

# Biologic Materials for Soft and Hard Tissue Regeneration

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[Instructions for Use](#)

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## 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 proteins, 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.

## Definitions

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

**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)

**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

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## Description of Services

Regenerative materials seek to facilitate the regeneration of bone and soft tissue lost due to disease, injury, or defect. These materials are typically used in combination with each other, or surgical procedures, which can make definitive determination of efficacy challenging. The development of various regenerative technologies in medicine and dentistry is rapidly advancing and the technologies outlined in this policy are not all inclusive.

## Clinical Evidence

### Autologous Platelet Concentrates

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 patients 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 6mm with the intrabony component having a minimum of 4mm. Clinical parameters measured at baseline and 6 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 after 6 months, the mean PD decreased 4.47mm 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 1.26mm, 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 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%  $\pm$ 7.57%, which was statistically significant compared with 21.6%  $\pm$ 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  $3.37 \pm 1.62$  mm in the control group and  $4.13 \pm 1.59$  mm in the test group. There was a significant difference in mean change in CAL in the control group ( $5.42 \pm 1.99$ ) and the test group ( $5.99 \pm 1.77$ ). Mean change in GI was  $1.89 \pm 0.32$  and  $1.68 \pm 0.58$  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  $1.06 \pm 0.81$  and  $1.0 \pm 0.97$  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  $\beta$ -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 patients were available for tooth survival analysis showing 81.8% of test and 86.4% of control teeth still in situ. Based on the 15 patients still available for split-mouth analysis, median CAL was 10.0 mm in test and 12.0 mm in control sites at baseline. After 1 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 chronic periodontitis patients 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, 3-, 6-, and 9-months post-surgery, respectively. Both PRF and ABG sites produced a significant improvement from baseline to 9 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 9 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  $\beta$ -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)  $\geq$  2.7 mm and linear bone growth (LBG)  $\geq$  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 it should be used in combination with bone grafts.

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 (MIST), or flapless approach for the treatment of periodontal probing depths greater than 5mm. 7 RCTs and 12 case series were included. The showed that EMD with MIST 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 MIST 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 without EMD, and more research is needed to substantiate these findings.

In a prospective 2-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)  $\geq$  6 mm, at least one interproximal intrabony defect  $\geq$  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 1 and 2 years. Twenty-two patients completed the 2-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 it's single arm design.

Matarraso et al. (2015) conducted a systematic review and meta-analysis was to assess the clinical efficacy of regenerative periodontal surgery of intrabony defects using a combination of enamel matrix derivative (EMD) and bone graft compared with that of EMD alone. The primary outcome was gain of clinical attachment (CAL). Weighted means and forest plots were calculated for CAL gain, probing depth (PD), and gingival recession (REC). Twelve studies reporting on 434 patients and 548 intrabony defects were selected for the analysis. Mean CAL gain amounted to  $3.76 \pm 1.07$  mm (median 3.63 95 % CI 3.51-3.75) following treatment with a combination of EMD and bone graft and to  $3.32 \pm 1.04$  mm (median 3.40; 95 % CI 3.28-3.52) following treatment with EMD alone. Mean PD reduction measured  $4.22 \pm 1.20$  mm (median 4.10; 95 % CI 3.96-4.24) at sites treated with EMD and bone graft and yielded  $4.12 \pm 1.07$  mm (median 4.00; 95 % CI 3.88-4.12) at sites treated with EMD alone. Mean REC increase amounted to  $0.76 \pm 0.42$  mm (median 0.63; 95 % CI 0.58-0.68) at sites treated with EMD and bone graft and to  $0.91 \pm 0.26$  mm (median 0.90; 95 % CI 0.87-0.93) at sites treated with EMD alone. The authors concluded results indicate that

the combination of EMD and bone grafts may result in additional clinical improvements in terms of CAL gain and PD reduction compared with those obtained with EMD alone.

Koop et al. (2012) conducted a systematic review to give an updated answer to the question of whether the additional use of EMD in periodontal therapy is more effective compared with a control or other regenerative procedures. The use of EMD in treatment of intrabony defects, furcations, and recessions was evaluated. 27 randomized controlled trials (20 for intrabony defects, one for furcation, and six for recession) with  $\geq 1$  year of follow-up were included. The primary outcome variable for intrabony defects was the change in clinical attachment level (CAL), for furcations the change in horizontal furcation depth, and for recession complete root coverage. The primary outcome variable for intrabony defects was the change in clinical attachment level (CAL), for furcations the change in horizontal furcation depth, and for recession complete root coverage. The results showed the treatment of intrabony defects with EMD showed a significant additional gain in CAL of 1.30 mm compared with open-flap debridement, root conditioning, or placebo, but no significant difference compared with resorbable membranes was shown. The use of EMD in combination with a coronally advanced flap compared with a coronally advanced flap alone showed significantly more complete root coverage, but compared with a connective tissue graft, the result was not significantly different. The use of EMD in furcations ( $2.6 \pm 1.8$  mm) gave significantly more improvement in horizontal defect depth compared with resorbable membranes ( $1.9 \pm 1.4$  mm) as shown in one study. The authors concluded the following: for intrabony defects, the use of EMD is superior to control treatments but as effective as resorbable membranes; the additional use of EMD with a coronally advanced flap for recession coverage will give superior results compared with a control but is as effective as a connective tissue graft; and the use of EMD in furcations will give more reduction in horizontal furcation defect depth compared with resorbable membranes.

## Bioactive Glass

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 in humans. Ten pairs of intrabony defects were surgically treated with PRF and bioactive glass putty (Test group) on one side or bioactive glass putty alone (Control group) on other side. The primary outcomes of the study included changes in probing depth; attachment level and bone fill of osseous defect. The clinical parameters were recorded at baseline, 3, 6, and 9 months. Radiographic assessment was done using standardized intraoral periapical radiographs. Differences between baseline and postoperative measurements between the control and test groups were calculated using independent t-test. Comparisons were made within each group between baseline, 3 months, 6 months and 9 months using the ANOVA test followed by Bonferroni test. The mean probing depth reduction was greater in the test group (bioactive glass putty and PRF) i.e., ( $3.2 \pm 2.3$  mm) than in the control group (bioactive glass putty alone) i.e., ( $3.15 \pm 1.06$  mm). The mean CAL gain was also greater in the test group ( $4.1 \pm 1.73$  mm) as compared to the control group ( $3.15 \pm 1.06$  mm), ( $p$ -value  $< 0.95$ ). Furthermore, significantly greater mean bone fill was found in the test group ( $7.1 \pm 1.37$  mm) as compared to the control group ( $5.7 \pm 1.64$  mm), ( $p$ -value  $< 0.043$ ). The results of this study showed both the groups bioactive glass putty alone (Control Group) and the combination of PRF and bioactive glass putty (Test Group) 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 the new bone regeneration.

Sohrabi et al. (2012) conducted a meta-analysis of randomized controlled clinical trials to evaluate bioactive glass in the treatment of intrabony and furcation defects. Criteria included publication in English, follow-up duration of  $\geq 6$  months, baseline and follow-up measures of probing depth (PD) and clinical attachment levels (CAL) with 95% confidence intervals (CIs), and an appropriate control arm. Twenty-five citations were identified, 15 of which were included in the final analysis. Pooled analyses showed that BG was superior to control for both measures. CAL heterogeneity appeared secondary to active controls versus open flap debridement (OFD) alone and to defect-type modifying BG treatment success. Per subgroup analyses, the benefit of BG over control treatment was highly significant only in studies comparing BG to OFD. The authors concluded that treatment of intrabony defects with BG imparts a significant improvement in both PD and CAL compared to both active controls and OFD.

## Bone Morphogenic Proteins

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 was compared to other surgical treatment utilizing growth factors, alloplastic, allogeneic grafts, and xenografts with follow-up period of at least 6 months were included. A total of 48 subjects in 2 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 9 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 6 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. BMPs have demonstrated beyond doubt their role as a superior alternative of autogenous bone graft. However, much of the data in BMP research has been derived from animal studies which are important as far as providing base line data for further clinical studies. The available data on use of rhBMP-2 and 7 in humans are promising in showing an osteoinductive potential in periodontal regeneration, but not conclusive in the predictability and consistency results to allow clinical use at this stage, other than in well-designed clinical trials. Since many other factors including smoking, age, steroid use, malnutrition, and disease severity play a role in determining the physiology of periodontal regeneration in humans, the true efficacy and safety of these agents for different scenarios must be established in carefully designed prospective randomized clinical trials before they are approved for use. Research should continue to focus on improving the use of BMPs in the current clinical applications.

Sasikumar et al. (2012) conducted a literature review regarding the application of bone morphogenetic proteins to periodontal and peri-implant tissue regeneration. Several studies showed significant regeneration of the periodontal tissues and it is important to understand the biologic processes of periodontal wound healing and the effects of these biologic processes on BMP activity. Further studies are needed for the development of delivery systems that have mechanical and surgical properties appropriate for controlled release of bone morphogenetic proteins and identifying optimal condition for the use of BMPs for periodontal regeneration.

## Amniotic Membranes

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, 3 and 6 months postoperatively. Both ACM and DBM putty demonstrated significant improvement in all clinical and radiographic outcomes at 6 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  $3.18 \pm 0.85$  mm PD reduction and  $2.25 \pm 0.75$  mm CAL gain, while DBM putty revealed  $3.45 \pm 1.08$  mm PD reduction and  $2.73 \pm 0.85$  mm CAL gain. Radiographic assessment showed that mean baseline BDA for ACM group was  $10.39 \pm 3.86$  mm<sup>2</sup>, which significantly reduced to  $5.21 \pm 2.38$  after 6 months. Mean BDA mm<sup>2</sup> in DBM putty group also significantly improved after 6 months,  $5.35 \pm 3.63$  mm<sup>2</sup> when compared to baseline values  $9.80 \pm 5.77$  mm<sup>2</sup>. Both ACM barrier and DBM putty allograft provided significant improvement in clinical and radiographic outcomes after 6 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 patients having isolated bilateral gingival recession defects were included in the study and were divided into two groups randomly. Group I were treated by coronally positioned

flap and amnion membrane, and Group II were treated by coronally positioned flap and collagen membrane (Healiguide)<sup>™</sup>. Clinical parameters, including dental 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 3 and 6 months postoperatively. The results showed statistically no significant difference ( $p > 0.05$ ) in dental PI improvement, GI and probing pocket depth for both groups. Significant reduction in gingival recession defects and gain in clinical attachment level was observed in both the 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.

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 convincingly the benefit of hAM in oral surgery compared to standard surgery. Several studies now suggest the interest of hAM for periodontal tissue repair. 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 patients 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 are needed before any clinical use can be recommended.

AlSarhan et al. (2019) performed a systematic review and meta-analysis of 4 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 make recommending firm conclusions cannot be drawn about using it as an alternative to CTG for root coverage, and further research is needed.

Chambone et al. (2018) also evaluated other root coverage procedures used for treating localized and multiple recession defects. Forty-five randomized controlled trials (RCTs) of at least 6 months duration, that treated Millers Class I or II  $\geq 3$ mm 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.



Atieh et al (2016- included in AlSarhan et al above). Several clinical trials describe the effectiveness of xenogeneic collagen matrix (XCM) as an alternative option to surgical mucogingival procedures for the treatment of marginal tissue recession and augmentation of insufficient zones of keratinized tissue (KT). The aim of this systematic review and meta-analysis was to evaluate the clinical and patient-centered outcomes of XCM compared to other mucogingival procedures. Applying guidelines of the Preferred Reporting Items for Systematic Reviews and Meta analyses statement, randomized controlled trials were searched for in electronic databases and complemented by hand searching. The risk of bias was assessed using the Cochrane Collaboration's Risk of Bias tool and data were analyzed using statistical software. A total of 645 studies were identified, of which, six trials were included with 487 mucogingival defects in 170 participants. Overall meta-analysis showed that connective tissue graft (CTG) in conjunction with the coronally advanced flap (CAF) had a significantly higher percentage of complete/mean root coverage and mean recession reduction than XCM. Insufficient evidence was found to determine any significant differences in width of KT between XCM and CTG. The XCM had a significantly higher mean root coverage, recession reduction and gain in KT compared to CAF alone. No significant differences in patient's aesthetic satisfaction were found between XCM and CTG, except for postoperative morbidity in favor of XCM. Operating time was significantly reduced with the use of XCM compared with CTG but not with CAF alone. There is no evidence to demonstrate the effectiveness of XCM in achieving greater root coverage, recession reduction and gain in KT compared to CTG plus CAF. Superior short-term results in treating root coverage compared with CAF alone are possible. The authors concluded that there is limited evidence that XCM may improve aesthetic satisfaction, reduce postoperative morbidity and shorten the operating time. Further long-term randomized controlled trials are required to endorse the advantages of XCM.

McGuire et al. (2014) conducted a study to compare the clinical parameters 5 years post operatively, of a previously reported split-mouth, randomized controlled trial. 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 +  $\beta$ -tricalcium phosphate (test), both in combination with a coronally advanced flap (CAF). Twenty of the original 30 patients were available for follow-up 5 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. Group results at 6 months and 5 years were compared with original baseline values. At 5 years, all parameters for both treatment protocols showed statistically significant improvements over baseline. The primary outcome parameter, change in recession depth at 5 years, demonstrated statistically significant improvements in recession over baseline, although intergroup comparisons favored the control group at both 6 months and 5 years. At 5 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.

Rosetti et al. (2013-reviewed in Cochrane above) completed a 30-month follow-up clinical trial to assess the long-term stability of the root coverage of subepithelial connective tissue graft (SCTG) and guided tissue regeneration combined with demineralized freeze-dried bone allograft (GTR-DFDBA). Twenty-four defects were treated in 12 patients who presented with canine or pre-molar Miller class I and/or II bilateral gingival recessions. GTR-DFDBA and SCTG treatments were performed in a randomized selection in a split-mouth design. The following clinical parameters were assessed at 6-, 18- and 30-months post-surgery: root coverage (RC), gingival recession (GR), probing depth (PD), clinical attachment level (CAL) and keratinized tissue width (KTW). The authors concluded that there were not significant differences in RC, GR, PD and CAL for both procedures, but the increase in KTW was significantly higher in the SCTG group than in the GTR-DFDBA group. The authors concluded that both procedures provide adequate root coverage over the long term, with the connective tissue graft procedure promoting a more favorable increase in keratinized tissue.

Moslemi et al. (2011) conducted a randomized clinical trial to compare the long-term results of subepithelial connective tissue graft (SCTG) versus acellular dermal matrix allograft (ADMA) in treatment of gingival recessions. There were 16 patients with bilateral Miller Class I/II gingival recessions selected. One side was treated with SCTG and the other side with ADMA. Clinical parameters of complete root coverage (CRC), reduction of recession depth (RD) and reduction of recession width (RW) were measured at baseline, 6 months, and at 5 years post-surgery. At 5 years, significant relapses were detected in CRC and reduction of RD and RW in both groups, with no statistically significant differences. Compared with baseline, the gingival width (GW) did not increase in ADMA-treated sites. The five-year results of SCTG and ADMA were similar in terms of CRC and reduction of RD and RW. (Both techniques showed a significant relapse associated with returning to horizontal toothbrushing habit). Increase of GW was stable in SCTG-treated sites but reached to pre-surgical values in ADMA-treated cases.

## 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 6-12 months.

Mancini et al. (2021) conducted a systematic review and meta-analysis with the aim of investigating 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 (PROs) such as pain perception and sensitivity reduction. Fourteen randomized controlled trials with a total of 275 patients 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 subjects 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 (7 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 patients 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, 6- 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  $1.98 \pm 0.33$  mm for SCPF + EMD and  $1.85 \pm 0.41$  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 patients 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 6 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 observed 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 patients with gingival recession. The eligibility criteria comprised randomized controlled trials (RCTs) and prospective controlled trials with follow-up periods of  $\geq 6$  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) Platelet-rich fibrin (PRF) is an autologous preparation that has encouraging effects in healing and regeneration. The aim of this randomized, parallel group-controlled trial was 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 patients 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 3 and 6 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 6 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

Deng et al (2016) conducted a systematic review and meta-analysis to evaluate the effect of regeneration techniques (RTs) on the outcome of periapical surgery with different protocols for different lesion types. Clinical evidence indicates that most of the repair or regeneration of the bone defect takes place during the first year after the procedure and that very few changes occur later, therefore this study only extracted data collected at 1 year after periapical surgery. PubMed, the Cochrane Library, and Embase were searched through December 30, 2014. Studies that met the inclusion criteria were systematically evaluated, and a meta-analysis was performed. Eight randomized controlled trials met the inclusion criteria. A significantly better outcome was found in the combination group (membranes plus bone replacement analogues) and bone replacement analogue-only group whereas no significant beneficial effect was found in the membrane-only group. The results of this meta-analysis showed that use of RTs in periapical surgery yielded better outcomes than traditional periapical surgery, which was inconsistent with a

previous meta-analysis (Tsesis et al 2011). The use of RTs favorably affected the outcome of periapical through-and-through lesions and large lesions ( $\geq 10$  mm). There was no significant benefit of using RTs for 4-wall lesions. Both the isolated use of bone replacement analogues and the combination of membranes and bone replacement analogues can improve the outcome of periapical surgery, whereas using membranes alone does not have significantly favorable effects. The use of RTs for through-and-through and large lesions should be recommended.

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 patients 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 3 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 2 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.

von Arx et al. (2011) conducted a literature review of the current clinical and experimental studies to evaluate the outcome of regenerative techniques (RT) in conjunction with apical surgery with regard to type of periapical lesions. A literature search with PubMed and Cochrane databases was conducted in April 2010 and a total of 11 clinical and 10 experimental studies fulfilled the inclusion criteria and included the following: The assessed outcome had to be periapical healing based on radiographic and clinical parameters for clinical studies, or periapical healing based on radiographic, histologic or histomorphometric parameters for experimental studies. The studies had to have a minimum of 10 teeth with a minimum follow-up period of 6 months for clinical studies and of 8 weeks for experimental studies. One clinical and one experimental study of those included differentiated between different types of lesions. The current literature studies do not contain strong evidence demonstrating the need for more research. However, based on the current literature, the authors concluded that the reviewed clinical and experimental studies show no or only minimal benefits of using RT in apical surgery for the treatment of osseous defects limited to the periapical area, (as unimpeded new bone formation can take place) and that the use of RT in apical surgery for treatment of lesions limited to the apical area is not warranted. None of the tested regenerative techniques or materials resulted in a better outcome when comparing test and control sites, except for Expanded Polytetrafluoroethylene Membranes (ePTFE) in two studies, however this material has also been associated with an increased risk of wound dehiscence and site infection in several other studies.

## ***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 wound 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 December 29, 2022)

Additional information specific to stem cell therapies can be found at: <https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies>. (Accessed December 29, 2022)

Currently, there are two biologic products approved by the FDA for regenerative periodontal therapy:

- GEM 21S™ (Osteohealth Company, Division of Luitpold Pharmaceuticals, Inc.); refer to the following website for more information: [http://www.accessdata.fda.gov/cdrh\\_docs/pdf4/P040013b.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf4/P040013b.pdf). (Accessed December 29, 2022)
- Emdogain™ (Straumann); refer to the following website for more information: <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P930021>. (Accessed December 29, 2022)

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 December 29, 2022)

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 December 29, 2022)

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## Policy History/Revision Information

Date	Summary of Changes
06/01/2023	<p><b>Coverage Rationale</b></p> <ul style="list-style-type: none"> <li>Removed content addressing coverage exclusions</li> </ul> <p><b>Definitions</b></p> <ul style="list-style-type: none"> <li>Removed definition of: <ul style="list-style-type: none"> <li>Experimental, Investigational or Unproven Services</li> <li>Necessary</li> </ul> </li> </ul> <p><b>Applicable Codes</b></p> <ul style="list-style-type: none"> <li>Removed CDT codes D4263, D4264, D7950, and D7953</li> </ul> <p><b>Supporting Information</b></p> <ul style="list-style-type: none"> <li>Archived previous policy version DCP047.01</li> </ul>

## Instructions for Use

This Dental Clinical Policy provides assistance in interpreting UnitedHealthcare standard dental benefit 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, please 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.