: no systemic disease, nonsmokers, good oral hygiene, a minimum of one or more 2- ,3- or combined 2, 3- wall intrabony defect with a defect angle of 20-40 degrees, with a minimum probing depth of 6 mm with the intrabony component having a minimum of 4 mm. Clinical parameters measured at

baseline and six months after surgery were pocket depth (PD), gingival recession (GR) and clinical attachment level (CAL). Fifteen patients received A-PRF+ (test) and fifteen received EMD (control). The results showed that after six months, the mean PD decreased 4.47 mm in both groups, the mean GR increase was 3.93 in the test group and 3.33 in the control group, and the mean CAL gain was 2.33 in the test group and 2.60 in the control. The authors concluded that A-PRF+ seems to be at least as clinically effective as EMD when treating intrabony periodontal defects. The authors acknowledge limitations of this study was a double arm and lacked a control group and isolated intrabony defects may fill without the addition of biologic materials. Larger randomized trials that include a control group, as well as histological evaluation of regeneration are needed to confirm these results.

Miron et al. (2021) conducted a systematic review and meta-analysis of 27 randomized controlled trials to compare the clinical outcomes of platelet rich fibrin (PRF) in the treatment of periodontal intrabony defects compared to other commonly used treatment modalities. Primary outcome measurements included decrease in probing depth (PD); increased clinical attachment level (CAL); and increased radiographic bone fill (RBF). The results of each modality compared to PRF are summarized below:

- Open flap debridement (OFD) alone versus OFD/PRF.
  - 14 Studies evaluated OFD alone vs OFD with PRF. On average, the results showed statistically significant improvements by way of a reduction in PD of 1.26 mm, CAL gain of 1.39 mm and statistically significant improved bone fill.
- OFD/bone graft (OFD/BG) versus OFD/PRF.
  - Five studies evaluated the use of a bone graft with OFD vs PRF with OFD. The results showed no statistically significant differences between the two groups, and PRF leads to comparable outcomes to BG when used for intrabony defect repair/regeneration.
- OFD/BG versus OFD/BG/PRF.
  - Six studies compared the use of a bone graft with OFD vs PRF + BG with OFD. Two of the six studies reported significant improvements in PD and CAL compared to BG alone while the other four reported no statistically significant difference. Meta-analysis showed approximately 1mm gain in CAL and improvements in RBF indicating some improvement is observed when PRF is added to a BG material.
- OFD/barrier membrane (BM), OFD/PRP, or OFD/enamel matrix derivative (EMD) versus OFD/PRF.
  - Eight studies investigating PRF versus a collagen barrier membrane (BM) showed no statistically significant difference in terms of PD reduction, however improvements were observed for CAL and RBF in favor of PRF compared to BM.
- OFD/EMD versus OFD/EMD/PRF.
  - No differences in any of the investigated parameters were found for single RCTs investigating PRP versus PRF EMD versus PRF or EMD versus EMD + PRF.

In a 2018 Cochrane database systematic review, Del Fabbro et al. sought to assess the effects of autologous platelet concentrates (APC) used as an adjunct to periodontal surgical therapies open flap debridement (OFD), OFD combined with bone grafting (BG), guided tissue regeneration (GTR), OFD combined with enamel matrix derivative (EMD) for the treatment of infrabony defects. The primary outcomes assessed were change in probing pocket depth (PD), change in clinical attachment level (CAL), and change in radiographic bone defect filling (RBF). The authors included randomized controlled trials (RCTs) of both parallel and split-mouth design, involving patients with infrabony defects requiring surgical treatment. Studies had to compare treatment outcomes of a specific surgical technique combined with APC, with the same technique when used alone. Data was organized into four groups, each comparing a specific surgical technique when applied with the adjunct of APC or alone: 1. APC + OFD versus OFD, 2. APC + OFD + BG versus OFD + BG, 3. APC + GTR versus GTR, and 4. APC + EMD versus EMD. Based on very low-quality evidence, the results showed:

- APC + OFD versus OFD alone: Twelve studies were included in this comparison, with a total of 510 infrabony defects. There is evidence of an advantage in using APC globally from split-mouth and parallel studies for all three primary outcomes.
- APC + OFD + BG versus OFD + BG: Seventeen studies were included in this comparison, with a total of 569 infrabony defects. Considering all follow-ups, as well as 3 to 6 months and 9 to 12 months, there is evidence of an advantage in using APC from both split-mouth and parallel studies for all three primary outcomes.
- APC + GTR versus GTR alone: Seven studies were included in this comparison, with a total of 248 infrabony defects. Considering all follow-ups, there is probably a benefit for APC for both PD and CAL. However, given the wide confidence intervals, there might be a possibility of a slight benefit for the control. When considering a 3 to 6 months and a 9 to 12 months follow-up, there were no benefits evidenced, except for CAL at 3 to 6 months. No RBF data were available.
- APC + EMD versus EMD: Two studies were included in this comparison, with a total of 75 infrabony defects. There is insufficient evidence of an overall advantage of using APC for all three primary outcomes.
- All studies in all groups reported a survival rate of 100% for the treated teeth. No complete pocket closure was reported.

The authors concluded that there is very low-quality evidence that the adjunct of APC to OFD or OFD + BG when treating infrabony defects may improve probing pocket depth, clinical attachment level, and radiographic bone defect filling. For GTR or EMD, insufficient evidence of an advantage in using APC was observed.

Patel et al. (2017-included in Miron 2021 systematic review and meta-analysis above) conducted a randomized controlled trial to assess the adjunctive use of platelet-rich fibrin (PRF) in regenerative management of intrabony defects in comparison with open flap debridement (OFD). Twenty-six bilateral defects (13 per group) in 13 patients were randomized as either PRF (test group) or OFD alone (control group) sites. Primary outcomes assessed were changes in PD, CAL, and percentages of bone fill at 6, 9, and 12 months. Secondary outcome was assessment of wound healing using a wound healing index (WHI). The PRF group showed significant improvement in clinical parameters compared with the control group at 6, 9, and 12 months. The PRF group showed a bone fill of 45.18% ±7.57%, which was statistically significant compared with 21.6% ±9.3% seen in the control group at the end of the study period. The PRF group also showed significant soft tissue healing and reduction in PD. WHI also showed significant advantages for the PRF group. The authors concluded that the adjunctive use of PRF to conventional OFD may be potentially used in the treatment of intrabony defects.

Miron et al. (2017) conducted a systematic review with the goal of gathering the extensive number of articles published to date on platelet rich fibrin (PRF) in the dental field to better understand the clinical procedures where PRF may be utilized to enhance tissue/bone formation. Randomized clinical trials were searched systematically until May 2016 and separated into the following categories: intrabony and furcation defect regeneration, extraction socket management, sinus lifting procedures, gingival recession treatment, and guided bone regeneration (GBR) including horizontal/vertical bone augmentation procedures. In total, 35 articles were selected and divided accordingly. Overall, the use of PRF has been most investigated in periodontology for the treatment of periodontal intrabony defects and gingival recessions where the majority of studies have demonstrated favorable results in soft tissue management and repair. Little to no randomized clinical trials were found for extraction socket management, although PRF has been shown to significantly decrease dry sockets complications in third molar sites. Little to no data was available directly investigating the effects of PRF on new bone formation in GBR, horizontal/vertical bone augmentation procedures, treatment of peri-implantitis, and sinus lifting procedures. The authors concluded that investigation supports the use of PRF for periodontal and soft tissue repair. There remains a lack of well-conducted studies demonstrating convincingly the role of PRF during hard tissue bone regeneration. Future human randomized clinical studies evaluating the use of PRF on bone formation are necessary.

Ravi et al. (2017) completed a split-mouth randomized controlled clinical trial to assess the effect of plasma rich growth factor (PRGF) associated with guided tissue regeneration (GTR) versus GTR only in the treatment of intrabony defects (IBDs) in patients with chronic periodontitis (CP). Patients with CP with 42 contralateral 2- and 3-walled defects were randomly assigned to test (PRGF + GTR) and control (GTR alone) treatment groups. Clinical and radiographic assessments performed at baseline and after 6 months were: gingival index (GI), probing depth (PD), clinical attachment level (CAL), radiologic defect depth, and bone fill. The results demonstrated that the parameters measured at baseline and after 6 months showed mean PD reduction of 3.37 ±1.62 mm in the control group and 4.13 ±1.59 mm in the test group. There was a significant difference in mean change in CAL in the control group (5.42 ±1.99) and the test group (5.99 ±1.77). Mean change in GI was 1.89 ±0.32 and 1.68 ±0.58 in the control group and test group, respectively, and the difference was statistically significant. When compared between groups, clinical parameters did not show any statistically significant variations. Mean radiographic bone fill was 1.06 ±0.81 and 1.0 ±0.97 in the control group and test group, respectively. However, the difference was not statistically significant. The authors concluded that PRGF with GTR, as well as GTR alone, was effective in improving clinical and radiographic parameters of patients with CP at the 6-month follow-up. There was no additive effect of PRGF when used along with GTR in the treatment of IBDs in patients with CP in terms of both clinical and radiologic outcomes.

Cieplik et al. (2017) completed a 13-year follow-up of a randomized controlled clinical split-mouth study on the influence of autogenous platelet concentrate (APC) on combined guided tissue regeneration (GTR)/graft therapy in intrabony defects. In 25 patients, two deep contra-lateral intrabony defects were treated according to GTR using ß-TCP and bio-resorbable membranes. In test defects, APC was applied additionally. After 13 years, clinical healing results were assessed and compared to results at baseline and after 1 year, and a tooth survival analysis completed. After 13 years, 22 participants were available for tooth survival analysis showing 81.8% of test and 86.4% of control teeth still in situ. Based on the 15 participants still available for split-mouth analysis, median CAL was 10.0 mm in test and 12.0 mm in control sites at baseline. After one year, both groups revealed significant CAL gains of 5.0 mm, followed by a new CAL loss of 1.0 mm in the following 12 years. There were no significant differences between test and control sites. The authors concluded that within the limits of this study, the data shows that most of the CAL gain following GTR can be maintained over 13 years. The additional use of APC had no positive influence on the long-term stability.

Galav et al. (2016) conducted a randomized controlled trial to compare the clinical efficacy of platelet-rich fibrin (PRF) with autogenous bone grafting (ABG) for the treatment of intra bony defects (IBD's) in chronic periodontitis. Twenty participants with chronic periodontitis with IBDs were randomly treated by PRF or ABG. Probing pocket depth (PPD), relative attachment level (RAL), surgical reentry bone fills, and radiographic bone fill (RBF) were recorded at baseline, three, six, and nine months post-surgery, respectively. The results showed that both PRF and ABG sites produced a significant improvement from baseline to nine months for all the parameters. However, there was no significant difference between the two treatment modalities in the reduction of PPD and RAL gain at nine months. In addition, ABG showed significantly greater RBF (30.34%) as compared to PRF (20.22%). Similar findings were supported by surgical reentry, where a surgical reentry of 65.31% at ABG sites and 43.64% at PRF sites was seen. The authors concluded that both ABG and PRF can be used predictably to reconstruct lost periodontal structures as indicated by PPD reduction and RAL gain. However, in terms of osseous defect fill, ABG yields more definitive outcome than PRF.

Shah et al. (2014) conducted a systematic review and meta-analysis to determine the clinical and radiographic outcomes of using platelet-rich fibrin (PRF) for the treatment of periodontal intra-bony defects (IBD) compared with open flap debridement (OFD). Studies having a test group using PRF alone and a control group with OFD alone with a minimum follow up of six months were included. A total of 298 sites were treated using PRF either in combination with graft or as a monotherapy in comparison to traditional OFD procedure. The meta-analysis showed a standard mean difference of 0.95 mm in clinical attachment level (CAL) and 2.33 mm in IBD after treatment of IBD with PRF compared with OFD. The authors concluded that clinically significant improvements in periodontal parameters such as CAL, IBD, and reduction in probing depth were achieved when IBDs were treated with PRF alone when compared to OFD.

Nevins et al. (2013) provided results from a 36-month extension study of a multicenter, randomized, controlled clinical trial evaluating the effect and long-term stability of homodimer platelet derived growth factor (PDGF-BB) treatment in patients with localized severe periodontal osseous defects. A total of 135 participants were enrolled from six clinical centers for this trial, and eighty-three individuals completed the study at 36 months and were included in the analysis. The study investigated the local application of β-tricalcium phosphate scaffold matrix with or without two different dose levels of PDGF (0.3 or 1.0 mg/mL PDGF-BB) in patients possessing one localized periodontal osseous defect. Clinical and radiographic evidence of treatment success was defined as percentage of cases with clinical attachment level (CAL) ≥ 2.7 mm and linear bone growth (LBG) ≥ 1.1 mm. Although there were no significant increases in CAL and LBG at 36 months among all groups, there were continued increases in CAL gain, LBG, and percentage bone fill over time, suggesting overall stability of the regenerative response. The authors concluded that PDGF-BB in a synthetic scaffold matrix promotes long-term stable clinical and radiographic improvements in patients with localized severe periodontal osseous defects.

Enamel Matrix Derivative (EMD)

In a 2022 American Academy of Periodontology systematic review and network meta-analysis, Tavelli et al. evaluated the effect of various biologic agents on the regenerative outcomes in treating infrabony periodontal defects either as a monotherapy or combined with bone grafts (BG) and/or absorbable guided tissue regeneration membranes. For EMD, the results showed significant improvements in regenerative outcomes in infrabony defects, and recommended for use in combination with bone grafts.

Miron et al. (2025) conducted a systematic review and meta-analysis of randomized controlled trials on the efficacy of EMD alone or as an adjunct when combined with open flap debridement (OFD), bone graft, and guided tissue regeneration (GTR). Conditions assessed included periodontal disease (non-surgical) for changes in probing pocket depth (PPD) and clinical attachment level (CAL); intrabony defect modifications in PPD and CAL; furcation defects in PPD, and vertical and horizontal CAL (VCAL and HCAL respectively); and in procedures for root coverage, changes in recession depth over the last 30 years. Follow up for non-surgical periodontal treatment was three months or nearest timeframe, for all others, follow up was 12 months or nearest timeframe. Sixty-seven randomized controlled trials met the inclusion criteria. The results were as follows:

- OFD vs. OFD + EMD was evaluated in 20 studies and showed that treatment with EMD showed an average of 1 mm greater reduction in PPD [95% Confidence interval (95% CI): 0.63–1.38], and a 1.14 mm greater gain (95% CI:0.83–1.46) in CAL than OFD alone. Both were statistically significant with a $p < 0.05$. However, there was a high degree of heterogeneity for both outcomes.
- Bone Graft vs. Bone Graft + EMD was assessed in 5 studies and the results showed that the combination therapy of BG + EMD resulted in an average 0.61 mm greater PPD reduction (95% CI: 0.03–1.19) and a 0.84 mm greater CAL gain (95% CI: 0.06–1.61) compared to BG alone. Both results showed statistical significance ($p < 0.05$) with a high degree of heterogeneity.
- EMD vs. EMD + Bone Graft included 12 studies and the results showed EMD + bone graft showed an average of 0.26 mm greater PPD reduction (95% CI: −0.02 to 0.53), and an .03 mm greater CAL gain (95% CI: 0.02–0.64) with CAL

reaching statistical significance ($p < 0.05$) with a moderate degree of heterogeneity. No difference was seen with type of bone graft used.
- EMD vs. GTR included 10 studies and the results showed that GTR showed a 0.51 mm greater PPD reduction (95% CI: −0.03 to 1.05) and a 0.19 mm greater CAL gain (95% CI: −0.15 to 0.52) compared to EMD. Neither reached statistical significance and showed high and moderate heterigeniety respectively.
- EMD vs. EMD + GTR included three studies and the results showed the combination of EMD and GTR resulted in an average greater PPD reduction of 0.32 mm (95% CI: −0.22 to 0.85) and a 0.28 mm greater CAL gain (95% CI: −0.25 to 0.81). Neither reached statistical significance and no heterogeneity was observed.
- Furcation Defects included four studies. Due to significant heterogeneity in the adjunct treatments, surgical techniques, defect classifications, and treatment protocols, a meta-analysis was not feasible.
- Root Coverage procedures did not show meaningful gains in efficacy.

The authors concluded that over the last 30 years, EMD has consistently shown improvements in PPD and CAL gain when used for periodontal regeneration in intrabony defects, with limited improvements in other indications. All included trials are limited by a moderate to high risk of biases as well as substantial heterogeneity. Addition high quality research is needed to evaluate the regenerative potential of EMD for other indications.

Estrin et al. (2022) conducted a systematic review and meta-analysis to assess the efficacy of enamel matrix derivative (EMD) using a minimally invasive surgical technique (MINST), or flapless approach for the treatment of periodontal probing depths greater than 5 mm. Seven RCTs and 12 case series were included. The results showed that EMD with MINST improved recession coverage (REC) and bone fill (BF) when compared to MIST without EMD. However, no difference in clinical attachment level (CAL) or pocket depth (PD) was observed between MIST + EMD vs MIST without EMD. No statistically significant advantage was found for employing the EMD via the flapless approach. The authors concluded that these findings suggest that MINST in combination with EMD led to improved clinical outcomes while EMD employed in nonsurgical flapless therapy yielded no clinical benefits when compared to nonsurgical therapy alone, and more research is needed to substantiate these findings.

In a prospective two-year clinical study conducted at two centers, Seshima et al. (2017) evaluated the outcomes of periodontal regenerative therapy using EMD for the treatment of intrabony defects. Inclusion criteria was interproximal sites with probing depth (PD) ≥ 6 mm, at least one interproximal intrabony defect ≥ 3 mm in depth, and adequate level of plaque control. Participants must have received initial periodontal therapy. Baseline parameters of pocket depth (PD), gingival recession (GR), clinical attachment level (CAL), bleeding on probing (BOP) and tooth mobility (TM) were recorded and reevaluated at one and two years. Twenty-two patients completed the two-year reevaluation and the results from baseline showed a significant improvement in CAL, PD (the contribution of GR to PD reduction was minimal), BOP and TM. The bone fill assessed showed improvements as well. The authors concluded that treating periodontal intrabony defects using EMD results in clinically significant gains in attachment. This study is limited by a small sample size and its single arm design.

Bioactive Glass

Jafari et al. (2026) conducted a systematic review and meta-analysis of randomized controlled trials to assess the clinical efficacy of bioactive glass (BG) in reducing probing depth (PD) and improving clinical attachment level (CAL) for periodontal regeneration. Included trials evaluated BG and open flap debridement (OFD) alone, or BG + enamel matrix derivative (EMD) + OFD vs EMD + OFD, provided that the only difference between test and control groups was the addition of BG. Twelve randomized controlled trials totaling 234 participants with 406 periodontal defects and eight split mouth and four parallel-group trials met the criteria. Follow-up ranged from six months to four years. For PD, the results in all twelve studies showed a significant reduction in the BG treated groups compared to the control groups with a mean difference of 1.27 mm (95% CI: 0.54 to 1.99 mm; $p = 0.0006$). Eleven trials reported the results of BG on CAL. These results also showed significant gain, with a mean difference of 1.49 mm (95% CI: 0.65 to 2.33 mm; $p = 0.0005$). Heterogeneity was high across all of the included studies in relation to BG composition, particle size, products handling protocols and patient related factors such as smoking and defect severity. Risk of bias was deemed low or uncertain, and certainty of evidence was graded as low due to risks of bias and blinding flaws. The authors concluded that BG may result in meaningful improvements for periodontal regeneration, but acknowledge that the substantial heterogeneity among the trials show a need for additional research in the form of well-designed, standardized, long-term studies.

In a 2024 systematic review and meta-analysis of 20 randomized controlled trials, Motta et al. examined the role and efficacy of bioactive glass compared to other interventions for the treatment of infrabony defects. Included were 376 individuals with 656 teeth in which PD measurements were assessed, and 327 with 558 teeth that assessed CAL measurements and combined intrabony defects, furcation involvement, or both. With regard to PD, the results showed at six months, autogenous cortical bone, BG, and platelet rich fibrin (PRF) resulted in statistically significant improvement

compared to open flap debridement (OFD) alone. For CAL at six months, the effect of BG is reduced and no longer significant. No adverse events were reported for BG. The authors concluded that the use of BG is effective for the treatment of intrabony defects for periodontal disease, but there is no impact on CAL. (Sohrabi et al. 2012, previously cited in this policy was included in this systematic review and meta-analysis).

A 2022 ECRI clinical evidence assessment entitled Bicera Bone Graft Substitute (Wiltrom Corp. Ltd.) for Filling Bone Defects reported on the safety and effectiveness of Bicera compared to bone grafts and other natural or synthetic bone substitutes. Bicera is a biocompatible ceramic composed of hydroxyapatite and beta-tricalcium. Evidence from one nonrandomized comparison study and two small case series is too limited in quantity and quality to determine how well Bicera works compared with autografts, allografts, or other bone graft materials bone fillers. Large well-designed studies are needed.

Naqvi et al. (2017) conducted a randomized controlled trial to compare the clinical effectiveness of the combination of PRF and bioactive glass putty and bioactive glass putty alone as regenerative techniques for intrabony defects. Ten pairs of intrabony defects were surgically treated with PRF and bioactive glass putty (treatment group) on one side or bioactive glass putty alone (control group) on the other side. The primary outcomes included changes in probing depth, attachment level, and bone fill. The clinical parameters were recorded at baseline, three, six and nine months. The results showed the mean probing depth reduction was greater in the test group (3.2 ±2.3 mm) than in the control group (3.15 ±1.06 mm). The mean CAL gain was also greater in the test group (4.1 ±1.73 mm) as compared to the control group (3.15 ±1.06 mm). Furthermore, significantly greater mean bone fill was found in the test group (7.1 ±1.37 mm) as compared to the control group (5.7 ±1.64 mm). The results of this study showed both the groups bioactive glass putty alone and the combination of PRF and bioactive glass putty are effective in the treatment of intrabony defects. The bioactive glass putty appears to be a suitable vehicle to administer biologic substances like PRF and growth factors to induce new bone regeneration.

Bone Morphogenic Protein

There is a paucity of evidence regarding the safety and efficacy of bone morphogenic proteins for periodontal regeneration. Human studies with large numbers of participants and long-term follow-up are lacking and the role of this biomaterial compared to standard grafting procedures for periodontal regeneration cannot be determined.

In a 2024 ECRI clinical evidence assessment on GEM 21S® growth factor-enhanced matrix (Lynch Biologics, LLC) for filling periodontal defects, it was concluded that based on two randomized controlled trials and two small comparison studies that there are too few data to draw conclusions about how GEM 21S's effectiveness compares with that of other treatments for gingival recession and infrabony defects. RCTs that compare GEM 21S with other standard approaches or other growth factor-enhanced matrix products used for periodontal defects are needed.

In a 2023 randomized controlled split mouth clinical trial, Garg et al. assessed the clinical and radiographic outcomes of recombinant human bone morphogenetic protein-2 (rhBMP-2) for the treatment of intraosseous abnormalities after periodontal flap surgery. A total of 14 participants with 28 intraosseous defects were included. The control group had open flap debridement with alloplast, and the treatment group underwent the same procedure with the addition of rhBMP-2. Plaque index (PI), gingival index (GI) probing pocket depth (PPD), clinical attachment level (Cal), and radiographic defect fill were collected at baseline and three, six and nine months. The results showed that PPD, GI and PI showed significant improvement in both groups. At both six and nine months, the control group had a significantly improved distance from the base of the defect to the alveolar crest. When measuring the distance from the cementoenamel junction and the base of the defect, the treatment group also showed improvement at six and nine months. Radiographically, both groups showed bone fill, however the treatment group's defect fill was noticeably better. The authors concluded that treating defects with and without rhBMP-2 both promote periodontal healing. This trial is limited by a small number of participants and further research with larger patient populations are needed to validate these findings.

Medikeri et al. (2019) conducted a systematic review to assess the amount of radiographic bone fill, clinical attachment level (CAL) gain, and reduction in pocket depth (PD) in patients with intrabony defects in periodontitis patients following the use of recombinant human bone morphogenetic protein-2 (rhBMP-2). Studies using rhBMP-2 to treat periodontal intrabony defects of the maxillary or mandibular region for the treatment of intrabony defects (1, 2, or 3-walled) for periodontal regeneration were compared to other surgical treatment utilizing growth factors, alloplastic, allogeneic grafts, and xenografts with follow-up period of at least six months were included. A total of 48 individuals in two studies met the inclusion criteria. The results found that rhBMP-2 showed statistically significant results with respect to radiographic defect resolution, CAL, and PD reduction at nine months compared to open-flap debridement but showed statistically significant results only with respect to radiographic bone fill when compared with platelet-rich fibrin at six months. The authors concluded that rhBMP-2 may provide a promising alternative to traditional grafting procedures therapy that can enhance periodontal regeneration in patients having intrabony defects, however due to limited human studies, no definitive evidence exists to ascertain the effectiveness of rhBMP-2 in the treatment of intrabony defects in periodontal diseases.

In a 2016 systematic review, Kaur et al. reviewed the clinical data currently available on the use of bone morphogenetic proteins (BMPs) in various periodontal applications. BMPs have been shown in preclinical and clinical studies to enhance periodontal regeneration, however, much of the data has been derived from animal studies. The available data on use of rhBMP-2 and 7 in humans is promising in showing an osteoinductive potential in periodontal regeneration, but not conclusive in the predictability and consistency of results. Future research on safety and efficacy, and well-designed studies are needed.

Amniotic Membranes

There is a paucity of evidence regarding the safety and efficacy of human amniotic membranes for periodontal regeneration. Studies with large numbers of participants and long term follow up are lacking, and the role of this biomaterial in periodontal regeneration cannot be determined.

Gulameabasse et al. (2020) performed a systematic review of the clinical applications where chorion membrane (CM) and amnion/chorion membrane (ACM) were used for oral tissue regeneration procedures. Seven clinical applications of CM and ACM in oral and periodontal surgery were identified: gingival recession treatment, intrabony and furcation defect treatment, alveolar ridge preservation, keratinized gum width augmentation around dental implants, maxillary sinus membrane repair, and large bone defect reconstruction. CM and ACM were compared to negative controls (conventional surgeries without membrane) or to the following materials: collagen membranes, dense polytetrafluoroethylene membranes, platelet-rich fibrin membranes, amnion membranes, and to a bone substitute. Several studies support the use of CM and ACM as an efficient alternative to current techniques for periodontal and oral soft tissue regeneration procedures. However, further studies are necessary to increase the level of evidence and to demonstrate their role for bone regeneration.

In a 2019 randomized clinical trial, Temraz et al. compared the clinical and radiographic outcomes of amnion chorion membrane (ACM) with demineralized bone matrix (DBM) in a putty form in management of periodontal intrabony defects. Twenty-two participants with severe chronic periodontitis and intrabony defects were randomly assigned in two equal parallel groups. Each group was treated with open flap debridement (OFD) and ACM or OFD and DBM putty. Plaque index, gingival index, pocket depth (PD), clinical attachment level (CAL) and radiographic measurement of bone defect area (BDA) were recorded at baseline, three and six months postoperatively. Both ACM and DBM putty demonstrated significant improvement in all clinical and radiographic outcomes at six months compared to baseline values. However, no significant difference was observed between the two treatment modalities when compared at different time intervals. Six months postoperatively, ACM showed 3.18 ±0.85 mm, PD reduction and 2.25 ±0.75 mm CAL gain, while DBM putty revealed 3.45 ±1.08 mm PD reduction and 2.73 ±0.85 mm CAL gain. Radiographic assessment showed that mean baseline BDA for ACM group was 10.39 ± 3.86 mm2, which significantly reduced to 5.21 ± 2.38 after 6 months. Mean BDA mm2 in DBM putty group also significantly improved after six months, 5.35 ± 3.63 mm2 when compared to baseline values 9.80 ± 5.77 mm2. Both ACM barrier and DBM putty allograft provided significant improvement in clinical and radiographic outcomes after six months, yet no significant differences were noticed between them. This trial implied that both biomaterials have a potential regenerative capacity in treating periodontal intrabony defects.

Mahajan et al. (2018) conducted a study to clinically compare the efficacy of placental membrane (Amnion) and collagen membrane (Healiguide) for the treatment of gingival recession. Twelve individuals with isolated bilateral gingival recession defects were included in the study, and randomly assigned to two groups. Group I were treated by coronally positioned flap and amnion membrane, and Group II were treated by coronally positioned flap and collagen membrane (Healiguide)™. Clinical parameters, including plaque index (PI), gingival index (GI), gingival recession depth, probing pocket depth, clinical attachment level, and gingival biotype, were recorded before surgery at baseline and then reevaluated at three and six months postoperatively. The results showed statistically no significant difference ($p > 0.05$) in l PI improvement, GI, and probing pocket depth in both groups. Significant reduction in gingival recession defects and gain in clinical attachment level was observed in both groups. Intergroup comparison of gingival recession defects and clinical attachment level yielded nonsignificant differences. However, a statistically significant increase ($p < 0.05$) in gingival tissue thickness was observed in Group II as compared to Group I. The authors concluded that both membranes are equally efficacious in the treatment of gingival recession, with more gingival tissue thickness (gingival biotype) enhancement observed in sites treated with collagen membrane. This study is limited by a small number of participants and a lack of long-term follow-up.

In a 2018 comprehensive systematic review, Fénelon et al. analyzed 17 articles including five areas of potential clinical application for human amniotic membrane (hAM): periodontal surgery, cleft palate and tumor reconstruction, prosthodontics, and peri-implant surgery. Overall, periodontal surgery was the only discipline to assess the efficacy of hAM with randomized clinical trials. The wide variability of preservation methods of hAM and the lack of objective measurements were observed in this study. There is weak clinical evidence demonstrating the benefit of hAM in oral surgery compared to standard surgery. Due to its biological and mechanical properties, hAM seems to be a promising

treatment for wound healing in various areas of oral reconstruction. However, further randomized clinical trials are needed to confirm these preliminary results.

Other Biological Materials

Novello et al. (2020) conducted a systematic review and meta-analysis to evaluate the potential efficacy of mesenchymal stem cells (MSCs) in periodontal regeneration in humans on clinical attachment level (CAL), probing depth (PD), and gingival recession (GR). Double-blind randomized controlled trials (RCTs) evaluating MSCs in periodontal regeneration were included in a meta-analysis if they compared administration of MSCs vs application of stem cell-free therapy in the control group, in healthy patients with periodontal defects, with a minimum of three months of follow-up. Only two small RCTs at high risk of bias, with a total of 59 individuals and 70 periodontal defects, were included in the meta-analysis. The results showed a small difference for CAL but not for PD or GR at three months. The authors concluded that low quality evidence indicates MSC based therapy may have a small impact on periodontal regeneration, but high-quality RCTs with larger numbers of participants and longer follow up are needed before any clinical use can be recommended.

Al Sarhan et al. (2019) performed a systematic review and meta-analysis of four randomized controlled trials to understand the efficacy of xenogeneic collagen matrix (CMX) compared to connective tissue grafts for the treatment of multiple, adjacent gingival Miller Class I and II recessions. The results showed that while recession depth, complete root coverage and mean root coverage were significantly lower with CMX, there was no statistically significant difference in the recession width. CMX also showed significantly lower probing depth, however there was no significant difference in clinical attachment level and keratinized tissue width observed. The average percentage of mean root coverage for CMX and CTG was 65.8% and 84.5% respectively, indicating that CMX was not as effective as CTG in multiple adjacent areas of recession. Although CMX provided acceptable clinical outcomes, heterogeneity among the included studies show that firm conclusions cannot be drawn about using it as an alternative to CTG for root coverage, and further research is needed (Atieh et al., 2016, previously cited in this policy was included in this systematic review and meta-analysis).

Chambone et al. (2018) evaluated other root coverage procedures used for treating localized and multiple recession defects. Forty-five randomized controlled trials (RCTs) of at least six months duration, that treated Millers Class I or II ≥ 3mm treated by root coverage periodontal plastic surgery procedures (RCPPS) were selected. The results showed there is insufficient evidence showing a reduction in gingival recession when using acellular dermal matrix grafts (ADMG) + coronally advanced flap (CAF) and subepithelial connective tissue graft (SCTG) + CAF or between enamel matrix protein (EMP) + CAF and SCTG + CAF. For clinical attachment levels, there was insufficient evidence of a difference between ADMG + CAF and SCTG + CAF, or between EMP + CAF and SCTG + CAF. Greater gains in the keratinized tissue were found for SCTG + CAF when compared to EMP + CAF and SCTG + CAF. There was insufficient evidence of a difference in keratinized tissue gain between ADMG + CAF and SCTG + CAF. The authors concluded that the available evidence base indicates that in cases where both root coverage and gain in the width of keratinized tissue are expected, the use of subepithelial connective tissue grafts shows a slight improvement in outcome, and low-quality evidence suggesting that acellular dermal matrix grafts may be the soft tissue substitute that may provide the most similar outcomes to those achieved by subepithelial connective tissue grafts. Further RCTs are necessary to identify possible factors associated with the prognosis of each RCPPS procedure.

McGuire et al. (2014) conducted a study to compare the five-year outcomes of a previously reported split-mouth, randomized controlled trial (McGuire et al., 2009). In that study, Miller Class II gingival recession defects were treated with either a connective tissue graft (CTG) (control) or recombinant human platelet-derived growth factor-BB + β-tricalcium phosphate (test), both in combination with a coronally advanced flap (CAF). Twenty of the original 30 patients were available for follow-up five years after the original surgery. Outcomes examined were recession depth, probing depth, clinical attachment level (CAL), height of keratinized tissue (wKT), and percentage of root coverage. At five years, all parameters for both treatment protocols showed statistically significant improvements over baseline. The primary outcome parameter, change in recession depth at five years, demonstrated statistically significant improvements in recession over baseline, although intergroup comparisons favored the control group at both six months and five years. At five years, intergroup comparisons also favored the test group for percentage root coverage and change in wKT, whereas no statistically significant intergroup differences were seen for 100% root coverage and changes to CAL. The authors concluded that treatment with either test or control treatments for Miller Class II recession defects appear to lead to stable, clinically effective results, although CTG + CAF resulted in greater reductions in recession, greater percentage of root coverage, and increased wKT.

Mucogingival Defects

In a 2021 systematic review and meta-analysis, Meza-Mauricio et al. aimed to compare the clinical effects of enamel matrix derivative (EMD) when used with coronally advanced flap (CAF), or CAF + connective tissue graft (CTG) when compared with CAF alone or CAF + CTG for the treatment of Miller class I and II gingival recessions (GR) in maxillary

teeth. Outcomes measured were reduction in amount of gingival recession (GR), gain in keratinized tissue width (KTW), and gain in clinical attachment level (CAL). Nine RCT's were identified and comprised 336 gingival recessions. The meta-analysis showed a statistically significant reduction in GR and CAL in CAF + EMD procedures, as well as CAF + CTG + EMD. The difference in KTW gain was not statistically significant in either group. The authors concluded that the results of this SR and meta-analysis provide moderate certainty evidence in favor of using EMD in addition to CAF and/or CTG surgeries to improve root coverage, but the differences in KTW gain were not statistically significant in both comparison groups. The studies analyzed did not show results beyond six-12 months.

Mancini et al. (2021) conducted a systematic review and meta-analysis to assess the efficacy of leukocyte-platelet-rich fibrin (L-PRF) in addition to coronally advanced flap surgery for treating single and multiple gingival recessions (GRs) compared to the CAF alone, and to the adjunct of a connective tissue graft (CTG). Outcomes measured included mean root coverage (mRC), recession reduction, keratinized tissue width gain (KTW), gingival thickness (GT) gain, and patient reported outcomes (PROms) such as pain perception and sensitivity reduction. Fourteen randomized controlled trials with a total of 275 individuals with 611 surgical sites were included. The results from the SR showed that PRF may provide superior mRC, KTW gain, GT gain and healing score compared to CAF alone, however the meta-analysis confirmed statistically significantly better results for CAF + L-PRF over CAF alone for GT and CAL gain and mRC only. When compared to CTG for single gingival recessions, only the GT gain was statistically significant. Patient reported outcomes were better for L-PRF compared to CTG. This may be due to the fact that CTG requires a second surgical site for the harvesting, and the palatal wound that can also have complications during healing, as well as accelerated wound healing promoted by the release of growth factor from L-PRF. The authors acknowledge many of these studies have a moderate or high risk of bias, and moderate/large heterogeneity. Additionally, no studies reported more than 12 months follow up, so the long-term results are not known. Other limitations include non-standardized spin protocols and handling of materials, and the inclusion of patients who smoke which can affect outcomes. The authors recommend future research reduce risks of bias and standardize protocols and that CTG remains the gold standard for treating gingival recession.

In a 2020 systematic review and meta-analysis, Miron et al. (included in Mancini systematic review and meta- analysis above) compared the results of the use of platelet rich fibrin (PRF) with other common procedures in the treatment of Miller Class I or II gingival recessions including flap surgeries, connective tissue grafts, and the use of enamel matrix derivative, amnion membrane to enhance tissue regeneration. The results showed, when compared to coronally advanced flap surgery alone, when PRF was added, relative root coverage and clinical attachment levels had a statistically significant increases, with no change in keratinized mucosa width or probing depth. The authors concluded that the use of PRF in conjunction with flap surgery improves root coverage and clinical attachment levels and may be beneficial in cases in which adequate keratinized mucosal width is present. Connective tissue grafting may be preferred over PRF when this is limited.

Discepoli et al. (2019) conducted a systematic review and meta-analysis to evaluate if enamel matrix derivatives are able to improve the quality of keratinized gingival tissue around natural teeth in patients with recession defects following periodontal surgical procedures. Twelve RCTs that included medium-low quality evidence evaluating root coverage procedures in combination with EMD with at least 10 individuals, and a minimum duration of six months, were included. In total 639 recessions were treated (334 tests and 305 control). The recessions defects were classified according to the classification of Miller (Class I, II, III, IV). Only one trial included Miller Class III recessions (seven in total). Enamel matrix derivatives were applied in conjunction with Coronally Advanced Flap (CAF), Coronally Advanced Flap + Sub Epithelial Connective Tissue Graft (CAF + CTG), Semilunar Flap (SF). For the group CAF vs CAF + EMD the mean difference between the keratinized tissue gain in the two procedures was 0.40 mm; for the comparison CAF + CTG + EMD vs. CAF + CTG the mean difference between the two groups resulted in 0.06 mm. The authors concluded that the application of Enamel Matrix Derivatives to surgical procedures aimed to cover gingival recessions does not add robust clinical benefit to conventional surgical procedures alone.

França-Grohmann et al. (2018) completed a clinical trial to evaluate the treatment of gingival recessions by semilunar coronally positioned flap plus enamel matrix derivative (SCPF + EMD). Thirty individuals with class I localized gingival recession were included. They were randomly allocated in two groups: SCPF + EMD and SCPF. Recession height (RH), recession width (RW), width of keratinized tissue (WKT), thickness of keratinized tissue (TKT), probing depth (PD), and clinical attachment level (CAL) were measured at baseline, six and 12-months post-surgery. Patient/professional evaluation of esthetics and root sensitivity was also performed. The result showed that after 12 months, mean root coverage was 1.98 ±0.33 mm for SCPF + EMD and 1.85 ±0.41 mm for SCPF (the esthetic evaluation by the patient showed preference for SCPF + EMD). According to the professional evaluation (QCE), the use of EMD decreases the appearance of postoperative scar tissue line. There was a significant reduction in root hypersensitivity with no further complaints by the patients. The results showed that the addition of EMD provides significantly better esthetics to SCPF, according to patient and professional assessments. SCPF + EMD are effective but not superior to SCPF for root coverage, after 12 months.

Alexiou et al (2017) conducted a study to compare the clinical efficiency of enamel matrix derivative (EMD) placed under a coronally advanced flap (CAF; test group), to a connective tissue graft (CTG) placed under a CAF (control group), in patients with multiple recession defects. Twelve individuals with multiple Miller's Class I or II gingival recessions in contralateral quadrants of the maxilla were selected. The primary outcome variable was the change in depth of the buccal recession (REC) at six months after surgery. The secondary outcome parameters included the clinical attachment level (CAL), the probing pocket depth (PPD), and the width of keratinized gingiva (WKT) apical to the recession. Recession defects were randomly divided to the test or control group by using a computer-generated randomization list. The results showed no statistically significant differences between test and control groups in regards with the depth of buccal recession with a mean REC of 1.82 mm (CTG) and 1.72 mm (EMD) respectively. Similarly, the mean PPD value was 1.3 mm for both groups, while the respective value for CAL was 1.7 mm (EMD) and 1.8 mm (CTG). Statistically significant differences were observed only for the WKT, which were 3.0 mm and 3.6 mm for the test and control groups respectively. The authors concluded that the use of EMD in conjunction with a CAF resulted in similar results as compared to the CTG plus CAF.

Moraschini et al. (2016- included in 2021 Mancini systematic review and meta- analysis above) conducted a systematic review and meta- analysis to evaluate the effects of platelet-rich fibrin (PRF) membranes on the outcomes of clinical treatments in individuals with gingival recession. The eligibility criteria comprised randomized controlled trials (RCTs) and prospective controlled trials with follow-up periods of ≥ six months that compared the performance of PRF to other biomaterials in the treatment of Miller Class I or II gingival recessions. Six RCTs and one prospective clinical trial are included in this review. The estimates of the intervention effects were expressed as the mean differences in percentages or millimeters. The results showed root coverage (RC), and clinical attachment level (CAL) did not differ significantly between the analyzed subgroups, and the keratinized mucosa width (KMW) gain was significantly greater in the subgroup that was treated with connective tissue grafts. The author’s conclusion suggests that the use of PRF membranes did not improve the RC, KMW, or CAL of Miller Class I and II gingival recessions compared with the other treatment modalities.

Keceli et al. (2016- included in 2021 Mancini systematic review and meta- analysis above) conducted a randomized, parallel group-controlled trial to evaluate the effectiveness of coronally advanced flap (CAF) + connective tissue graft (CTG) + PRF in Miller Class I and II recession treatment compared to CAF + CTG. Forty participants were treated surgically with either CAF + CTG + PRF (test group) or CAF + CTG (control group). Clinical parameters of plaque index, gingival index, vertical recession (VR), probing depth, clinical attachment level (CAL), keratinized tissue width (KTW), horizontal recession (HR), mucogingival junction localization, and tissue thickness (TT) were recorded at baseline and three and six months after surgery. Root coverage (RC), complete RC (CRC), attachment gain (AG), and keratinized tissue change (KTC) were also calculated. All individuals completed the entire study period. At baseline, mean VR, HR, CAL, KTW, and TT values were similar. In both groups, all parameters showed significant improvement after treatment except TT. No intergroup difference was observed at six months after surgery. The amount of RC and AG, but not KTC and CRC, was higher in the PRF-applied group. According to the results, the addition of PRF did not further develop the outcomes of CAF + CTG treatment except increasing the TT. However, this single trial is not sufficient to advocate the true clinical effect of PRF on recession treatment with CAF + CTG, and additional trials are needed.

Periradicular Surgery

Yahata et al. (2023) conducted a multicenter randomized clinical trial to evaluate the effects of concentrated growth factor (CGF), a new-generation autologous platelet concentrate on bone healing in combination with apical microsurgery. Twenty-four participants undergoing apical microsurgery were randomly assigned 1:1, with the treatment group receiving CGF following root end filling, and the control group microsurgery only. The results showed no significant differences in success between the two groups; however, lesion volume reduction was reduced in the treatment group. The authors concluded that CGF is a promising treatment option to stimulate healing following apical microsurgery. Further well-designed research is needed to validate these findings.

Dhiman et al. (2015) conducted a prospective randomized controlled trial to evaluate the healing outcomes of platelet-rich fibrin (PRF) in periapical surgeries involving apicomarginal defects, and to compare these results with surgeries not using any guided tissue regeneration techniques. Thirty individuals with suppurative chronic apical periodontitis and apicomarginal communication were randomly assigned to either the PRF or the control group. Clinical and radiographic parameters including pocket depth (PD), clinical attachment level, gingival marginal position, size of periapical lesion, and percentage reduction of the periapical radiolucency were recorded at baseline and at an interval of three months for a period of 12 months. The results showed an overall success rate of 83.33%, with a success rate of 86.66% (13 of 15 teeth) for PRF group and 80% (12 of 15 teeth) for control group. Both the groups exhibited a significant reduction in PD, clinical attachment level, gingival marginal position, and size of periapical lesion at 12-month period. No significant differences were observed between the groups for these parameters except PD, which showed a statistically significant reduction in the PRF group. The authors concluded that the adjunctive use of regenerative techniques may not promote healing of apicomarginal defects of endodontic origin.

Clinical Practice Guidelines

American Academy of Periodontology (AAP)

In a 2022 best evidence consensus statement (Avila-Ortiz et al.), the APP makes the following recommendations regarding the use of biologics in clinical practice:

- Root Coverage and Gingival Augmentation Therapy
  - Autogenous subepithelial connective tissue graft (SCTG) remains the gold standard in bilaminar root coverage procedures.
  - The adjunctive use of biologics enhances initial postoperative healing after root coverage and gingival augmentation therapy.
- Infrabony Defects
  - Biologics are effective for the treatment of periodontal infrabony defects and show added benefits when combined with biocompatible/biodegradable scaffolds (e.g., xenografts, allografts).
    - Recombinant human platelet-derived growth factor BB (rhPDGF-BB) and platelet-rich fibrin (PRF) are associated with superior clinical and radiographic outcomes compared to enamel matrix derivative (EMD) and platelet-rich plasma (PRP).
    - Xenogeneic bone grafts with rhPDGF-BB or PRF are the best combination therapy to maintain the stability of the gingival margin following regenerative treatment of periodontal infrabony defects.
- Alveolar Ridge Preservation (ARP)/Alveolar Ridge Reconstruction (ARR) and Implant Site Development (ISD).
  - There is limited evidence to support that the use of biologics either as a monotherapy or in combination with graft materials results in superior clinical and radiographic outcomes when compared with conventional interventions.

Based on this limited evidence, the AAP states that clinicians should consider the use of biologics for the following:

- Patients with the potential of compromised wound healing, or a shortened would healing time is necessary.
- When defects present with lower predictability.
- When ideal soft tissue healing is desired (esthetic zone).
- Patients with a history of therapy failure or unsatisfactory results after conventional treatment.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Tissue grafting products from donated human skin are regulated by the FDA as human tissue for transplantation, as are products used for bone grafts and they are processed and marketed in accordance with the FDA's requirements for banked human tissue (21 CFR, Part 1270, and Part 1271) and Standards for Tissue Banking of the American Association of Tissue Banks (AATB). Information is available at: http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm. (Accessed February 23, 2026)

There are a number of bioactive glass regenerative products cleared by the FDA under the 510(k) pathway. Refer to the following website and search using product code LYC: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed February 23, 2026,)

In 1996 Emdogain™ (Straumann) received Premarket Approval. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P930021. (Accessed February 23, 2026)

There are several devices cleared for marketing by FDA for point-of-care preparation of platelet-rich plasma (PRP) from a sample of a patient's blood (see listings under product code JQC for additional devices). Refer to the following website for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed February 23, 2026)

In April 2003, the FDA approved the use of the GPS™ Platelet Separation Kit. The GPS™ separation kit aids separation of the patient's own blood components by density through the use of the GPS™-Thermo International Equipment Company (IEC) centrifuge. The GPS separation kit permits platelet rich plasma to be rapidly prepared from a small volume of the patient's blood that is drawn at the time of treatment. The GPS Platelet Separation Kit is designed for use in the clinical laboratory or intraoperatively at point of care, for the safe and effective preparation of platelet poor plasma and platelet concentrate from a small sample (50-60 ml) of whole blood. Refer to the following website for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K030555. (Accessed February 23, 2026)

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Policy History/Revision Information

Date	Summary of Changes
05/01/2026	**Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version DCP047.04

Instructions for Use

This Dental Clinical Policy provides assistance in interpreting UnitedHealthcare standard and Medicare Advantage dental plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard dental plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Dental Clinical Policy is provided for informational purposes. It does not constitute medical advice.