Review

Hell J Surg. 2025 Jul-Sep;95(3):127–139
doi: 10.59869/25073

Regenerative Therapies in Oral and Maxillofacial Surgery: Current Clinical Evidence

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ABSTRACT

Background: Regenerative medicine is increasingly used in oral and maxillofacial surgery (OMFS), but clinical evidence remains heterogeneous. This review assessed reproducible clinical benefit, comparison with established reconstruction, and clinical maturity. **Objective:** To evaluate stem cell therapies, platelet-derived autologous biologics, and emerging regenerative technologies by indication, surgical role, comparative evidence, limitations, and readiness. **Methods:** PubMed/MEDLINE, Scopus, and Web of Science Core Collection were searched from 2010 onwards using "mesenchymal stem cells"/"mesenchymal stromal cells", "stem cell therapy", "oral and maxillofacial surgery", "craniofacial bone regeneration", "alveolar ridge preservation", "maxillary sinus augmentation", "alveolar cleft", "periodontal regeneration", "platelet-rich plasma", "platelet-rich fibrin", "advanced platelet-rich fibrin", "concentrated growth factors", "bone marrow aspirate concentrate", "secretome", "extracellular vesicles"/"exosomes", "biomaterials", and "3D bioprinting", with Medical Subject Headings (MeSH) terms "Mesenchymal Stem Cells", "Platelet-Rich Plasma", "Bone Regeneration", "Tissue Engineering", and "Maxillary Sinus Augmentation". Human evidence was prioritised, including randomised trials, systematic reviews, meta-analyses, and prospective studies; no formal risk-of-bias assessment or quantitative meta-analysis was performed. **Results:** PRF/PRP are clinically integrated adjuncts for selected indications, particularly soft-tissue healing. MSCs show clinical proof of concept, but evidence is limited by small cohorts, heterogeneous cell products, scaffold variability, and insufficient long-term comparative data. BMAC/CGF occupy an intermediate translational position, whereas secretome, extracellular vesicles/exosomes, advanced biomaterials, bioprinting, and AI-enabled platforms remain investigational. **Conclusions:** Regenerative therapies should complement, not replace, established reconstruction. Adoption depends on reproducible incremental benefit over contemporary standards and reduced donor-site morbidity, operative burden, treatment time, complications, or reconstructive failure.

Key words: *Regenerative medicine; mesenchymal stromal cells; platelet-rich fibrin; alveolar ridge preservation; maxillary sinus augmentation; clinical translation*

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Submission: 06.09.2026, Acceptance: 23.10.2026

INTRODUCTION

The originally laboratory-based concept of regenerative medicine is increasingly being applied in a selective clinical manner in the field of oral and maxillofacial surgery (OMFS). Translation of in vitro evidence for a biological product that can stimulate cells to improved reconstruction of OMFS defects in the clinical setting of patients is

hampered by a number of constraints including defect geometry, vascularity and surrounding soft tissues, risk of infection, functional loading and aesthetic requirements. Therefore, more than evidence of a biological product that can stimulate cells in vitro is needed by the surgeon. The only clinically relevant question is whether the intervention leads to an improvement in patient reconstruction compared with a modern surgical standard [1,2,3].

In addition to their potential for cell differentiation, mesenchymal stromal cells (MSCs) exert various effects through their paracrine actions, such as providing trophic support, modulating the immune system, and promoting angiogenesis [4,5]. Even a plausible mechanism of action does not necessarily translate into clinical superiority. Human studies investigating the treatment of defects in the oral cavity have been designed with substantial variability in several factors, including the type and processing of cells, cell number, type of scaffold, route of application, extent and type of oral cavity defect, clinical endpoint(s), and duration of follow-up [1,3,4,6,7].

Other types of translational models include autologous platelet concentrates. Although platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) contain platelets, fibrin, growth factors, cytokines, and leukocytes from the patient, these are not expanded in culture before they are applied. Their relatively low logistical burden has facilitated their clinical adoption. It is the same field with a lot of variability in protocols. However, there is much more clinical value in selected end-point measures for healing, than in predictable de novo hard tissue formation [8,9,10,11,12,13,14].

The early clinical translation, established adjunctive care, and investigational approaches for each of the modalities are reviewed within the framework of five key questions. The five key questions used as a framework for this review of the various modalities are as follows: (1) where would you use it; (2) how would it be incorporated into the surgical procedure; (3) what benefit could reasonably be expected; (4) what is the strength of the clinical evidence; and (5) is the technology ready to change routine surgical practice?

REVIEW APPROACH AND EVIDENCE FRAMEWORK

The primary search terms included "mesenchymal stem cells", "mesenchymal stromal cells", "stem cell therapy", "oral and maxillofacial surgery", "craniofacial bone regeneration", "alveolar ridge preservation", "maxillary sinus augmentation", "alveolar cleft", "periodontal regeneration", "platelet-rich plasma", "platelet-rich fibrin", "advanced platelet-rich fibrin", "concentrated growth factors", "bone marrow aspirate concentrate", "secretome", "extracellular vesicles", "exosomes", "biomaterials", and "3D bioprinting"; the principal MeSH terms included "Mesenchymal Stem Cells", "Platelet-Rich Plasma", "Bone Regeneration", "Tissue Engineering", and "Maxillary Sinus Augmentation".

This review is part of a narrative search of the databases PubMed/MEDLINE, Scopus, and Web of Science Core Collection for English-language publications from 2010 onwards. During the manuscript revision process, the evidence base was updated by searching PubMed and publisher databases for relevant 2026 systematic reviews and meta-analyses. The highest-quality evidence was considered for inclusion in this manuscript. This consisted of randomised clinical trials, controlled clinical studies, systematic reviews, meta-analyses, and studies reporting clinically relevant outcomes.

In assessing the maturity of the evidence for the many different regenerative interventions currently under development, we have used clinical rather than purely biological criteria. Because regenerative interventions are highly heterogeneous, "clinically integrated" refers to a modality that can be used in an adjunctive fashion, added to established surgical procedures, and applied safely and effectively on the basis of sufficient clinical evidence. "Early clinical translation" refers to human studies that report on feasibility and preliminary efficacy, but do not provide sufficient evidence for routine clinical adoption. "Investigational" refers to approaches for which the available clinical evidence remains too limited, inconsistent, or immature to support their use in standard surgical practice. In this section, we will outline the principal categories through which clinical translation of regenerative therapies in OMFS can be assessed, and describe the general biological pathways that are involved in the clinical translation of regenerative therapies depicted in Figure 1.

A summary of the resulting clinical evidence framework and the current surgical readiness of the principal regenerative approaches across relevant OMFS indications is presented in Table 1. The table provides a clinically oriented overview of the best-supported human evidence, the principal reported clinical benefit, the major evidence limitations, and the current role of each regenerative strategy relative to established surgical treatment.

STEM CELL-BASED THERAPIES: WHERE DO THEY CURRENTLY FIT IN OMFS?

Stem cell-based regeneration should not be regarded as a single treatment. In clinical practice, the outcome depends on the cell source, processing, dose, scaffold, delivery method, defect environment, and the quality of the underlying surgical reconstruction. MSCs derived from bone marrow, adipose tissue, and dental-associated tissues

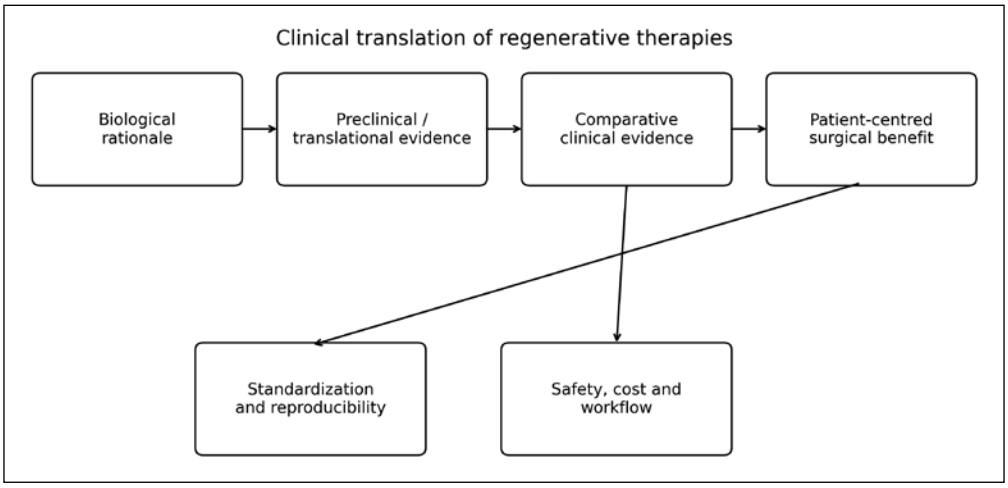

FIGURE 1. Clinical adoption requires convergence of evidence, reproducibility and meaningful surgical benefit.

TABLE 1. Clinical evidence and surgical readiness of regenerative approaches by indication.

Clinical indication	Regenerative strategy / surgical role	Comparator / standard treatment	Highest level of human evidence	Main reported benefit	Key evidence limitation	Current clinical role
Alveolar ridge augmentation	MSC/cell-enriched adjunct to graft or scaffold	Conventional grafting or scaffold-based augmentation	Small clinical studies and heterogeneous comparative evidence	Potential to enhance bone regeneration and reduce graft requirements in selected settings	Small, heterogeneous clinical studies; limited evidence of superiority over conventional grafting	Investigational / early clinical translation
Maxillary sinus augmentation	MSC-assisted grafting in a contained defect	Conventional sinus augmentation with grafting	Clinical studies and systematic/meta-analytic evidence	Human clinical feasibility; a 2026 meta-analysis found no significant implant-success advantage over conventional treatment [15]	Small RCT evidence base; heterogeneous protocols; clinical superiority not established	Early clinical translation
Periodontal regeneration	MSC-assisted regenerative periodontal surgery	Conventional periodontal regenerative therapy	Clinical studies and systematic review/ meta-analysis [16]	Improvements in selected periodontal parameters reported in clinical studies	Limited number of trials; variable cell sources, scaffolds, and clinical endpoints	Early clinical translation
Alveolar cleft / complex craniofacial defects	Cell + biomaterial reconstruction	Conventional bone grafting or reconstructive surgery	Small clinical study demonstrating feasibility of MSC-assisted alveolar cleft repair [17]	Feasibility of biologically enhanced reconstruction in complex defects	Small cohorts and limited long-term comparative data	Investigational
Extraction, ridge preservation and selected regenerative procedures	PRF / platelet concentrates as surgical adjuncts	Conventional healing or graft-based ridge preservation	Randomised clinical trials and systematic reviews [18,19]	Supportive effects on soft-tissue healing and selected postoperative or ridge-preservation outcomes	Protocol heterogeneity; inconsistent hard-tissue effects; not a predictable substitute for grafting	Clinically integrated adjunct in selected indications

Abbreviations: MSC = mesenchymal stromal cell; PRF = platelet-rich fibrin.

have been investigated because of their osteogenic, trophic, angiogenic, and immunomodulatory properties [3,4,5,6].

Alveolar ridge reconstruction

Indication and surgical role: The clinically relevant indication is a deficient alveolar ridge in which conventional augmentation would require substantial graft volume or a donor site. MSC-based approaches have been studied as cell-enriched grafting or scaffold-based adjuncts to provide osteogenic or pro-regenerative activity within a mechanically stable defect [1,3,7].

Expected benefit: There are more expected benefits to the proposed advantage (i.e. faster bone formation) than just that alone, including a reduced amount of autogenous graft required, enhanced biologic activity in the grafted area, and potentially improved regeneration of difficult defects. However, these advantages remain incompletely demonstrated in comparative human studies [1,3,6,7].

Most studies investigated the feasibility of MSC-based therapy for different defects using different cell preparations, carrier systems, and other protocols. Therefore, a direct comparison of MSC-based therapy with contemporary grafting was not possible. Recently, a systematic review and meta-analysis on clinical stem cell therapy for oral and craniofacial bone-regeneration procedures similarly found heterogeneous evidence. Stem-cell therapy improves histological bone quality and 3D radiographic bone volume but does not increase periodontal clinical attachment level or linear bone height/width above levels achieved by conventional therapy [15]. In summary, the evidence supports a clinical investigation rather than routine substitution of established augmentation techniques.

Surgical readiness: INVESTIGATIONAL/EARLY TRANSLATION. MSC-assisted alveolar reconstruction can be considered for cases treated in specialised centres within the framework of clinical trials. However, for alveolar reconstruction, MSC-assisted approaches should not replace established methods of autogenous, allogeneic, xenogeneic, or synthetic grafting solely on the basis of their regenerative potential.

Maxillary sinus augmentation

Indication and technique: Maxillary sinus augmentation is a clinical indication in which a contained 3D space is available for a biologically active graft. Subsequent protection and support of the graft by the surrounding tissue are required. Cell-assisted bone regeneration strategies have been investigated as adjuncts to grafting, with the aim of increasing bone formation while reducing the need for autogenous bone [7,20].

Comparative evidence: The randomised clinical trial by Kaigler et al. demonstrated the feasibility of enriched CD90+ bone marrow-derived stem cell therapy for maxillary sinus bone regeneration [20]. This is important proof-of-concept because it moves the field beyond laboratory findings; however, a single positive trial does not establish superiority across routine implant patients or different cell-processing systems. Of note is a systematic review and meta-analysis from 2026 consisting of 6 RCTs (74 patients, 222 implants) that investigated the success of implants grafted with MSCs in comparison to implants grafted with conventional grafting materials. There were no significant differences between the two groups (RR 0.98; 95% CI 0.94–1.03). For continuous bone-neoformation outcomes, the control group values for conventional augmentation were higher than those of the study group for MSC-assisted augmentation of the sinuses. However, for dichotomous bone-regeneration outcomes, there were no significant differences between the two groups of patients [21]. Therefore, MSC-assisted sinus augmentation remains a promising but unproven clinical strategy rather than an established replacement for conventional grafting.

Surgical interpretation: The evidence currently supports the use of sinus lift as a potential consideration for the further development of cell-based materials for clinical application. However, not all indications for bone grafting will be suitable for the use of cell-based materials. The additional requirements for cell harvesting, processing, regulatory considerations, and cost must be justified by a measurable clinical benefit.

Craniofacial and alveolar cleft reconstruction

Reconstruction of craniofacial defects is a significant translational challenge. In order to achieve adequate function of the reconstructed part, in addition to lasting structural support of the reconstructed skull, sufficient amounts of soft tissue must be provided to allow for successful rehabilitation. Human MSCs have been used to repair alveolar clefts and have demonstrated clinical feasibility [17]. However, there is not enough evidence to support cell-based therapy as the new gold standard of care.

Until sufficient data exist to establish MSC therapy as a stand-alone treatment within reconstructive algorithms, MSCs should be viewed as an adjunct under investigation to enhance the effects of established reconstructive algorithms.

Periodontal and peri-implant regeneration

Periodontal defects are complex and therefore difficult to close biologically. For successful regeneration of a periodontal defect, in addition to cementum, the periodontal ligament has to be regenerated and the alveolar bone has to be rebuilt. Isolated

bone fill is not sufficient. In probing depth, clinical attachment level, and radiographic parameters, clinical studies and systematic evidence have demonstrated potential improvements with MSC-based approaches in selected periodontal defects [7,16].

More importantly, for the practicing clinician, the question is whether adding cell therapy to thorough debridement, the selection of appropriate defects, the use of established periodontal regenerative membranes/scaffolds, and conventional periodontal regenerative surgery provides any additional benefit to the patient. To date, there is insufficient evidence to support the routine use of cell transplantation for the average periodontal patient. Therefore, such treatment would only be indicated for highly selected defects which are to be treated within controlled clinical investigations.

AUTOLOGOUS BIOLOGICS: THE MOST CLINICALLY ACCESSIBLE REGENERATIVE ADJUNCTS

Autologous biologics have a fundamentally different surgical value proposition from cell therapy. Intraoperative preparation of autologous biologic products usually does not add substantial operative complexity. Most established surgical procedures can incorporate autologous biologics after minor modification. Their clinical accessibility has facilitated their rapid adoption. However, this accessibility does not mean that they have proven efficacy. Finally, growth factors in PRP and PRF are able to create a better wound-healing environment, yet they are not able to create tissue with the necessary mechanical properties, cover a wound with vascularised tissue, achieve wound closure by proper management of a defect, or provide a sufficiently sized and sound graft of appropriate quality [8,9,10,12,13,14].

Platelet-rich plasma (PRP)

Indication and technique: For periodontal and other dental surgeries, including extraction socket healing, implant procedures, bone grafting and sinus lift. [8,10]

Expected benefit: Early soft-tissue healing and postoperative recovery can be accelerated or modulated by the action of platelet-derived growth factors (such as platelet-derived growth factor [PDGF], transforming growth factor-β [TGF-β], and vascular endothelial growth factor [VEGF]) in the early stages of healing. These are credible clinical endpoints rather than a predictable replacement of missing bone [8,9,12].

Limitations: The lack of standardisation of PRP preparation, i.e. the number of platelets, the number of leukocytes, the method of activation, the type and concentration of anticoagulant(s), centrifugation and application methods, results in different biological activities of PRP. Thus, results obtained with one PRP system may be difficult to extrapolate to another [9,11,12].

Surgical readiness: PRP is clinically integrated as an adjunct to support the clinical benefit anticipated from other treatments. It should be used when the expected supportive benefit justifies the additional preparation burden and should not be presented as an independent regenerative treatment.

Platelet-rich fibrin (PRF)

Indication and technique: PRF is produced without anticoagulants and forms a fibrin matrix containing platelets and leukocytes. Depending on the formulation, it can be used as a membrane, plug, clot or injectable preparation [8,9,11,12].

Expected benefit: The clinically attractive feature is the combination of biological mediator release with a manipulable fibrin matrix. Evidence is most consistent for soft-tissue healing, wound maturation, postoperative discomfort and selected extraction-socket outcomes [8,10,13,14].

Hard-tissue interpretation: PRF should not be equated with a structural bone graft. Meta-analytic evidence suggests benefits in selected hard- and soft-tissue endpoints, but results are heterogeneous and do not establish predictable large-volume bone reconstruction or superiority over established grafting strategies [12,14]. A 2026 systematic review and meta-analysis of randomised controlled trials found that PRF alone reduced alveolar ridge height loss at selected follow-up intervals compared with spontaneous healing, although the pooled ridge-height analysis showed substantial heterogeneity ($I^2 = 80\%$) [18]. More importantly for surgical decision-making, a 2026 meta-analysis published in the International Journal of Oral and Maxillofacial Surgery that directly compared PRF with bone grafts found greater ridge-height and ridge-width loss in the PRF groups, while bone density did not differ significantly [19]. Thus, PRF may improve healing and preserve dimensions relative to unassisted healing in selected settings, but current comparative evidence does not support treating PRF as equivalent to a structural graft for ridge preservation.

Surgical readiness: CLINICALLY INTEGRATED ADJUNCT. PRF is currently one of the most practical regenerative tools in OMFS, particularly when the surgical objective is to improve the early healing environment rather than to provide primary structural regeneration.

Standardisation is a surgical issue, not only a laboratory issue

Standardisation of promising biologicals is mandatory to make them useful in clinical practice as surgical procedures. Apparently similar interventions in oral and maxillofacial surgery can vary significantly according to the cell source, cell processing, dose, scaffold, platelet concentration, centrifugation force and duration, activation method, carrier material, defect characteristics, and timing of application. Such variability can substantially influence treatment outcomes and limits the reproducibility and interpretation of clinical evidence. There are several variables that can affect the biological composition and clinical effects of a final product. In summary, direct comparison between individual studies is often not possible, and therefore the reproducibility and transferability of the results obtained from single studies are limited. This is particularly relevant for platelet concentrates, which are prepared using substantially different methods and may consequently differ markedly in their biological composition and clinical effects despite being described using the same general terminology [9,11,12,13]. Surgical standardisation therefore extends to the full description of the clinical intervention that was performed under study conditions. The description of the regenerative product used has to be complete and include the preparation and processing of the regenerative product, as well as the use of additional materials. A complete description of the clinical intervention should also include the defect morphology, surgical technique, comparator treatment, timing of application, and clinically meaningful outcome measures. This level of reporting is essential to allow meaningful interpretation, comparison, and reproducibility of the results. For platelet concentrates, the following information needs to be consistently reported: relative centrifugal force, centrifugation time, tube type, platelet and white blood cell numbers, handling, activation, and delivery method. The consistent reporting of these parameters will allow for a more accurate assessment of the effects of a regenerative treatment. It will also allow the distinction between true treatment effects and effects related to the preparation protocol, patient selection, defect type, or surgical technique [9,11,12,13].

Evaluating current evidence for a regenerative product that causes measurable biological or radiographic effects under a specific set of circumstances does not necessarily translate to the same clinical benefit when the product is prepared differently or applied under different clinical conditions or for a different surgical indication. Consequently, terms such as PRP and PRF should not be interpreted as referring to biologically identical interventions across studies. The preparation protocol should be regarded as an integral part of the intervention itself, rather than as a secondary laboratory detail.

Standardisation of regenerative products is not only a matter for the laboratory. It is a prerequisite for reproducible surgical decisions and for meaningful comparative effectiveness research. It is a prerequisite for the integration of these therapies into the routine clinical practice of OMFS. It is crucial to consider any efficacy claims in the light of the specific preparation system, the specific surgical indication and the overall clinical protocol within which evidence of efficacy has been obtained.

Why promising regenerative therapies have not yet become standard surgical care

There are no interventions currently performed on a routine basis, as there is a lack of consistent evidence that they provide any clinical benefit over and above that already achieved by established methods of reconstructive surgery. Studies report improvements in histological, radiographic or early healing parameters. However, the translation of these improvements into reduced donor-site morbidity, fewer procedures, complications, and reoperations, shorter times to implant placement, etc. (true patient-centered outcomes) remains unclear. In the field of OMFS, even the smallest biological change is not worth the additional procedural complexity, cost and regulatory requirements.

A second set of barriers are related to the heterogeneity of the intervention. Most reports on the use of mesenchymal stem cells (MSCs), platelet-rich plasma (PRP) or platelet-rich fibrin (PRF) describe a variety of different products that are vastly different from each other with regard to the cell source, processing, dose, etc., whether or not they use a scaffold and differing in terms of centrifugation parameters, cellular composition, activation method, and delivery. Consequently, apparently similar interventions may not represent the same biological treatment across studies. This heterogeneity limits reproducibility and makes it difficult to determine whether apparently conflicting results reflect differences in biological efficacy or differences in the intervention itself. Standardised preparation and reporting are therefore necessary before findings can be generalised across centres, products, or surgical indications.

The comparative evidence is also incomplete. A 2026 systematic review and meta-analysis of clinical stem-cell therapy in oral and craniofacial bone regeneration found improvements in selected histological and volumetric outcomes, but no significant advantage over conventional

treatment for periodontal clinical attachment level or linear bone height and width [15]. Similarly, a 2026 systematic review and meta-analysis of MSC-assisted maxillary sinus augmentation found no significant difference in implant success compared with conventional grafting, despite evidence of clinical feasibility and biological activity [21]. Evidence from platelet-based ridge-preservation studies is likewise mixed. A 2026 meta-analysis found that PRF alone reduced alveolar ridge height loss compared with spontaneous healing, although substantial heterogeneity was reported, while a separate 2026 meta-analysis directly comparing PRF with bone grafts found greater ridge-height and ridge-width loss in the PRF groups, with no significant difference in bone density [18,19].

These findings do not indicate that regenerative therapies are ineffective. Rather, they show that biological activity and selected surrogate improvements have not yet translated consistently into superior surgical outcomes. The clinically relevant question is therefore not whether a regenerative intervention produces a measurable biological effect, but whether that effect is sufficiently large and reproducible to improve the outcome that would otherwise be achieved with contemporary reconstructive surgery.

A further limitation is the short duration and scale of many clinical studies. Small cohorts, single-centre designs, variable follow-up periods, and inconsistent outcome definitions make it difficult to determine whether early gains remain stable and whether they translate into durable functional benefit. For a surgical technology to become the standard of care, evidence should demonstrate reproducible performance across surgeons and patient populations, with adequate follow-up and direct comparison against the treatment that would otherwise be selected in routine practice.

Finally, clinical translation requires more than efficacy. A regenerative intervention must fit within the operative workflow, have a reproducible manufacturing or preparation process, maintain an acceptable safety profile, and provide a benefit large enough to justify its additional complexity and cost. In summary, while some of the autologous biologics can be used on a selective, indication-specific basis, most of the cell-based and engineered approaches are still in the early stages of clinical translation and investigation. The factors that will be considered in future trials are whether the treatments change any of the key decisions made by the surgeon for the patient and whether they affect any of the main outcomes of interest to patients.

Key differences between PRP and PRF exist that make a difference for clinical use. These differences affect the matrix formation, the release of mediators and the clinical outcomes that have been reported, while also influencing their handling and the way in which their effects are interpreted across different clinical studies. PRF has been studied more extensively in the available evidence base, particularly for soft-tissue healing, periodontal applications, postoperative management, and alveolar ridge preservation [8,9,10,13,14,18,19]. However, the available literature does not establish either PRP or PRF as universally superior, and clinical effects should remain linked to the specific preparation protocol and surgical indication. These differences and the principal evidence limitations are summarised in Table 2.

OTHER AUTOLOGOUS BIOLOGICS: CONCENTRATED GROWTH FACTOR (CGF) AND BONE MARROW ASPIRATE CONCENTRATE (BMAC)

Concentrated growth factor (CGF)

CGF is a modified platelet-derived preparation designed to generate a relatively dense fibrin matrix containing platelets, leukocytes and growth factors [22]. A scaffold and sustained release of biological mediators could be of value in a surgical context; however, to date there is no evidence to suggest that CGF is superior to PRF or other platelet concentrates. CGF is best used as an adjunctive, investigational tool until more clinical information is gathered and until the tool is translated into other forms of clinical use.

Surgical readiness: EARLY TRANSLATION. Early consideration for use in selected cases of regenerative surgery but need for comparative clinical trials to establish clinical benefit over other established platelet concentrates.

Bone marrow aspirate concentrate (BMAC)

BMAC is particularly relevant for the surgeon, as BMAC is a mix of cells and growth factors that do not need to go through prolonged ex vivo expansion. It contains a heterogeneous mixture of stromal/progenitor cells, growth factors, cytokines and other marrow-derived elements [4,20].

The distinction between BMAC and culture-expanded MSC therapy is clinically important. The randomised maxillary sinus study by Kaigler et al. evaluated enriched CD90+ bone marrow-derived cells rather than generic BMAC [20]. Therefore, evidence from that trial should not be used to imply that every BMAC preparation has the same efficacy.

Surgical readiness: EARLY TRANSLATION / INVESTIGATIONAL. BMAC may become attractive when a one-stage

TABLE 2. Direct clinical comparison of platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in oral and maxillofacial regenerative surgery.

Domain	Platelet-rich plasma (PRP)	Platelet-rich fibrin (PRF)	Clinical interpretation / evidence limitation
Preparation principle	Platelet-enriched plasma obtained after blood collection and centrifugation; preparation commonly involves anticoagulation and may include one- or two-step processing	Blood is centrifuged without anticoagulants, allowing formation of a fibrin matrix containing platelets and leukocytes [8,9,11]	Preparation protocols vary substantially among platelet concentrates, limiting direct comparison across studies [8,9,11]
Biological architecture	Predominantly a platelet-enriched plasma fraction that delivers platelet-derived mediators	Three-dimensional fibrin matrix that entraps platelets and leukocytes and provides a biologically active scaffold [8,9,12]	The structural distinction may influence retention and release kinetics, but biological differences should not automatically be interpreted as clinical superiority
Growth-factor release	Relatively rapid release of platelet-derived mediators following activation	Fibrin matrix provides a more sustained release environment for platelet-derived mediators [8,9,12]	Sustained release is a proposed biological advantage of PRF, although its clinical significance remains indication-dependent
Handling and surgical application	Can be applied as a liquid preparation or after activation and may be incorporated into grafting or regenerative procedures	Forms a fibrin clot or membrane that can be manipulated and adapted to the surgical site [8,9,10,13]	PRF may provide practical advantages where a membrane or stable fibrin matrix is desirable, whereas PRP may be advantageous where a liquid preparation is required
Soft-tissue healing	Platelet concentrates may support soft-tissue repair through delivery of platelet-derived mediators	Systematic evidence supports beneficial effects of PRF on soft-tissue wound healing [8,9]	Evidence is stronger for healing-related outcomes than for predictable hard-tissue regeneration
Postoperative pain and morbidity	May be used as a biological adjunct in selected surgical procedures	Clinical evidence supports reductions in postoperative morbidity in selected oral surgical procedures [13,14]	Magnitude of benefit depends on procedure, protocol, and outcome definition; evidence should not be generalised across all indications
Bone regeneration / ridge preservation	May be used as an adjunct to graft-based regenerative procedures	PRF has been investigated extensively for ridge preservation and bone-healing applications [10,12,14,18,19]	Recent systematic reviews support potential benefit in selected ridge-preservation outcomes, but PRF should not be considered a predictable replacement for bone grafting [18,19]
Periodontal regeneration	Platelet-based concentrates may be incorporated as adjuncts to periodontal regenerative procedures	PRF has demonstrated regenerative potential in periodontal applications [9,10,13]	Clinical outcomes remain heterogeneous and are influenced by defect characteristics, preparation protocol, and concomitant regenerative treatment
Fibrin matrix formation	Does not primarily rely on formation of a dense autologous fibrin scaffold	Formation of an endogenous fibrin matrix is a defining characteristic of PRF [8,9,11]	Fibrin architecture represents one of the principal biological differences between PRP and PRF
Need for exogenous anticoagulant	Commonly used during PRP preparation	Not required for conventional PRF preparation [11]	Avoidance of anticoagulants permits endogenous fibrin polymerisation during PRF preparation
Protocol standardisation	Considerable variation in platelet concentration, leukocyte content, activation methods, and centrifugation protocols	Also substantial variation among PRF formulations, centrifugation protocols, and preparation systems [11,13]	Protocol heterogeneity is a major limitation when comparing platelet-concentrate studies and interpreting pooled clinical evidence
Overall clinical position	Platelet-concentrate adjunct with potential application in selected regenerative and healing procedures	Clinically integrated adjunct with the strongest evidence in selected healing, periodontal, and ridge-preservation applications [8,10,13,14,18,19]	Neither PRP nor PRF should currently be regarded as a universal substitute for established grafting or reconstructive procedures

Abbreviations: PRP = platelet-rich plasma; PRF = platelet-rich fibrin.

autologous cellular approach can provide a measurable reduction in graft burden or donor-site morbidity, but current evidence is insufficient for routine use.

WHAT REGENERATIVE THERAPY CAN ACTUALLY CHANGE IN THE OPERATION?

The central surgical test is incremental value. A regenerative modality becomes clinically relevant when it changes an outcome that matters to the patient or surgeon, such as reducing autogenous graft harvesting or donor-site morbidity, decreasing the number of procedures, accelerating functional rehabilitation, improving the predictability of reconstruction, reducing complications or reoperation, or providing more durable restoration of tissue architecture. Even though biological activity, histological changes and radiographic improvements are good to know about when deciding on a treatment, they do not necessarily translate into clinically relevant results that demonstrate superiority to established surgical methods and techniques. In most current applications, regenerative technologies are best understood as adjuncts to sound surgical principles rather than binary alternatives to conventional reconstruction; they cannot compensate for inadequate vascularity, infection, poor soft-tissue coverage, instability, inappropriate defect selection, or inadequate space maintenance.

EMERGING TECHNOLOGIES: PROMISING, BUT NOT YET READY FOR ROUTINE SURGERY

Cell-free secretome therapies

The secretome of MSCs contains soluble mediators and extracellular vesicles that may reproduce part of the therapeutic effect of transplanted cells [23]. The attraction for surgery is obvious: a cell-free product could potentially reduce concerns related to cell survival, differentiation, manufacturing complexity and storage. However, the composition of the secretome is influenced by cell source and culture conditions, and standardised dosing and potency remain unresolved. Clinical evidence in OMFS is insufficient for routine use.

Extracellular vesicles and exosomes

Extracellular vesicles can transfer proteins, lipids and nucleic acids between cells and may provide a controllable mechanism for modifying inflammation, angiogenesis and tissue regeneration [24]. Their current limitations include isolation and characterisation, batch consistency, scalable manufacture, dosing, delivery, storage, regulatory classification and lack of robust human efficacy data. They should therefore remain within the scope of investigational research.

Advanced biomaterials and bioactive scaffolds

The next generation of scaffolds is designed not merely to occupy a defect but to provide mechanical support while presenting biochemical and structural cues to cells [25]. For OMFS, the clinically important opportunity is patient-specific reconstruction of complex defects where current grafting strategies are limited by volume, resorption or donor-site morbidity. At present, however, most advanced bioactive scaffolds lack the comparative human evidence required to replace established reconstructive materials.

Three-dimensional bioprinting

Three-dimensional bioprinting may ultimately allow patient-specific constructs containing cells, biomaterials and biological signals to be fabricated according to defect geometry [26]. However, a number of significant barriers have to be overcome, i.e. vascularisation, matureness of the printed construct, mechanical performance, manufacturing reproducibility and regulatory validation. Its present role in OMFS therefore remains experimental, and further research is required before it can be considered for routine clinical application.

Artificial intelligence and computational planning

Artificial intelligence (AI) and machine learning can indirectly help improve regenerative surgery by optimising scaffolds, analysing images, predicting tissue reactions and enabling patient-specific planning [27,28,29]. All of the above enabling technologies are not yet considered to be regenerative therapies. Clinical value will be established through prospective validation and comparison with external data sets, explainability, reproducibility and, most importantly, clinical outcomes.

PRACTICAL EVIDENCE-BASED RECOMMENDATIONS FOR THE OMFS SURGEON

For the OMFS surgeon, the current evidence supports a selective, indication-specific approach to the use of regenerative therapies in a selective and indication-specific manner rather than their routine use on the basis of biological plausibility. The relevant clinical question is whether an intervention, added to a current technique, has a reproducible, additive effect and whether this provides clinically meaningful benefits, such as improved healing, preserva-

tion of tissue dimensions, reduced donor-site morbidity, reduced graft requirements, fewer procedures, improved functional recovery, or greater predictability of reconstruction. Biological activity, histological changes, or radiographic improvements may support the treatment rationale, but should not be interpreted as evidence of clinical superiority in the absence of appropriate comparative data.

The current position of regenerative therapies can therefore be understood as a clinical-readiness continuum rather than as a binary distinction between effective and ineffective treatments. At one end are investigational approaches for which human clinical evidence remains limited or insufficient for routine surgical use; intermediate positions include technologies in early clinical translation, where clinical feasibility has been demonstrated but comparative evidence remains incomplete; and at the clinically integrated end are selected adjunctive approaches that can be incorporated into established surgical workflows with a relatively defensible evidence and safety profile (Figure 2). This continuum reflects not only the presence of biological activity, but also the consistency of human evidence, reproducibility of the intervention, comparative effectiveness, and the extent to which a technology can provide a meaningful incremental benefit over contemporary surgical care.

PRF and selected platelet-concentrate applications currently occupy the clinically integrated end of this continuum because they can be incorporated into established surgical workflows with relatively limited additional complexity. Here, as with the other approaches, their role is as an adjunct to indication-specific therapy and they should not be seen as alternatives to structural grafts for substantial 3D reconstruction [8,9,12,14,18,19]. Of note, MSC-based therapies and CGF are described at earlier stages of clinical translation, reflecting satisfying biological activity and clinical feasibility, but their clinical translation remains limited by insufficient comparative evidence, variability in preparation and application protocols, and the need for more consistent evidence of clinically meaningful benefit [1,7,15,16,20,21,22]. BMAC is considered to be under investigation within the current evidence framework, largely due to the lack of modality-specific clinical evidence to establish routine efficacy and comparative superiority to other available therapies. Therefore, cell-free secretome and extracellular vesicle-based therapies, as well as advanced biomaterials and three-dimensional bioprinting, remain predominantly investigational and should currently be restricted to appropriately designed clinical or translational research [11,23,24,25,26]. Enabling technologies, such as AI and computational tools, may support regenerative treatments; however, their clinical impact has not yet been prospectively validated [27,28,29].

The clinical-readiness continuum does not represent a hierarchy between therapies. Instead, every modality is located on the continuum according to the specific clinical indication. For now, a modality that is sufficiently integrated for a certain healing indication may remain investigational for other applications, such as structural reconstruction. Its position may also change as comparative clinical evidence accumulates, and apparent biological or radiographic benefits should not automatically be interpreted as evidence of a higher level of clinical readiness. Thus, the choice of a regenerative intervention must correspond to the specific surgical problem and must complement established reconstructive options in an optimal fashion.

In reality, any expected clinical benefit must be proportionate to the additional time, increased complexity, costs, and approval requirements associated with the respective procedure. The preparation and delivery protocols must be standardised and described in sufficient detail to allow adequate interpretation and reproducibility of the results. The absence of demonstrated superiority should not be interpreted as evidence of no biological or clinical value; rather, the strength and scope of any claimed benefit should remain linked to the specific indication, preparation protocol, comparator, and outcome for which evidence exists. The clinical-readiness matrix in Table 3 provides a practical summary of this evidence-based position.

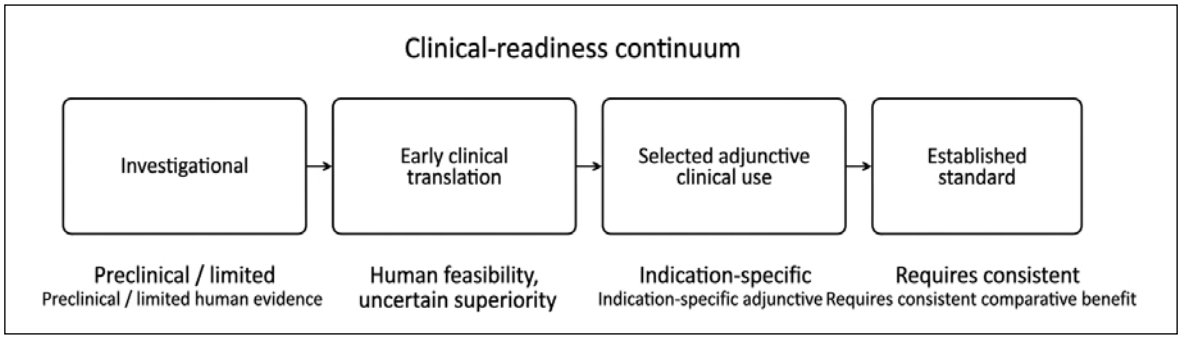

FIGURE 2. Movement to the right requires reproducible comparative evidence, safety and patient-centred benefit.

TABLE 3. Selected regenerative modalities of major regenerative modalities in oral and maxillofacial surgery.

Regenerative modality	Principal therapeutic rationale	Human clinical evidence	Main clinical signal	Key evidence limitation	Translational maturity	Current clinical position
Mesenchymal stromal/stem cells (MSCs)	Cell-based osteogenic, angiogenic and immunomodulatory regeneration, generally combined with grafts or scaffolds [1,3,4,6]	Clinical studies and systematic reviews across selected OMFS indications [7,15,16,17,20,21]	Clinical feasibility and potential improvement in bone and periodontal regeneration in selected indications	Small and heterogeneous trials; variable cell sources, processing methods, scaffolds, dosing and outcome measures; limited evidence of superiority over standard treatment [1,7,15,16,21]	Early clinical translation	Investigational adjunct; not established as a routine replacement for conventional grafting
Platelet-rich plasma (PRP)	Autologous delivery of platelets and growth factors to support healing and tissue regeneration	Clinical evidence from platelet-concentrate literature	Potential benefit in selected healing and regenerative applications	Substantial variation in platelet concentration, leukocyte content, activation and preparation protocols; inconsistent hard-tissue outcomes	Clinically integrated in selected applications	Adjunctive modality; indication-specific
Platelet-rich fibrin (PRF)	Autologous fibrin-based matrix providing platelets, leukocytes and growth factors within a three-dimensional scaffold [8,9,11,12]	Multiple clinical studies, systematic reviews and recent meta-analyses [10,13,14,18,19]	Clinical signal for improved soft-tissue healing and selected postoperative, periodontal and ridge-preservation outcomes	Protocol heterogeneity and variable clinical endpoints; evidence does not support predictable substitution for grafting [18,19]	Clinically integrated	Clinically integrated adjunct in selected oral and maxillofacial procedures
Concentrated growth factor (CGF)	Autologous platelet concentrate with a dense fibrin network and concentrated growth factors [22]	Mainly biological and limited clinical evidence	Potential regenerative and healing effects in oral and maxillofacial applications	Limited high-level comparative evidence; heterogeneous preparation protocols; insufficient long-term clinical data	Early clinical translation	Emerging adjunctive modality
Bone marrow aspirate concentrate (BMAC)	Delivery of autologous marrow-derived cellular and trophic components to support bone regeneration	Limited modality-specific evidence within the present reference set	Biological rationale and potential role as a cell-enriched adjunct to graft-based reconstruction	Insufficient modality-specific clinical evidence to establish efficacy or comparative superiority	Investigational	Experimental / investigational adjunct
MSC secretome / conditioned medium	Cell-free delivery of soluble paracrine factors with regenerative and immunomodulatory activity [23]	Predominantly preclinical and translational evidence	Strong biological rationale and regenerative potential without direct transplantation of viable cells	Variable secretome composition; lack of standardised production, dosing, potency assessment and clinical validation [23]	Investigational	Experimental; not established for routine surgical use
Extracellular vesicles (EVs) / exosome-based approaches	Cell-free delivery of proteins, lipids and nucleic acids mediating paracrine regenerative effects [24]	Predominantly preclinical evidence	Promising biological potential for tissue repair and regeneration	Major challenges in isolation, characterisation, dose definition, potency testing, standardisation and clinical translation [24]	Investigational	Experimental; not established for routine clinical use

Abbreviations: MSC = mesenchymal stromal cell; PRP = platelet-rich plasma; PRF = platelet-rich fibrin; CGF = concentrated growth factor; BMAC = bone marrow aspirate concentrate; EVs = extracellular vesicles.

FUTURE RESEARCH PRIORITIES

Future studies should be designed around surgical decision-making rather than biological novelty. First, randomised trials should compare regenerative interventions directly with the current standard of care, not only with no treatment. Second, protocols should report the complete intervention—cell source and dose, preparation method, scaffold, centrifugation parameters, defect characteristics and surgical technique—so that results are reproducible [9,11,12].

Third, outcomes should prioritise patient-centred and surgical endpoints: donor-site morbidity, operative time, number of procedures, complications, implant placement readiness, functional recovery, reoperation, long-term volumetric stability and cost-effectiveness. Fourth, follow-up should be long enough to determine whether an early radiographic or healing advantage persists. Finally, multicentre studies are needed to determine whether apparently promising technologies remain effective across different surgeons, patient populations and defect types.

The decisive research question should therefore be: does the regenerative intervention produce an incremental benefit large enough to justify its additional cost, complexity, regulatory burden and impact on the operative workflow? Technologies that cannot answer this question are unlikely to change routine OMFS practice regardless of their mechanistic sophistication.

CONCLUSION

Oral and maxillofacial surgery is increasingly being combined with regenerative medicine. However, the clinical maturity of the different treatments is very heterogeneous. The most clinically integrated approaches are autologous platelet concentrates, such as PRF, used as adjuncts for healing and selected regenerative indications, whereas MSC-based therapies, BMAC, and CGF remain at earlier stages of clinical translation. Cell-free and engineered approaches remain predominantly investigational. Across these modalities, biological plausibility alone is insufficient to justify replacing established reconstructive strategies.

The most clinically relevant future advances will therefore be those that demonstrate a reproducible and meaningful incremental benefit over contemporary surgical standards, particularly through reduction of donor-site morbidity, operative burden, number of procedures, complications, or reconstructive failure. Until such advantages are demonstrated in adequately designed comparative clinical studies, regenerative therapies should be adopted selectively, according to indication-specific evidence and clinical readiness, and used to complement rather than replace established surgical principles.

Acknowledgements: *The author acknowledges Dr Orestis Ioannidis for supervision and academic guidance.*

Author Contributions: *Marina Gkelsini: Conceptualization, literature search, evidence synthesis, and writing—original draft. Elissavet Anestiadou: Writing—review and editing, critical revision, and refinement of the manuscript. Orestis Ioannidis: Supervision, writing—review and editing, critical revision, and refinement of the manuscript. All authors have read and approved the final version of the manuscript.*

Funding: *No external funding was received for this work.*

Conflict of Interest: *The author declares no conflict of interest.*

Ethics Approval: *Not applicable. This article is a review of published literature and does not involve human participants or identifiable patient data.*

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