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Salivaomics And Artificial Intelligence: A New Frontier in Periodontal Diagnostics

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Abstract
Periodontitis is a highly prevalent, largely silent inflammatory disease. Conventional diagnosis relies on clinical and radiographic parameters that represent cumulative tissue destruction rather than real time disease activity. Two converging fields are starting to change the diagnostic paradigm in the past few years: salivary biomarker science and artificial intelligence (AI). Saliva is an easily accessible and non-invasively sampled biofluid that harbors a vast repertoire of inflammatory cytokines, proteolytic enzymes, oxidative stress markers, microbial signatures and more and more extracellular vesicles, microRNAs and metabolomic markers reflecting the host-microbial interface driving periodontal destruction. Meanwhile, machine learning and deep learning methods are being increasingly trained on these molecular data sets achieving diagnostic accuracies matching or exceeding single-biomarker assays, while enabling multiclass disease staging, biomarker-panel optimization and point-of-care device engineering. This review summarizes the periodontology literature on salivary biomarkers and AI-enabled diagnostics published from 2020 to 2026. It discusses the well-established and emerging classes of biomarkers, the main AI architectures used for the analysis of salivary data, and the use of AI in conjunction with biosensor and microfluidic platforms including wearable and paper-based devices. We discuss translational barriers that still separate promising research findings from everyday chairside application, including biomarker standardization, small and non-generalizable datasets, algorithmic interpretability, costs, and regulatory pathways, as well as future directions such as multiomic data fusion and federated learning. Collectively, these developments foreshadow a shift in periodontal care from a reactive, damage-based diagnosis to a predictive, non-invasive and personalized disease monitoring.

Keywords: *Saliva; Biomarkers; Periodontitis; Artificial Intelligence; Machine Learning; Point-of-care diagnostics*

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I. INTRODUCTION

Periodontitis is one of the most common chronic inflammatory diseases of humans. Severe forms are estimated to affect several hundred million people globally and are a leading cause of tooth loss, with a substantial and increasing disease burden documented by global burden analyzes over the past three decades [1]. Periodontitis is now recognized to be bidirectionally linked to systemic conditions, most notably diabetes mellitus and cardiovascular disease, in addition to its locally destructive effects on the tooth-supporting apparatus. The relationship has been formalized in joint consensus reporting between periodontal and cardiovascular medicine bodies.

Despite this burden, the diagnostic tools available to clinicians have changed relatively little over the past few decades. Probing depth, clinical attachment loss, bleeding on probing and radiographic bone loss remain the cornerstones of periodontal assessment, but each of these parameters is essentially retrospective in that it quantifies the accumulated result of previous tissue destruction rather than the current biological activity of disease. This limitation limits the identification of early or subclinical disease, makes it difficult to differentiate between currently active and quiescent sites, and provides little insight into an individual patient's risk of future progression.

The search for objective biologically informed diagnostic adjuncts has therefore increasingly turned to host-derived and microbial molecules present in oral fluids. Saliva has remained a collection medium of research interest because it can be collected rapidly and repeatedly without the discomfort or technique sensitivity of gingival crevicular fluid (GCF) sampling, and its molecular content reflects local periodontal inflammation and, to a lesser extent, systemic host status. At the same time, artificial intelligence (AI) and machine learning (ML) have evolved from a specialized research interest to a dominant part of dental informatics, with expanding applications in diagnostic imaging, caries detection, orthodontic planning, and periodontal prognostication [3,4].

When applied to the complex, multidimensional datasets generated by salivary biomarker panels, AI offers the possibility of integrating numerous analytes, clinical parameters, and microbial signatures into a single, interpretable diagnostic classification or risk score — a task poorly suited to traditional univariate statistical approaches.

This review synthesizes literature published between 2020 and 2026 addressing the intersection of salivary biomarker science and AI-enabled analytics in periodontology. Saliva is first established as a diagnostic medium, before established and emerging salivary biomarker classes are surveyed, the principles and applications of AI in this domain are examined, the convergence of AI with biosensor and microfluidic hardware is described, and finally the translational, ethical, and regulatory considerations that will determine clinical adoption are discussed.

II. SALIVA AS A DIAGNOSTIC MEDIUM

Whole saliva is a complex biofluid secreted by major and minor salivary glands and further enriched at periodontally involved sites by gingival crevicular fluid (GCF), a serum transudate/exudate that exudes from the gingival sulcus and often contains higher local concentrations of inflammatory mediators than whole saliva. Therefore, whole-mouth saliva provides a diluted, but field-representative sample of the entire oral cavity, whereas site-specific GCF sampling yields higher analyte concentrations but is technique-sensitive, site-limited and time-consuming to collect; a trade-off that has driven the gradual move within the biomarker literature toward whole saliva for population-level screening and point-of-care applications.

Advantages of saliva as a diagnostic medium are many and practical: collection is non-invasive and painless and requires no specialized clinical skill, is inexpensive relative to serum or GCF sampling and can be repeated frequently to support longitudinal monitoring or even home-based and tele dentistry-linked testing. These properties make saliva particularly attractive for population screening, risk stratification and treatment-response monitoring in cases where repeated invasive sampling would be impractical. However, against these advantages must be weighed a set of pre-analytical variables that remain a recurrent source of heterogeneity in the biomarker literature. Measured analyte concentrations can be materially altered by collection method (unstimulated passive drool vs. stimulated saliva, spitting, swab or absorbent-device collection), time of day and circadian variation, recent oral hygiene or food intake, and sample storage and freeze–thaw stability. A 2023 meta-analysis that pooled data from dozens of studies attributed much of the wide variation in reported biomarker accuracy to this preanalytical and cohort-level heterogeneity, and warned against overinterpretation of any single diagnostic cutoff value across populations [5].

These considerations have led to the concept of ‘salivaomics’ – the comprehensive high-throughput analysis of the proteomic, transcriptomic, metabolomic and microbiomic content of saliva as an integrated diagnostic framework rather than the study of single analytes in isolation [6]. This omics-based framing underpins the ensuing discussion of biomarkers and provides the natural substrate for the multivariate, pattern-recognition strengths of artificial intelligence.

III. SALIVARY BIOMARKERS IN PERIODONTAL DISEASE

Inflammatory Cytokines and Chemokines

Pro-inflammatory cytokines released by resident and infiltrating immune cells in response to subgingival biofilm remain the most extensively studied class of salivary periodontal biomarkers. A 2020 meta-analysis of single salivary biomarkers reported sensitivity/specificity values of 78.7%/78.0% for IL-1β, 72.0%/73.0% for IL-6, 72.5%/70.5% for MMP-8, 70.3%/81.5% for MMP-9, and 72.0%/75.2% for hemoglobin in distinguishing periodontitis from periodontal health in systemically healthy subjects, identifying IL-1β and MMP-8 as the most extensively researched and clinically fair-performing single markers [7]. Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are similarly implicated, with a 2024 case-control study identifying salivary IL-1β and IL-10 as key biomarkers tracking with periodontitis severity (stage III/IV disease showing significantly elevated IL-6 and IL-1β relative to healthy controls) rather than simple presence/absence of disease [8], suggesting a role for cytokine panels in staging and grading as well as screening.

Because no single cytokine offers sufficient discriminatory power for routine clinical use, combination panels have been a major focus of recent meta-analytic work. A 2023 systematic review and meta-analysis of oral-fluid biomarker combinations found that dual combinations of IL-1β, IL-6, and MMP-8 achieved excellent diagnostic ability to detect periodontitis in saliva, concluding that adding further biomarkers beyond two did not substantially improve accuracy [5]. The same body of work has shown that the ratio of a pro-inflammatory cytokine to the anti-inflammatory cytokine IL-2 achieves especially high sensitivity in smokers (exceeding 95%) but with reduced specificity, reflecting the immunosuppressive confounding effect of tobacco use on cytokine-based diagnostics, and that age and smoking status more broadly influence the diagnostic thresholds and predictive capacity of salivary cytokines such as IL-1β [5,9].

Enzymatic and Tissue-Destruction Markers

Matrix metalloproteinase-8 (MMP-8) is a neutrophil- and fibroblast-derived collagenase and a well-validated saliva marker of active periodontal tissue destruction, indicating its role in the degradation of extracellular matrix and collagen thru enzymatic activity. A case-control study of salivary MMP-8, MMP-9 and tissue inhibitor of metalloproteinase-1 (TIMP-1) in 2022 reported area-under-the-curve (AUC) values of 0.892, 0.844 and 0.920 respectively for differentiating periodontitis from periodontal health and these values increased to 0.986 and 1.000 when MMP-8 and MMP-9 were expressed as ratios to TIMP-, a finding consistent with the broader principle that combining a protease with its natural inhibitor compensates for individual biomarker fluctuation and improves diagnostic accuracy [10]. This diagnostic strength has been validated sufficiently to justify a clinically validated, chair-side lateral-flow point-of-care active-MMP-8 (aMMP-8) test capable of distinguishing periodontal health, gingivitis and periodontitis stages and grades from an oral rinse sample, a platform currently being explored as a substrate for automated, AI-assisted interpretation of test-line intensity [11].

Oxidative Stress Markers

Periodontal inflammation is accompanied by local and systemic oxidative stress, reflected in saliva by markers such as 8-hydroxy-2′-deoxyguanosine (8-OHdG), malondialdehyde, and measures of total antioxidant capacity. These markers are consistently reported as elevated (or, for antioxidant capacity, reduced) in periodontitis relative to periodontal health, and are increasingly included alongside cytokine and enzymatic panels in comprehensive salivary biomarker reviews as complementary indicators of the host oxidative burden accompanying chronic inflammation [12,13]. Their diagnostic accuracy in isolation is generally more modest than that of the cytokine and enzymatic markers described above, positioning them primarily as adjunctive rather than stand-alone diagnostic tools.

Microbial and Host-Response DNA Markers

Saliva also contains microbial DNA that can be quantified to estimate bacterial load of periodontal pathogens including the classical ‘red-complex’ species Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola. One influential study measured the copy numbers of nine periodontal pathogens in nearly 700 mouthwash samples using multiplex quantitative PCR. Neural network, support vector machine and random forest models were trained on salivary bacterial copy number data alone, and achieved average classification accuracies of approximately 90 – 93 % for the classification of periodontal health versus chronic periodontitis of varying severity. This was an early and influential demonstration that microbial burden data, independent of host inflammatory markers, contains sufficient diagnostic signal for algorithmic classification [14]. This approach captures a dimension of periodontal pathobiology - microbial burden - that is mechanistically distinct from and complementary to the host inflammatory response captured by cytokine and enzymatic panels.

Bone Turnover and Other Biochemical Markers

Markers of alveolar bone remodeling, including the receptor activator of nuclear factor kappa-B ligand to osteoprotegerin (RANKL/OPG) ratio and calprotectin, provide additional insight into the balance between bone resorption and formation that ultimately determines periodontal attachment loss. Salivary hemoglobin, reflecting subclinical bleeding from the inflamed sulcus, has also re-emerged as a practical early biomarker (with a pooled sensitivity of approximately 72% in meta-analytic data [7]), forming the analytical target of recently described machine-learning-optimized paper-based microfluidic point-of-care devices.

Diagnostic Performance Summary

Reported accuracy figures should be viewed with care considering the pre-analytical and cohort-related heterogeneity described above, but the overall trend being fair-to-good performance for individual analytes, with notable improvement in combination panels, is consistent across the recent literature and provides an empirical basis for the multivariate, AI-based approaches discussed later in this review.

Table 1: Summarizes the representative diagnostic performance of the major salivary biomarker classes.

Biomarker / Class	Biological Role	Reported Diagnostic Performance	Validation Stage
IL-1β	Osteoclastogenic pro-inflammatory cytokine	Pooled sensitivity 78.7%, specificity 78.0% [7]	Most extensively studied single marker
IL-6	Pro-inflammatory cytokine; tracks severity	Pooled sensitivity 72.0%, specificity 73.0% [7]; elevated in stage III/IV vs. healthy controls [8]	Widely studied; not yet standardized

IL-1β + IL-6 + MMP-8 (dual combinations)	Combined inflammatory/enzymatic signal	Excellent ability to detect periodontitis in pooled meta-analysis; ≥95% sensitivity in smokers via IL-2 ratio [5]	Meta-analytically supported
MMP-8 / MMP-9 / TIMP-1 (and ratios)	Collagenase, gelatinase, and natural inhibitor	AUC 0.892 / 0.844 / 0.920; ratios up to 0.986–1.000 [10]	Case-control validated
MMP-8 (aMMP-8)	Collagenase; active tissue destruction	Validated chairside point-of-care lateral-flow test [11]	Clinically available assay
Oxidative stress markers (8-OHdG, MDA)	Host oxidative burden	Consistently elevated in disease; modest standalone accuracy [12,13]	Adjunctive marker
Salivary bacterial copy number (red-complex pathogens)	Microbial burden	ML classification accuracy ≈90–93% [14]	Research / ML-integrated
RANKL/OPG, salivary hemoglobin	Bone turnover / subclinical bleeding	Hemoglobin pooled sensitivity ≈72% [7]; substrate for AI-optimized microfluidic devices	Emerging device integration

IV. EMERGING 'OMICS' AND NOVEL BIOMARKER CLASSES

Extracellular Vesicles (Exosomes)

Salivary extracellular vesicles, particularly exosomes, are membrane-bound nanoparticles secreted by host and, in some cases, microbial cells that carry protected cargo of proteins, lipids, and nucleic acids, including microRNAs. Because their lipid bilayer shields cargo from salivary nucleases and proteases, exosomal content is comparatively stable relative to free-circulating salivary molecules, an attractive property for a diagnostic medium subject to considerable pre-analytical variability. Exosomal microRNA profiling has been proposed as a biomarker strategy for both periodontitis and oral cancers, reflecting a shared interest in exosomes as a stable, information-rich diagnostic substrate across oral disease domains [15]. Recent work suggests that salivary exosomal microRNAs may offer superior diagnostic specificity relative to traditional soluble markers, although clinical translation remains constrained by technical variability in isolation methods, limited in vivo validation, and inter-individual differences in exosome yield and cargo [16].

MicroRNAs and Epigenetic Markers

In addition to their exosomal packaging, free and vesicle-associated microRNAs (miRNAs) have independently surfaced as one of the most explored new biomarker classes in periodontology. Initial foundational work identified miR-146a and miR-155 as biomarkers in the crevicular fluid for distinguishing periodontitis in both non-diabetic and type 2 diabetic patients [17], followed by a subsequent salivary pilot study that expanded this to a four-miRNA panel (miR-146a, miR-146b, miR-155, and miR-203) and reported that miR-155 was the best predictor of periodontitis in non-diabetic subjects, while miR-146a was the best predictor in patients with diabetes [18]. Salivary miR-155 and miR-146a expression also have been shown to have independent clinical value for monitoring periodontitis [19], and a recent meta-analysis summarizing this body of work identified miR-146a, miR-155 and miR-223 as the most reproducibly reported periodontitis-associated microRNAs, with miR-146a and miR-155 showing the strongest diagnostic accuracy [16].

Salivary Metabolomics and Proteomics

The development of high-throughput mass spectrometry-based metabolomic and proteomic platforms has enabled untargeted profiling of the broader salivary molecular landscape in periodontal disease, moving from hypothesis-driven single-analyte assays to discovery of metabolite and protein signatures capable of discriminating between periodontal health, gingivitis, and periodontitis as discrete molecular states [6,20]. Untargeted SWATH mass-spectrometry approaches applied to saliva have identified panels of proteins that achieve outstanding diagnostic accuracy for periodontitis when adjusted for age, demonstrating that combining omics-scale discovery with careful covariate adjustment can substantially improve on the performance of individual candidate proteins [20]. These approaches produce high-dimensional data sets, often on the order of hundreds to thousands of features per sample. These data sets are well suited to the pattern recognition capabilities of machine learning.

Cell-Free DNA and Microbiome/Metagenomic Signatures

Beyond enumeration of pathogen copy numbers, metagenomic and metatranscriptomic tools now permit the characterization of whole-community dysbiosis, including loss of health-associated commensal taxa and alterations in functional gene expression, as an integrated biomarker of periodontal risk, separate from, but complementary to, classical red-complex pathogen quantitation [21]. Another emerging analyte class within this

framework is cell-free DNA (both host and microbe-derived), although its periodontal-specific validation is comparatively early-stage relative to the miRNA and exosomal literature described above.

V. ARTIFICIAL INTELLIGENCE: CONCEPTS RELEVANT TO PERIODONTAL DIAGNOSTICS

Artificial intelligence (AI) is a catchall term for computational approaches that execute tasks that typically require human intelligence; machine learning (ML), the AI subset most relevant to salivary biomarker analysis, represents algorithms that learn patterns directly from data rather than by following explicitly programmed rules. There is a large gap in ML between classical algorithms (e.g., Random Forest, Support Vector Machine, Gradient-Boosting methods such as Extreme Gradient Boosting (XGBoost)) and deep learning approaches based on artificial neural networks (ANNs) with more complex architectures such as convolutional neural networks (CNNs) generally used for image data. Classical ML models are generally well suited for the moderately dimensional tabular data of salivary biomarker panels (a few to a few dozen analytes per patient), while deep learning architectures excel on larger, higher dimensional, or image-based datasets, such as those generated by omics platforms or intraoral photography [3,4].

To critically appraise the AI-based diagnostic literature, clinicians need to understand several methodological concepts. Models are usually trained on a training dataset, fine-tuned on a validation dataset, and tested on a held-out test dataset. Ideally, performance is corroborated on an external dataset from a different patient population or institution to demonstrate generalizability. The diagnostic performance is usually summarized by the area under receiver operating characteristic curve (AUC-ROC) and sensitivity and specificity at a chosen operating threshold. A common limitation of the current literature on periodontal AI is that many published models only report internal cross-validation performance without external validation, limiting confidence in their generalizability to the real world.

Another methodological concern is the interpretability of models, which is particularly important for clinical and regulatory adoption. Many high-performing ML and deep learning models are relative 'black boxes' with little insight into which input features drove a prediction. As regulatory structures for AI-based diagnostic tools mature, explainability techniques such as SHAP (SHapley Additive exPlanations) values and feature-importance ranking are increasingly used to make model outputs more transparent to clinicians, and are likely to become a de facto requirement. A brief note is warranted on generative AI and large language models which are increasingly talked about in dentistry for documentation and communication with patients; these are a different application domain from the diagnostic classification models which are the subject of this review and are not discussed further here.

VI. ARTIFICIAL INTELLIGENCE APPLIED TO SALIVARY BIOMARKER DATA

Machine Learning Models Trained on Salivary/GCF Biomarker Panels

More and more studies are applying classical ML algorithms to integrate salivary biomarker and clinical parameter datasets for periodontal diagnosis and staging. Deng et al. developed a machine learning based multiclass screening tool, capable of discriminating periodontal health, gingivitis and different stages of periodontitis, by combining clinical parameters and salivary biomarkers. This proved that multiclass staging, instead of binary health/disease classification, is possible with panel-based salivary data [22]. In the wider literature, AI models trained on features derived from saliva have achieved AUC values ranging from approximately 0.93 to 0.96, with algorithms such as random forest, artificial neural networks, and gradient-boosting algorithms exhibiting robust discriminative ability in both binary (healthy vs diseased) and multiclass (health, gingivitis, and periodontitis stages) classification tasks [23].

AI for Salivary Microbial Load and Microbiome-Based Prediction

Machine learning has also been applied specifically to microbial features derived from saliva. As noted above, models trained on multiplex-qPCR-derived salivary bacterial copy number data achieved average classification accuracies of roughly 90–93% for distinguishing periodontal health from varying severities of chronic periodontitis, an early and influential demonstration that microbial burden data, independent of host inflammatory markers, carries sufficient diagnostic signal for algorithmic classification [14]. This line of work anticipates the more recent metagenomic and dysbiosis-index approaches described above and suggests substantial room for models that integrate microbial and host-response features jointly.

AI in Biomarker Discovery and Validation Pipelines

Beyond diagnostic classification, AI is increasingly used earlier in the biomarker pipeline — for feature selection, panel optimization, and discovery of candidate biomarkers from high-dimensional omics data. A dedicated review of AI applications in salivary biomarker discovery and validation across oral and maxillofacial disease highlights this expanding role, noting that AI-based approaches can help prioritize candidate analytes from

proteomic and metabolomic datasets before they proceed to targeted, clinically oriented validation studies, and observing that the equivocal accuracy of many salivary biomarkers during validation is itself a motivation for incorporating more sophisticated analytical techniques earlier in the discovery pipeline [24]. This discovery-stage application of AI is methodologically distinct from, but complementary to, the diagnostic-classification applications described above, and is likely to become increasingly important as multi-omic datasets grow in scale.

Systematic Review and Meta-Analytic Evidence (2025–2026)

A 2025 systematic review and meta-analysis that specifically assessed AI models trained on non-invasive or minimally invasive biomarkers – saliva, GCF, and immunologic profiles – for periodontitis diagnosis found a small number of eligible studies using models such as random forest, artificial neural networks, and gradient boosting, several of which derived biomarkers directly from saliva or saliva-derived oral rinse [23]. The review concluded that AI models trained on non-invasive or minimally invasive biomarkers, particularly salivary ones, can achieve diagnostic performance that aligns well with the goals of precision dentistry. It explicitly notes that the evidence base is still limited to a small number of studies, pointing to the need for larger, externally validated trials before these tools can be considered ready for routine clinical use [23]. This tension – good point-estimate diagnostic performance combined with a still narrow evidence base – is a recurrent theme in the AI-periodontology literature.

VII. INTEGRATED PLATFORMS: BIOSENSORS, LAB-ON-CHIP, AND AI CONVERGENCE

Point-of-Care Biosensors

Point-of-care (POC) biosensing platforms aim to enable translation of laboratory-validated salivary biomarkers into chairside-actionable tests. The most mature example is still the clinically available lateral-flow aMMP-8 point-of-care test, which allows for rapid discrimination of periodontal health and disease without laboratory processing [11]. In addition to MMP-8, a larger family of electrochemical and optical biosensing platforms are under development, with recent narrative reviews pointing out that the central unanswered question that POC biosensors are being designed to solve, increasingly in tandem with machine learning-based signal interpretation, is differentiating active, ongoing periodontal disease from just recording its cumulative past damage [25,26]. This literature repeatedly emphasizes the requirement for standardized and clinically validated point-of-care diagnostic devices for periodontitis, in view of the fragmented landscape of platforms with different levels of technical and clinical maturity that currently exists [27].

Microfluidic and Paper-Based Analytical Devices

One of the most active areas of convergence of AI and biosensors is in the domain of microfluidic paper-based analytical devices (μPADs), because of their low cost and suitability for resource-limited settings. A 2025 study proposed a cyclic optimizing strategy powered by machine learning to iteratively optimize design and engineering parameters of μPADs for colorimetric detection of salivary hemoglobin, an early biomarker of periodontitis. The strategy combined computer vision, back-propagation neural network, and genetic algorithm. The optimized devices thus obtained showed high accuracy (R2 values of 0.998 and 0.992 for two colorimetric output signals) and low detection limits (about 1.6 and 3 μg/mL, respectively) and were successfully applied to clinical saliva samples [28]. In a similar direction, microfluidic devices based on organic electrochemical transistors (OECTs) have been developed for accurate early diagnosis of periodontal disease from saliva-based point-of-care testing, representing ongoing innovation in transducer technology beyond conventional colorimetric or electrochemical formats [29].

Wearable and Smart-Device Integration

Wearable biosensors integrated into intraoral devices represent perhaps the most forward-looking convergence of salivary diagnostics and AI. Jeon and colleagues (2025) reported a wearable electrochemical biosensor, integrated into a smart mouthguard, that uses a molecularly imprinted polymer (MIP) electrode based on poly(o-phenylenediamine) with a graphene oxide interlayer for non-invasive, label-free, impedance-based detection of salivary MMP-8, coupled with a deep learning-assisted data analysis framework for noise filtering and identification of disease-progression trends. Clinical validation against patient saliva samples demonstrated high specificity and reproducibility, and the platform's wearable mouthguard format was designed explicitly to enable continuous monitoring of oral inflammation and facilitate early therapeutic intervention [30].

Lab-on-a-Chip and Multiplex Platforms

Lab-on-a-chip and multiplex biosensing platforms aim to combine several of the biomarker classes discussed above — for example, simultaneous cytokine, enzymatic, and microbial detection — onto a single miniaturized device, with AI-based algorithms used to interpret the resulting multiplexed signal pattern as a

composite diagnostic or staging output rather than a series of independent single-analyte results. This multiplex, panel-based design directly mirrors the combination-biomarker diagnostic gains reported for dual and triple cytokine/enzyme panels and represents a natural hardware counterpart to the multivariate ML models described above.

7.5 Convergent AI-in-Periodontics Innovations

Beyond biomarker-specific platforms, deep learning is being applied to adjacent, non-biomarker data streams that form part of the same broader AI-in-periodontics landscape. Tao and colleagues developed a global activation pooling-based multi-instance deep learning model, built on a pretrained ResNet50 architecture, that screens for stage II–IV periodontitis directly from oral digital photographs without relying on manually annotated anatomical landmarks, validating the approach in two independent samples against a clinical periodontal examination reference standard [31]. The analysis of panoramic radiographs based on convolutional neural network has also been used for periodontal prognostication and alveolar bone loss detection [32]. At the regulatory level, a manual search of the United States Food and Drug Administration 510(k) premarket notification database revealed more than fifty AI/ML-enabled dental devices approved thru late 2024, with oral radiology representing the largest share and a smaller but increasing share addressing periodontal disease assessment specifically [33], and a complementary review identified nearly thirty FDA-approved AI dental imaging products covering caries detection, periodontal disease assessment, cephalometric analysis, and automated charting [34]. Importantly, these regulatory approvals are still heavily skewed toward imaging AI compared to biomarker AI, which indicates that AI tools specific to salivary biomarkers are further behind in the translational and regulatory pipeline compared to imaging AI.

VIII. CLINICAL TRANSLATION AND PRECISION PERIODONTICS

AI-driven salivary diagnostics should be integrated into existing periodontal workflows, and not replace the established clinical examination, to realize their clinical value. A realistic short-term model places salivary AI-based testing as a chair-side adjunct: a rapid, inexpensive screen to identify patients for more detailed clinical and radiographic evaluation, assist risk stratification for personalizing recall intervals or provide an objective, quantitative marker of treatment response after non-surgical periodontal therapy. Active disease cannot be measured by current clinical parameters, only the cumulative damage. Salivary AI diagnostics should be considered as an adjunct to traditional periodontal charting, not a competitor.

A further precision-medicine rationale for salivary AI diagnostics is the systemic associations of periodontitis with, e.g., diabetes mellitus and cardiovascular disease [2]. Several of the above-discussed biomarkers, including IL-6, miR-155, and RANKL/OPG, have documented associations with periodontal as well as systemic inflammatory conditions. AI models trained on combined periodontal–systemic biomarker data could in principle facilitate integrated risk assessment across oral and systemic health, although this is largely a prospective rather than clinically realized application at this time.

Regulatory pathways will play a large role in the speed of clinical translation. So far, AI/ML dental device clearances have been very heavily concentrated in imaging applications, with periodontal disease assessment being a smaller but growing category [33,34]. Salivary biomarker-based AI diagnostics face an additional layer of regulatory complexity relative to imaging-based tools, as they tend to combine a novel diagnostic assay (the biomarker test itself) with a novel software component (the AI classifier), which may be subject to different regulatory requirements. Early engagement with regulations, and explicit design for interpretability, are likely to be important determinants of which platforms successfully transition from research prototypes to cleared clinical devices.

IX. CHALLENGES, LIMITATIONS, AND ETHICAL CONSIDERATIONS

Several interlocking challenges continue to separate the promising diagnostic performance reported in the literature from routine clinical use. The wide ranges in reported sensitivity and specificity throughout this review are directly attributable to, first, pre-analytical heterogeneity (variability in collection method, timing and storage) and, second, the absence of standardized biomarker collection and processing protocols [5,7]. Second, the evidence base specific to AI remains limited to a small number of eligible studies with often modest sample sizes and, in many cases, lack of external validation on independent cohorts, raising legitimate concern regarding generalizability to new populations, ethnicities and clinical settings [23].

Third, many ML and deep learning models are limited in their interpretability, a real barrier to clinician trust and increasingly regulatory acceptance; transparent, explainable model outputs will likely become a practical prerequisite for clinical adoption, not an optional enhancement. Fourth, cost and infrastructure requirements (for biosensor hardware, data connectivity, and computational resources) might limit equal access to AI-enabled salivary diagnostics, especially in low-resource practice settings, despite the continued drop in device costs. Finally, the use of AI models trained on patient-derived biomarker data raises data privacy and governance

considerations that are not unique to periodontology but are nonetheless directly relevant: as AI diagnostic tools move toward multi-institutional training datasets to address the sample-size limitations noted above, approaches capable of enabling collaborative model development without centralizing sensitive patient data — such as federated learning — are gaining attention specifically because they can help reconcile the need for larger, more generalizable training datasets with legitimate privacy and regulatory constraints [35].

X. FUTURE DIRECTIONS

Several avenues are likely to define the next phase of research at the crossroads of salivary biomarkers and AI in periodontology. The integration of multi-omic data, such as proteomic, transcriptomic (including miRNA), metabolomic, and microbiomic salivary data, with clinical and, when available, imaging features, within the framework of multimodal AI models, is a natural progression from the single-domain approaches discussed above, and may greatly improve diagnostic and prognostic accuracy compared to using any single data type alone.

A possible route to overcome the main current limitation of larger, more generalizable and externally validated datasets is federated learning, i.e. where models are trained collaboratively across multiple institutions without direct sharing of raw patient data. This approach simultaneously addresses data privacy and regulatory concerns, is already gaining interest in adjacent regulatory and healthcare-AI contexts, and appears directly applicable to multi-center salivary biomarker research [35]. A larger database will require large prospective validation studies and regulatory grade clinical trials to move past the current evidence base, which is largely retrospective and from single centers. Finally, non-invasiveness and repeatability of salivary sampling position this field for integration with home-based and teledentistry-linked diagnostic workflows, potentially enabling longitudinal, AI-supported periodontal disease monitoring outside of the traditional clinical setting.

XI. CONCLUSION

The science of salivary biomarkers and artificial intelligence is converging to shift periodontal diagnostics from a damage based retrospective paradigm to one that can capture real time disease activity. The biological substrate is provided by established markers such as IL-1β, IL-6 and MMP-8, alongside novel classes like exosomal microRNAs and metabolomic signatures, while the analytical capacity to integrate these multidimensional data into clinically actionable outputs comes from machine learning and deep learning, increasingly integrated within point-of-care biosensors, microfluidic devices and wearable platforms. Realizing this potential in routine practice will depend on addressing persistent challenges in biomarker standardization, model validation and interpretability, cost, and regulatory pathways. With continued methodological rigor and multi-institutional collaboration, AI-enabled salivary diagnostics have the potential to become a meaningful component of predictive, personalized periodontal care.

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