SALIVARY AND GINGIVAL CREVICULAR BIOMARKERS IN PERIODONTAL DISEASE: FROM EARLY DIAGNOSIS TO PRECISION-GUIDED THERAPEUTIC STRATEGIES

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ABSTRACT

Periodontal disease is a complex chronic inflammatory condition characterized by dysbiotic biofilm-host interactions, progressive connective tissue breakdown, and alveolar bone loss. In recent years, growing interest has focused on salivary and gingival crevicular fluid biomarkers as minimally invasive tools capable of improving early diagnosis, disease monitoring, and therapeutic stratification. This review examines the biological rationale for biomarker use in periodontal disease and synthesizes current evidence regarding salivary, crevicular, microbiome-derived, proteomic, and regulatory molecular markers. Particular attention is given to inflammatory mediators, matrix-degrading enzymes, protein-based biomarkers, microRNAs, and microbiome-associated signatures that reflect ongoing periodontal activity beyond conventional clinical and radiographic parameters. The review also discusses the emerging role of multimarker panels, artificial intelligence-assisted analysis, and molecular profiling in the transition toward precision-guided periodontal care. Although available evidence supports the diagnostic and translational potential of these biomarkers, important challenges remain, including methodological heterogeneity, lack of standardized sampling and analysis, and insufficient prospective validation. Overall, salivary and gingival crevicular biomarkers represent a promising direction for more personalized, predictive, and biologically grounded periodontal diagnostics and treatment planning.

Keywords: periodontal disease, saliva, gingival crevicular fluid, biomarkers, early diagnosis, precision dentistry

1. Introduction

Periodontal disease remains one of the most prevalent chronic inflammatory conditions affecting the oral cavity and constitutes a major cause of attachment loss, alveolar bone destruction, tooth mobility, and eventual tooth loss in adults. Beyond its local effects, periodontitis is increasingly recognized as a biologically complex disorder in which microbial dysbiosis, host immune dysregulation, and tissue remodeling interact dynamically over time, generating highly variable clinical phenotypes and therapeutic responses. In this context, conventional diagnostic parameters, although essential in daily practice, are often limited by their retrospective character, as they primarily reflect tissue damage that has already occurred rather than ongoing molecular activity. This limitation has stimulated growing interest in salivary and gingival crevicular fluid biomarkers as tools capable of capturing disease-related biochemical alterations in a minimally invasive and clinically accessible manner [1-3].

Recent reviews have emphasized that salivary biomarkers may substantially improve the early detection of periodontitis by identifying inflammatory and proteolytic signatures before extensive structural breakdown becomes clinically evident,

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thereby supporting a shift toward more preventive and personalized periodontal care [2]. At the same time, advances in regenerative oral medicine and tissue engineering have shown that the biological microenvironment of periodontal and peri-implant tissues plays a decisive role in healing, remodeling, and therapeutic success, further strengthening the importance of biochemical profiling in oral diagnostics [3]. This broader translational relevance is also reflected in the surgical management of peri-implant inflammatory lesions, where disease activity and treatment outcomes are closely linked to local biological conditions rather than to morphology alone [4].

In parallel, the clinical expression of periodontal inflammation extends beyond attachment loss, encompassing manifestations such as halitosis, which has been associated with volatile sulfur compounds and may reflect shifts in both microbial metabolism and inflammatory burden [5]. Such observations reinforce the concept that oral fluids can provide real-time information about disease activity. In this regard, saliva and other oral fluids are increasingly viewed not only as passive diagnostic substrates, but as biologically informative media capable of reflecting dynamic interactions between dysbiotic biofilms and host inflammatory response [1,5]. This broader interpretive value is especially relevant in periodontal disease, where clinical signs may not always correspond precisely to ongoing molecular activity. Moreover, the emergence of advanced drug delivery systems for oral pathogens has highlighted the need for biomarker-guided therapeutic strategies capable of matching local treatment to the biological profile of the lesion [6]. Such an approach is consistent with the transition toward precision-based periodontal care, in which therapeutic decisions are increasingly informed by disease-specific molecular and microbiological characteristics rather than by morphology alone [1,6]. The prognostic significance of disease severity is further supported by evidence linking stages 3 and 4 periodontitis with increased short-term tooth loss, underscoring the need for more sensitive tools for risk stratification and monitoring [7].

The biological plausibility of fluid-based diagnostics is strengthened by oral microbiome studies demonstrating distinct microbial signatures in gingivitis and periodontitis, as well as by epidemiological data connecting periodontal inflammation with atherosclerotic cardiovascular disease [8,9]. In addition, innovations in pediatric dental drug delivery, periodontal phenotype assessment, and the systemic interpretation of periodontal disease support a precision-based framework for oral healthcare [10-12]. More recent evidence focusing on salivary MMP-8, gingival crevicular fluid components, and microbiome-derived biomarkers further consolidates the diagnostic relevance of these molecular indicators [13-15]. Therefore, this review aims to synthesize current evidence on salivary and gingival crevicular biomarkers in periodontal disease, with particular emphasis on their role in early diagnosis, disease monitoring, and precision-guided therapeutic strategies.

Figure 1. Biological and translational framework of salivary and gingival crevicular fluid biomarkers in periodontal disease. Periodontal disease arises from the interaction between subgingival dysbiosis and a dysregulated

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host immune response, resulting in chronic inflammation, connective tissue degradation, and alveolar bone loss. These processes generate measurable molecular changes in saliva and gingival crevicular fluid, including inflammatory mediators, proteolytic enzymes, microbial signatures, and tissue remodeling markers. The detection of these biomarkers supports early diagnosis, disease monitoring, risk stratification, and the development of precision-guided therapeutic strategies in periodontal care.

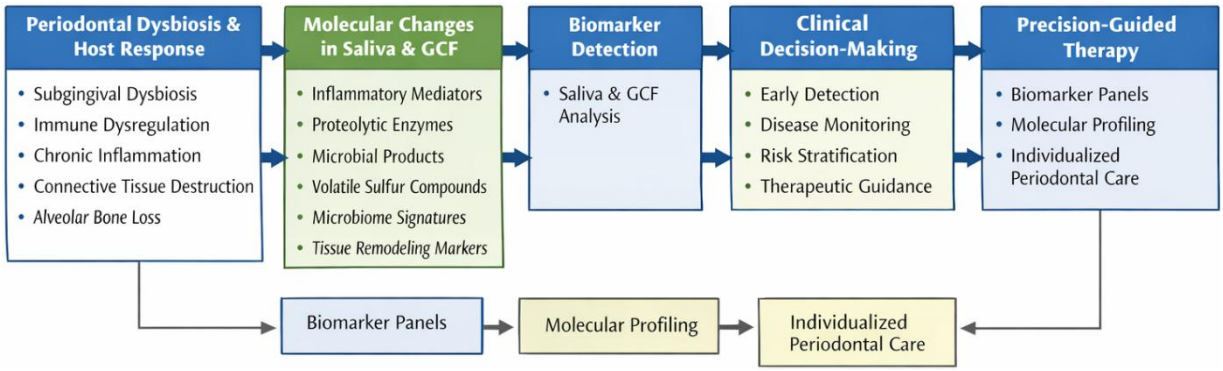

Figure 1. Biological and translational framework of salivary and gingival crevicular fluid biomarkers in periodontal disease.

2. Biological basis of periodontal disease and the rationale for biomarker use

Periodontal disease is currently understood as a biologically complex condition resulting from the interaction between microbial dysbiosis and a dysregulated host inflammatory response, ultimately leading to connective tissue breakdown, alveolar bone resorption, and progressive loss of tooth-supporting structures. In this framework, the biological basis of periodontal destruction cannot be reduced to the mere presence of pathogenic bacteria, but must be interpreted as the consequence of dynamic host–microbe interactions that vary in intensity, composition, and clinical expression across individuals. Recent systematic evidence has shown that microbiome-derived biomarkers may distinguish periodontitis from periodontal health with relevant diagnostic performance, supporting the concept that disease-related microbial shifts are not only etiologically important but also clinically exploitable as measurable indicators of periodontal pathology [15].

At the same time, the biological rationale for biomarker use in periodontology extends beyond microbial composition alone. Oral fluids reflect a broad range of host-derived molecular events, including inflammatory signaling, proteolysis, immune activation, and tissue remodeling. This is particularly important because conventional periodontal diagnosis relies largely on clinical and radiographic signs that document established tissue damage rather than ongoing biological activity. In contrast, saliva offers access to real-time biochemical information, making it an attractive medium for identifying active disease processes, monitoring progression, and evaluating treatment response [16]. From this perspective, biomarkers are valuable precisely because they can capture disease biology at a

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molecular level before, during, and after clinically visible changes occur.

Further support for this approach comes from studies focusing on regulatory molecules involved in periodontal inflammation. Molecular profiling of oral fluids has increasingly emphasized the contribution of small non-coding RNAs, especially microRNAs, which appear to reflect inflammatory regulation and tissue response in periodontal disease. Their growing relevance illustrates a broader shift from single-marker models toward integrated molecular phenotyping, in which disease is characterized through interacting biomarker networks rather than isolated variables [17]. This conceptual evolution is important because it aligns periodontal diagnostics with the broader trend toward biologically stratified medicine, where molecular complexity is interpreted as clinically meaningful rather than incidental. In this framework, microRNAs may provide added value not only as biomarkers of current inflammatory activity, but also as indicators of regulatory processes that help explain interindividual variation in disease expression and tissue response [17]. They are therefore of particular interest in a disease such as periodontitis, in which clinical presentation, inflammatory burden, and tissue destruction may vary substantially among patients despite apparently similar local etiologic factors. This regulatory dimension broadens the interpretive value of oral fluid analysis and supports a more nuanced understanding of disease activity at the molecular level [17]. This transition is reinforced by advances in artificial intelligence, which enable the interpretation of large and complex salivary datasets, facilitating the identification of patterns that may better correspond to biological heterogeneity among periodontal patients [18]. In practical terms, AI-assisted analysis may support the transformation of complex molecular information into clinically interpretable models with greater diagnostic and predictive potential [18].

Moreover, biomarker rationale is strengthened by evidence that diagnostic accuracy improves when multiple molecular markers are combined. Multiplex biomarker models and proteomics-based investigations suggest that periodontal disease is best represented by composite molecular signatures encompassing inflammation, host response, and tissue degradation pathways [19,20]. This is biologically plausible because periodontitis is a multifactorial condition in which no single analyte can fully reflect the diversity of active pathogenic processes. Meta-analytic evidence on protein-based salivary biomarkers further supports the idea that oral fluid analysis can provide clinically meaningful diagnostic information, while also underscoring the need for methodological standardization [21]. Together, these findings suggest that future biomarker-based diagnostics will likely rely less on isolated markers and more on integrated molecular panels capable of capturing the multidimensional nature of periodontal disease [19-21]. Collectively, these findings justify the use of biomarkers as biologically grounded tools for a more precise and dynamic understanding of periodontal disease.

The principal biological mechanisms underlying periodontal disease and their implications for biomarker-based diagnostics are summarized in Table 1.

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Table 1. Key biological mechanisms underlying periodontal disease and their relevance for biomarker-based diagnostics

Biological concept	Pathogenic significance	Relevance for biomarker-based assessment	Ref.
Microbial dysbiosis and host-microbe interaction	Periodontal disease results from a dynamic interaction between dysbiotic microbial communities and a dysregulated host immune-inflammatory response, leading to connective tissue breakdown and alveolar bone resorption.	Supports the use of microbiome-derived biomarkers as measurable indicators of disease-related ecological shifts and biologically active periodontal pathology.	[15]
Oral fluids as mirrors of periodontal biology	Saliva and gingival crevicular fluid reflect ongoing molecular events within periodontal tissues, including inflammatory signaling, proteolysis, immune activation, and tissue remodeling.	Provides the rationale for using oral fluids as minimally invasive diagnostic media capable of capturing real-time disease activity beyond conventional clinical findings.	[16]
Regulatory molecular mechanisms	Small non-coding RNAs, particularly microRNAs, participate in the regulation of inflammation and tissue response in periodontal disease.	Expands biomarker assessment from conventional protein mediators toward molecular phenotyping based on regulatory signatures.	[17]
Data complexity and biological heterogeneity	Periodontal disease exhibits marked interindividual variability in inflammatory activity, microbial profile, and clinical expression.	Artificial intelligence-assisted analysis may help identify complex salivary patterns that better reflect biological heterogeneity and improve diagnostic interpretation.	[18]
Multiplex biomarker profiling	Periodontal disease is not represented adequately by a single molecular alteration, but rather by interacting pathways involving inflammation, host response, and tissue degradation.	Supports the use of combined biomarker panels with improved diagnostic performance over isolated markers.	[19]
Proteomic characterization of periodontal activity	Proteomics-based investigations allow broader identification of proteins associated with periodontal inflammation and tissue destruction.	Strengthens the concept of composite molecular signatures for disease characterization and monitoring.	[20]
Protein-based salivary biomarkers	Protein biomarkers in oral fluids have shown clinically meaningful associations with periodontal disease.	Confirms the translational potential of salivary diagnostics, while highlighting the need for methodological standardization and validation.	[21]

3. Salivary biomarkers in early detection and disease monitoring

Saliva has emerged as one of the most promising diagnostic media in periodontology because it allows rapid, non-invasive, and repeatable assessment of molecular changes associated with periodontal inflammation and tissue destruction. Unlike conventional clinical parameters, which mainly reflect already established damage, salivary biomarkers may provide biologically relevant information about ongoing disease activity, thereby supporting earlier diagnosis and

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more refined monitoring of periodontal progression [1,2]. This diagnostic potential is particularly important in a disease characterized by temporal variability, site-specific activity, and marked heterogeneity in host response.

Among the salivary biomarkers most extensively investigated, matrix metalloproteinase-8 (MMP-8) has shown particular relevance because it directly reflects collagen degradation and periodontal tissue breakdown. Recent systematic evidence supports its value as a sensitive indicator of periodontal disease, especially when interpreted in the context of inflammatory burden and clinical findings [13]. Protein-based salivary markers more broadly, including inflammatory mediators, proteolytic enzymes, and host-response molecules, have also demonstrated meaningful diagnostic performance, particularly when used in combination rather than isolation [19,21]. This multiplex approach is increasingly favored because periodontal disease is biologically complex and unlikely to be accurately represented by a single analyte.

The principal categories of salivary biomarkers and their clinical relevance in early periodontal diagnosis and disease monitoring are summarized in Table 2.

Table 2. Main salivary biomarkers and their relevance in early periodontal diagnosis and disease monitoring

Salivary biomarker category	Biological significance	Clinical relevance in periodontology	Ref.
Inflammatory and proteolytic biomarkers	Reflect host inflammatory activation, collagen degradation, and periodontal tissue breakdown.	Useful for early detection of active periodontal destruction and for monitoring disease activity beyond conventional clinical parameters.	[1,2,13]
Matrix metalloproteinase-8 (MMP-8)	Indicates collagen degradation and connective tissue breakdown.	Considered one of the most relevant salivary biomarkers for identifying periodontitis and assessing inflammatory burden.	[13]
Protein-based salivary biomarker panels	Integrate multiple host-response and tissue-destructive pathways.	Improve diagnostic performance when used in multiplex models rather than as isolated biomarkers.	[19,21]
Microbial and metabolite-derived biomarkers	Reflect dysbiosis and microbial metabolic activity, including volatile sulfur compounds.	Support discrimination between periodontal health, gingivitis, and periodontitis, and may complement host-derived biomarker assessment.	[5,8,15]
Proteomics-derived salivary profiles	Provide broader molecular characterization of disease-related pathways.	May enhance disease stratification, severity assessment, and identification of composite diagnostic signatures.	[20]
Saliva as a monitoring medium	Allows repeated, non-invasive sampling over time.	Particularly suitable for longitudinal monitoring, follow-up evaluation, and precision-guided periodontal care.	[16,18]

In addition to host-derived proteins, salivary diagnostics may incorporate information related to microbial metabolism and dysbiosis. Volatile sulfur compounds, for example, have been associated with gingivitis and periodontitis

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and may reflect both inflammatory changes and microbial activity within the periodontal environment [5]. Likewise, microbiome-based analyses indicate that salivary and oral microbial profiles can discriminate between periodontal health and disease, further extending the role of saliva beyond inflammatory biomarker detection alone [8,15]. Proteomics-based investigations have strengthened this perspective by identifying broader molecular patterns linked to disease status and severity [20].

The clinical relevance of salivary biomarkers lies not only in diagnosis, but also in longitudinal monitoring and therapeutic stratification. Saliva can be repeatedly collected with minimal discomfort, making it particularly suitable for follow-up evaluation, response assessment, and potentially chairside testing [16]. In this context, salivary biomarker profiling represents an important step toward precision-guided periodontal care, where diagnostic decisions are increasingly informed by biological activity rather than by structural damage alone [1,18].

4. Gingival crevicular fluid biomarkers and their diagnostic performance

Gingival crevicular fluid (GCF) is a particularly valuable diagnostic medium in periodontology because it originates directly from the periodontal sulcus and therefore reflects local inflammatory and tissue-destructive processes more specifically than whole saliva. As an exudative fluid enriched with host cells, inflammatory mediators, enzymes, and degradation products, GCF provides biologically relevant information on the active periodontal microenvironment and may detect molecular changes associated with disease activity before they become fully evident clinically [14,16]. This site-specificity gives GCF a distinct advantage in the assessment of periodontal lesions, especially when the objective is to identify active inflammation and ongoing tissue breakdown. In contrast to broader oral diagnostic media, GCF is more closely linked to the immediate periodontal environment and may therefore offer a more lesion-oriented perspective on disease activity [14]. This characteristic is particularly relevant in periodontitis, where tissue destruction is often site-specific and biologically heterogeneous, making local molecular assessment especially valuable for early identification and targeted monitoring [16-19].

Among the most relevant GCF-associated biomarkers are proteolytic enzymes, inflammatory cytokines, and molecules involved in connective tissue degradation. Their diagnostic significance lies in the fact that they directly mirror the biological events underlying periodontal destruction, including collagen breakdown, leukocyte recruitment, and host-response amplification [1,14]. Because these molecules are released within the periodontal sulcus during active disease, their presence in GCF provides a biologically plausible link between molecular activity and clinical progression [14,18]. This makes GCF particularly useful not only for detecting the presence of periodontal inflammation, but also for better understanding the intensity and local character of tissue-destructive processes. In this respect, GCF analysis may complement conventional clinical examination by adding a molecular dimension to the

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interpretation of probing depth, bleeding, and attachment loss [14].

In recent years, interest has expanded toward more refined molecular signatures, including microRNAs detected in crevicular fluid, which may provide additional insight into inflammatory regulation and periodontal tissue response [17]. This evolution from conventional inflammatory markers to more complex molecular profiles reflects a broader transition toward precision-oriented diagnostics. Rather than relying exclusively on isolated mediators, current research increasingly supports the value of integrated molecular signatures capable of capturing different aspects of host response and tissue remodeling [17,18]. In this framework, microRNAs are particularly relevant because they may reflect regulatory mechanisms that are not fully represented by protein-based biomarkers alone, thereby enriching the biologic interpretation of periodontal activity [17,20]. Their inclusion in GCF-based profiling therefore supports a more nuanced and mechanistically informed assessment of local disease processes.

The diagnostic performance of GCF biomarkers appears to improve when they are interpreted as part of combined biomarker panels rather than as isolated indicators. Systematic evidence suggests that multimarker approaches may enhance discrimination between periodontal health and disease by integrating signals related to inflammation, proteolysis, and host regulation [19]. This is consistent with the multifactorial nature of periodontitis, in which no single analyte is likely to reflect the full complexity of active disease. Multimarker models may therefore provide better diagnostic resolution and improve the biologic stratification of periodontal lesions, particularly in cases with variable inflammatory expression or mixed clinical presentation [14,19]. Such an approach is also more compatible with the current view of periodontal disease as a dynamic condition driven by interacting molecular pathways rather than by a single pathogenic mechanism.

In parallel, microbiome-derived and proteomics-based strategies have broadened the understanding of how local molecular patterns in oral fluids may contribute to more accurate periodontal characterization [15,20]. These approaches expand GCF diagnostics beyond traditional inflammatory markers and support the identification of composite molecular profiles associated with disease status, severity, and tissue response [15]. Proteomics, in particular, may help reveal broader networks of proteins linked to host response and tissue destruction, while microbiome-based signatures may contribute additional information on local dysbiosis and lesion-specific biologic activity [15,16,20]. Together, these developments strengthen the translational potential of GCF as a diagnostic substrate and support its inclusion within more advanced molecular frameworks for periodontal assessment.

Collectively, these findings support GCF as a highly informative and biologically grounded substrate for periodontal diagnosis, with substantial potential for disease monitoring and individualized risk assessment. Its main diagnostic strength lies in its close relationship with the periodontal lesion itself, which allows more direct assessment of local inflammatory and destructive events than is possible with less site-

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specific fluids [14,16]. Although further standardization and validation remain necessary, current evidence indicates that GCF biomarkers may play an increasingly important role in the transition from conventional periodontal diagnostics toward precision-guided, biologically stratified clinical care [17,19,20].

5. From molecular profiling to precision-guided therapeutic strategies

The transition from conventional periodontal assessment to molecular profiling has created the foundation for precision-guided therapeutic strategies, in which diagnosis, risk estimation, and treatment planning are increasingly informed by biological activity rather than by clinical parameters alone. Salivary and gingival crevicular biomarkers provide access to dynamic information on inflammation, proteolysis, dysbiosis, and tissue response, thereby allowing a more individualized understanding of disease status and progression [1,14,16]. In this context, the value of biomarkers lies not only in detecting periodontitis, but also in stratifying patients according to biological risk and probable therapeutic responsiveness.

This approach is particularly relevant because periodontal disease is heterogeneous in both severity and host response. Evidence linking advanced periodontitis with short-term tooth loss highlights the clinical importance of identifying patients with a biologically active and prognostically unfavorable profile [7]. Similarly, microbiome-derived biomarkers may contribute to therapeutic personalization by distinguishing dysbiotic patterns associated with different disease states, while proteomics-based analyses expand the ability to identify molecular networks involved in tissue destruction and healing [15,20]. Such data support a shift from static diagnostic labels toward biologically informed disease phenotyping.

Precision-guided therapy also has implications for local treatment delivery and regenerative management. Advances in drug delivery systems for oral pathogens and the development of bioresponsive nanotechnological platforms indicate that therapeutic efficacy may increasingly depend on matching the intervention to the molecular characteristics of the lesion and host environment [6,10]. In parallel, broader translational perspectives in oral diagnostics, including artificial intelligence-assisted biomarker interpretation, may facilitate integration of complex molecular data into clinically applicable decision models [18]. Altogether, these developments suggest that biomarker-guided periodontology may improve early intervention, optimize treatment selection, and support more personalized long-term periodontal care [1,19].

6. Current limitations, translational challenges, and future directions

Despite the considerable progress in salivary and gingival crevicular fluid biomarker research, several important limitations continue to hinder the routine clinical implementation of these approaches in periodontology. One of the main challenges is the marked heterogeneity across studies in relation to patient selection, disease classification, sampling protocols, analytical methods, and outcome definitions. This variability complicates direct comparison between investigations and reduces the reproducibility of reported

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diagnostic thresholds and biomarker performance [2,13,19,21]. In addition, periodontal disease is biologically and clinically heterogeneous, meaning that the same biomarker may not perform equally across different disease stages, phenotypes, or systemic backgrounds [1,11].

Another critical issue is the lack of standardization in oral fluid collection and processing. Salivary biomarker concentrations may be influenced by salivary flow rate, circadian variation, oral hygiene status, recent food intake, and concomitant oral or systemic conditions, while gingival crevicular fluid analysis may be affected by sampling technique and site selection [14,16]. Moreover, although many biomarkers have shown statistical associations with periodontitis, fewer have demonstrated sufficient robustness for chairside diagnostic deployment or longitudinal therapeutic monitoring in real-world clinical settings [17,20]. For this reason, the translational gap between biomarker discovery and validated clinical application remains substantial.

A further challenge concerns the interpretation of biomarkers in isolation. Current evidence increasingly supports the superiority of multimarker approaches integrating inflammatory, proteolytic, microbiological, and host-response data over single-analyte models [15,18,19]. However, such integrated strategies require advanced computational support, harmonized validation frameworks, and clinically meaningful cutoff values before they can be incorporated into routine practice. Artificial intelligence may help address part of this complexity by identifying clinically relevant molecular patterns and supporting predictive decision models [18].

Future research should therefore prioritize large, well-standardized prospective studies aimed at validating biomarker panels across diverse populations and periodontal phenotypes [1,19]. Particular attention should be given to combining salivary, crevicular, microbiome, and proteomic data into clinically applicable platforms that support early diagnosis, risk stratification, and treatment personalization [15,16,20]. Ultimately, the future of biomarker-guided periodontology depends on transforming promising molecular signals into reproducible, cost-effective, and clinically actionable diagnostic tools.

Conclusions

Salivary and gingival crevicular fluid biomarkers represent a major step toward a more biologically informed understanding of periodontal disease. By reflecting inflammation, proteolysis, dysbiosis, and tissue remodeling, these molecular indicators extend periodontal assessment beyond conventional clinical and radiographic parameters. Current evidence supports their relevance for early detection, disease monitoring, and improved characterization of periodontal activity. In particular, the integration of salivary and crevicular biomarkers offers a promising framework for identifying active disease processes earlier and for aligning periodontal diagnostics with the broader principles of precision-guided oral healthcare.

At the same time, the translation of these biomarkers into routine clinical practice still requires careful validation, methodological standardization, and stronger evidence from prospective studies. The future of periodontal diagnostics will

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likely depend not on isolated biomarkers, but on composite molecular panels integrating host-response, microbiome, and proteomic data into clinically interpretable models. Such an approach may improve risk stratification, therapeutic selection, and longitudinal monitoring, particularly when supported by digital tools and artificial intelligence-based analysis. Overall, salivary and gingival crevicular biomarkers should be regarded not merely as adjunctive laboratory findings, but as emerging instruments capable of reshaping periodontal diagnosis and supporting more personalized, predictive, and therapeutically relevant patient care.

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