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Data-driven precision diagnosis of periodontal disease: from biological features analysis to clinical applications

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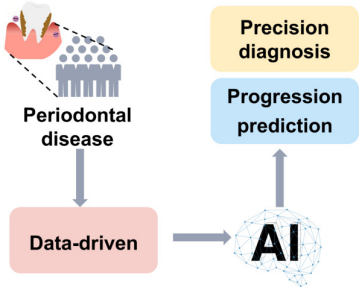
ABSTRACT: Periodontal disease is a prevalent chronic inflammatory condition, and its heterogeneity and complex pathophysiology pose significant diagnostic challenges. Traditional methods remain limited in precision and early detection. With the advancement of precision medicine, data-driven diagnostics are shifting periodontal assessment from a "one-size-fits-all" model to a more precise approach. Moreover, numerous studies highlight the vast potential of artificial intelligence (AI) in periodontal risk assessment and diagnosis. Integrating AI with data-driven diagnostic models enables deeper analysis, potentially surpassing the limitations of conventional empirical medicine and establishing a new paradigm for precision oral healthcare. This review explores recent advances in data-driven and AI-based strategies for periodontal disease diagnosis, emphasizing the multidimensional integration of biological features analysis and providing new insights into periodontal precision diagnostics.



KEYWORDS: data-driven, precision medicine, periodontal diagnosis, omics analysis, artificial intelligence

1 Introduction

Periodontal disease encompasses gingivitis and periodontitis, with the progression of gingivitis to periodontitis if left untreated. Periodontitis is the sixth most prevalent disease worldwide, with severe cases impacting 11.2% of the adult population[1,2]. This destructive process is primarily initiated by dental plaque biofilm, leading to the destruction of periodontal supportive structures. Manifestations of this process include loss of clinical attachment, periodontal pocket formation, gingival bleeding, and alveolar bone resorption[3]. The systemic implications of periodontitis extend beyond the destruction of the oral cavity, maintaining bidirectional associations with multiple chronic conditions such as diabetes, cardiovascular diseases, and Alzheimer's disease[1,4,5]. Chronic periodontal inflammation, if left untreated, ultimately results in tooth mobility and loss, severely compromising masticatory function, esthetics, and overall quality of life[6,7]. This pathological cascade poses a dual threat to patients' physical and psychological well-being, whilst concomitantly contributing significantly to the global healthcare burden through complex treatment needs and associated comorbidities.

Accurate periodontal diagnosis is fundamental to the development of effective prevention and treatment strategies[8]. Conventional diagnostic methodologies, including visual inspection, bleeding on probing (BOP), periodontal pocket depth measurement, and radiographic imaging assessment, are characterized by inherent subjectivity (e.g., examiner-dependent variability) and retrospective nature[9]. These methods merely document the extent of tissue destruction that has already occurred, as opposed to providing a predictive capability or identifying active biological processes[10]. Such diagnostic constraints particularly impede early detection and prognostic evaluation, highlighting the urgent need for more sophisticated diagnostic approaches. The molecularization of diagnostics is one of the trends in clinical care, and "biomarkers" derived from gingival crevicular fluid (GCF) or saliva, which are objective and provide diagnostic results in a short period of time, are an aid to clinical diagnosis. Consequently, a plethora of potential biomarkers have been postulated as candidates for the diagnosis of periodontal disease, with a view to enhancing diagnostic accuracy and facilitating early detection.

In 2017, the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) collaboratively introduced a novel classification framework that revolutionized the diagnosis of periodontal disease. This system integrates multidimensional parameters, including disease progression patterns, systemic health influences, and biomarker profiles, to establish a staging-grading diagnostic matrix for periodontitis. It is important to note that the framework under discussion places particular emphasis on the prognostic value of the detection of biomarkers in oral biofluids, including saliva, serum and GCF. These biomarkers have the potential to serve as critical

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determinants for the refinement of disease severity stratification[11,12]. Notwithstanding these conceptual advances, the establishment of standardized, biomarker-based diagnostic criteria remains elusive. The present body of research is predominantly focused on exploratory validation of candidate molecules.

Concurrently, the advent of precision medicine, driven by breakthroughs in life sciences and biotechnology, has introduced a transformative potential for periodontal diagnostics. Personalized medicine is predicated on the identification of individual-specific risk factors and disease mechanisms. This is achieved by integrating genomics, microbiomics, proteomics, metabolomics, and big data analysis. The objective is to develop targeted interventions. This approach has the potential to facilitate the identification of disease-specific biomarkers and to offer more precise methods for disease prevention, diagnosis, and treatment[13]. In the field of periodontology, the integration of validated biomarker panels into diagnostic classifications signifies a pivotal initial step toward the implementation of customized disease management strategies. Recent findings indicate that the integration of data-driven machine learning algorithms with molecular profiling has the potential to enhance diagnostic precision by elucidating intricate biomarker-disease associations[8].

The realization of data-driven personalized periodontal diagnostics necessitates the systematic integration of multidimensional datasets spanning both population-level and molecular-level domains， coupled with advanced computational algorithms and artificial intelligence (AI) tools (e.g., machine learning, deep learning models) to enable in-depth exploration of disease pathogenesis， not only the doctor's consultation data, electronic medical record data, clinical imaging data (which includes X-ray imaging data and pathology image information), but also the big data of genetics, epigenetics, transcriptome, proteome, metabolome data, and microbiome, many kinds of biomarker information and so on[14,15], which are illustrated in Figure 1. Within periodontal diagnostics, data-driven approaches demonstrate transformative potential through systematic multidimensional data integration, exhibiting enhanced early detection rates compared to conventional diagnostic protocols and robust potential in clinical management[16].

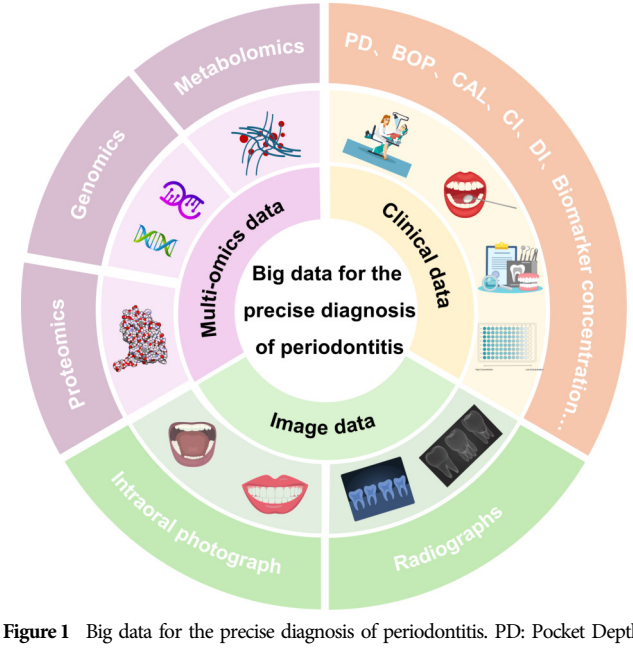

Figure 1 Big data for the precise diagnosis of periodontitis. PD: Pocket Depth; BOP: Bleeding on Probing; CAL: Clinical Attachment Level; CI: Calculus Index; DI: Debris Index.

In recent years, AI technology has demonstrated considerable potential in the domains of periodontal disease risk assessment and diagnosis precision. Numerous studies have substantiated the robust capabilities of AI in three critical dimensions: high-throughput biomarker discovery through pattern recognition algorithms; big data analysis integrating clinical, radiographic, and molecular profiles; and assistance in diagnosis to optimize diagnostic accuracy[17-20]. The integration of AI facilitates the incorporation of a comprehensive array of personalized patient data, including clinical records, radiographic imaging, biomarkers, multi-omics information, and other relevant data sets. This integration enables the identification of individualized risks and characteristics, which in turn can inform the development of precision therapeutic strategies tailored to specific pathobiological endotypes.

This review comprehensively synthesizes the rapidly evolving convergence of omics-derived biomarker research, AI technologies, and precision diagnostics within periodontology. While existing reviews have effectively covered individual aspects, such as single-omics methodologies[21,22], AI applications in dentistry[23], or the potential of specific biomarkers[24,25]. It is a significant gap persists in critically appraising the integrated pathway from molecular discovery through AI-facilitated data fusion to clinically actionable diagnostic systems. This systematic review also elucidating breakthrough innovations in AI-enhanced periodontal diagnostics and proposes a conceptual framework for the development of next-generation personalized periodontal healthcare systems. These systems are grounded in responsible AI implementation and cross-disciplinary data synergy.

2 Biological features analysis: from omics to personalized diagnosis

Biological features, defined as unique, quantifiable characteristics that enable organism identification and differentiation, are having a profound impact on the field of modern medicine, particularly in the realm of disease conceptualization and diagnostic paradigms. In the field of periodontology, the inherent limitations of conventional diagnostic methods in terms of accuracy, early detection, and progression monitoring have precipitated a paradigm shift toward precision diagnostics. This shift is rooted in biological signature analysis, with molecular signatures providing scientific substantiation at microscopic resolution. The advent of high-throughput sequencing technologies and advanced bioinformatics pipelines has transformed periodontal molecular profiling from single-marker detection to integrative multi-omics exploration[26,27]. A variety of "omics" disciplines have been endeavoring to develop molecular tools for the diagnosis of periodontal disease[28]. Omics disciplines, including genomics, proteomics, metabolomics, and microbiomics, converge on a unified objective: identifying and characterizing molecular signatures associated with periodontal inflammation. As indicated by the extant literature, these signatures possess the potential to exert a transformative effect on the prediction of disease trajectories, the refinement of diagnostic specificity, prognostic stratification, and therapeutic monitoring[29,30].

By employing systematic omics profiling, researchers can elucidate the molecular pathogenesis of periodontitis and identify

biomarkers with diagnostic, therapeutic, and preventive relevance. This methodological evolution addresses two critical gaps in traditional diagnostics. First, it replaces subjective clinical classifications with molecularly defined disease endotypes. Second, it unveils dynamic host-microbe interactomes governing disease progression. The establishment of biologically grounded taxonomies is facilitated by multi-omics signatures, which provide objective molecular criteria for disease subtyping, mechanistic targets for precision interventions, and predictive frameworks for personalized risk assessment. Collectively, these advances form the biological foundation for data-driven clinical decision-making, thereby bridging the chasm between molecular discoveries and actionable therapeutic strategies.

2.1 Genomics and genetic biomarkers

In recent years, strongly driven by the rapid development of genomics technology, researchers have been able to explore the genetic basis of periodontal diseases with unprecedented precision and breadth. Through large-scale sequencing and analysis, a series of genetic markers (e.g., single nucleotide polymorphisms) that are closely associated with the onset, progression, and severity of periodontal diseases have been gradually revealed. These key findings have not only deepened our understanding of the complexity of periodontal disease etiology, but more importantly, laid a solid scientific foundation for achieving early warning of the disease (identifying high-risk populations), precise risk stratification assessment, and the development of personalized preventive and therapeutic strategies tailored to the individual's genetic background[31,32]. In this process, Genome-Wide Association Study (GWAS), a revolutionary research strategy that systematically scans millions of genetic variants in the genomes of thousands of individuals and statistically correlates them with disease phenotypes, has greatly facilitated the understanding of complex diseases. GWAS has greatly advanced the resolution of the multigene genetic architecture behind complex diseases, including many oral diseases[32]. This unbiased, high-throughput data-based analysis overcomes the limitations of traditional candidate gene studies and becomes a powerful tool for revealing genetic susceptibility to disease.

In the field of dentistry research, GWAS has been successfully and widely applied to identify genetic factors that influence a wide range of oral health conditions and traits. Of particular interest is its remarkable progress in periodontology, where a series of genetic risk loci and susceptibility genes significantly associated with two major periodontitis phenotypes, aggressive periodontitis (AgP) and chronic periodontitis (CP), have been successfully identified. These GWAS results not only validated the genetic susceptibility of periodontitis, but also finely mapped its genetic risk, providing key genetic clues for subsequent in-depth investigation of its molecular mechanisms and translational applications[22,33].

AgP is marked by accelerated periodontal tissue destruction. It has been observed to exhibit a notable familial aggregation pattern, which is considered a hallmark of genetic susceptibility in its etiology[34]. In a seminal GWAS involving 438 AgP cases and 1,320 controls, Schaefer et al. identified the single nucleotide polymorphism (SNP) rs1537415 within the *GLT6D1* locus as a significant susceptibility factor, achieving genome-wide significance (p=5.51×10^{-9}; OR=1.59, 95% CI=1.36–1.86), suggesting that this locus is an important susceptibility factor[35]. Concurrent investigations leveraging Japanese genomic databases have revealed novel loci associated with AgP, with single-nucleotide polymorphism (SNP) rs143793106 in the lipase A (*LIPA*) gene emerging as a risk variant. The elevated minor allele frequency of rs143793106 in AgP patients compared to healthy controls further substantiates its pathogenic relevance, suggesting yet another risk locus[36]. The findings, when considered collectively, underscore the existence of conserved and population-specific genetic architectures that underpin AgP susceptibility.

Expanding the genetic landscape of periodontitis, recent investigations have identified novel risk loci spanning both AgP and CP forms, offering critical insights into shared etiopathogenetic mechanisms. A pivotal GWAS interrogating genetic variants across AgP and CP cohorts revealed nucleotide polymorphisms in the *SIGLEC5* and *DEFA1A3* genomic regions exhibiting genome-wide significant associations with periodontitis susceptibility, and correlated with genome-wide significance levels for periodontitis in mixed samples, proposing these two loci as risk loci for periodontitis[37]. Subsequent analyses of Northwestern European populations identified two additional loci: a pseudogene (*MTND1P5*) on chromosome 8 and the long non-coding RNA LOC107984137 near *SHISA9* on chromosome 16, both demonstrating genome-wide significance in periodontitis risk stratification[38]. Notably, a large-scale GWAS involving 1306 stage III/IV grade C periodontitis patients (<35 years) pinpointed *FCER1G* (p=1.0×10^{-9}) and *HMCN2* (p=6.1×10^{-8}) as novel susceptibility loci, further diversifying the genetic architecture of severe early-onset disease[30]. Complementary evidence from haplotype analyses of the *plasminogen* (*PLG*) region demonstrated significant associations between downstream variants and both AgP (rs1247559; p=0.002, OR=1.33) and CP (p=0.02, OR=1.15), implicating PLG-mediated pathways in periodontal inflammation[39]. The information is detailed in Table 1. These multilayered discoveries collectively refine the molecular taxonomy of periodontitis, establishing a framework for risk prediction models and mechanistically informed therapeutic development.

The pathogenesis of periodontal diseases is the result of a

Table 1 Genomics.

Sample	Gene/Locus	SNP	*P* value	Conclusion	References
AgP	*GLT6D1*	rs1537415	5.51×10^{-9}	significant susceptibility factor	[35]
AgP	*LIPA*	rs143793106	3.7×10^{-2}	risk locus	[36]
AgP/CP	*SIGLEC5, DEFA1A3*	rs4284742 rs2738058	1.09×10^{-8} 5.48×10^{-10}	novel risk loci	[37]
AgP/CP	*MTND1P5, SHISA9*	rs16870060, -G; rs729876, -T	3.69×10^{-9} 9.77×10^{-9}	risk locus	[38]
stage III/IV grade C	*FCER1G*	rs2070902	1.02×10^{-9}	novel susceptibility loci	[30]
CP	*PLG*	rs1247559	2×10^{-3}	PLG-mediated pathways in periodontal inflammation	[39]

complex interplay among dysregulated host immune responses, genetic predisposition, and microbial dysbiosis. Genomic profiling and biomarker analytics now complement conventional clinical examinations and radiographic assessments, addressing critical gaps in disease phenotyping and prognostic prediction[24,40]. Elucidation of genetic regulatory networks governing disease progression is a critical step in providing actionable insights into three clinical imperatives: quantifying disease activity; stratifying progression risk; and predicting therapeutic responsiveness. Key genetic signatures associated with inflammatory cascades offer dual diagnostic and mechanistic value, enabling the development of precision biomarkers for disease prediction, early detection, and preventive stratification. These advances have led to significant advancements in our understanding of periodontal pathobiology. In addition, they have provided researchers with a more nuanced understanding of the molecular profiles of individual patients, which in turn has informed the development of more personalized intervention strategies[37].

Notwithstanding these advances, the genetic architecture underpinning periodontal susceptibility remains to a large extent uncharted. The prospective integration of genomic data with multi-omics biomarkers (e.g., proteomic, metabolomic, microbiomics) has the potential to surmount extant diagnostic limitations, thereby enabling clinicians to achieve precision-guided disease management through systems-level pathobiological insights.

2.2 Proteomics and biomarkers

High-throughput proteomics technology has shown strong potential in the field of disease-related biomarker discovery by virtue of its ability to analyze protein expression profiles on a large scale and systematically. The technology can deeply reveal the complex links between gene expression, protein function and disease development, providing key insights for molecular medicine research. Given its unique advantages in resolving the molecular mechanisms of disease, high-throughput proteomics has broad relevance and significant application prospects in the diagnosis and study of periodontal disease[41,42]. In recent years, saliva and GCF, as important biological samples for the study of oral diseases, have received widespread attention in proteomics research because of their relatively noninvasive and convenient collection process and their ability to faithfully reflect the local microenvironmental status of the oral cavity (containing abundant host-derived proteins, microbial products, and inflammatory mediators, etc.)[43]. The protein information contained in these samples is crucial for the development of noninvasive or minimally invasive diagnostic tools with high clinical value.

In the field of periodontology research, proteomic approaches have emerged as key technical tools for exploring and characterizing biomarkers[25,44]. By systematically comparing the protein expression profiles (including differences in expression amount, modification status, etc.) in saliva and GCF of periodontitis (e.g., CP, AgP) patients and healthy control individuals, researchers were able to screen a series of specific protein markers closely related to inflammation, destruction, and restoration processes of periodontal tissues. Key biomarkers such as matrix metalloproteinases (MMPs), cytokines (e.g., Interleukin-1β, Tumor Necrosis Factor-α), and antimicrobial peptides not only serve as diagnostic indicators but also elucidate pathobiological mechanisms. Clinically, these signatures enable objective disease severity assessment, real-time therapeutic monitoring, and differentiation between aggressive and chronic disease subtypes[44,45]. The discovery of these markers is not only expected to promote the development of highly sensitive and specific tools for early diagnosis of periodontal disease and assessment of disease activity/severity, but also to provide a solid molecular basis for optimizing individualized treatment protocols, real-time monitoring of treatment efficacy, and predicting the regression of the disease, which will significantly improve the clinical management of periodontal disease.

Cutting-edge proteomic technologies have enabled systematic discovery of periodontal disease biomarkers through large-scale biofluid analyses. Shin et al. employed shotgun proteomics with two-dimensional liquid chromatography-tandem mass spectrometry (2D-LC-MS/MS) to profile saliva from 207 subjects, revealing significantly elevated S100A8 and S100A9 levels in periodontitis patients, a finding corroborating these proteins' candidacy as diagnostic biomarkers[46]. Parallel investigations of GCF proteomes by Kim et al. identified Galectin-10 overexpression in chronic periodontitis patients, showing strong correlations with clinical inflammation indices, suggesting that Galectin 10 may serve as a biomarker for periodontitis[47]. Notably, Bellei et al. expanded this paradigm through differential proteomic analysis of severe periodontitis GCF, comprising 14 upregulated and 12 downregulated biomarkers at diseased sites. These molecular signatures predominantly encompass inflammatory mediators, immune response modulators, and host-derived enzymatic regulators. Following rigorous validation in multi-center longitudinal studies, these candidate proteins may serve as clinically actionable biomarkers for precise staging and risk stratification of periodontitis[44]. Furthermore, in biomarker validation research employing case-control salivary proteomic analysis (n=20 pairs), investigators identified approximately 20 differentially expressed proteins in periodontitis-affected saliva. Notably, this investigation successfully replicated the diagnostic validity of established biomarkers including matrix metalloproteinases (MMP-8/-9), α2-macroglobulin, and complement C3 - proteins previously characterized in conventional periodontal diagnostics. Crucially, the study demonstrated that subtle quantitative variations in these protein profiles serve as robust discriminators between periodontitis patients and healthy controls at the molecular level[48]. Recent innovations highlight novel biomarker combinations: Lee et al. validated elevated DEFA-1 levels in the GCF of periodontitis patients compared to healthy controls through proteomic analysis. Comparative evaluation against previously proposed biomarkers (such as galectin-10, odontogenic ameloblast-associated protein, and nitrophorin) revealed DEFA-1's superior diagnostic specificity in distinguishing periodontal health from disease. While multi-center validation across disease severity strata is required to confirm its clinical utility, DEFA-1 quantification establishes a molecular foundation for developing non-invasive diagnostic protocols targeting active periodontal inflammation[49]. Additionally, Blanco-Pintos et al. leveraged sequential window acquisition of all theoretical mass spectra (SWATH-MS) technology to profile GCF samples from 44 healthy controls and 40 stage III–IV periodontitis patients. Through systematic proteomic screening, they identified a novel five-marker panel (e.g. GAPDH, ZG16B, carbonic anhydrase 1, plasma protease inhibitor C1, and hemoglobin subunit beta) exhibiting diagnostic sensitivity/specificity exceeding 80% for advanced periodontitis detection. This biomarker combination demonstrates robust discriminative capacity while addressing

current limitations in disease staging precision through quantitative proteomic signatures[50]. The information is detailed in Table 2. These transformative findings substantiate the multifaceted diagnostic potential of biomarkers in periodontal disease stratification, therapeutic prognostication, and longitudinal disease monitoring, thereby establishing a molecular foundation for developing non-invasive precision diagnostic frameworks.

By transitioning from symptom-based evaluation to mechanism-driven diagnostics, proteomics redefines periodontal disease management through molecular precision, bridging biomarker discovery to personalized therapeutic strategies. While proteomic analyses enable unbiased profiling of salivary and GCF proteins, technical limitations in detection sensitivity, protein recovery efficiency, and analytical reproducibility continue to hinder comprehensive proteome characterization. Additionally, the inherent complexity and dynamic range of protein composition, compounded by the necessity for large-scale cohorts and standardized protocols to mitigate intra- and inter-individual variability, pose significant challenges in biomarker discovery pipelines[51]. Nevertheless, emerging innovations in high-resolution mass spectrometry, multiplex assay platforms, and AI-driven data normalization strategies are progressively addressing these limitations, thereby enhancing the translational potential of proteomics for elucidating periodontal pathobiology[52].

2.3 Microbiomics and metabolomics

Under periodontal health, the oral microbiome exhibits high microbial diversity dominated by commensal taxa, such as Streptococcus and Actinomyces, which maintain ecological balance through structured biofilm communities. However, when the local microenvironment is perturbed by factors such as altered host immune status (e.g., smoking, diabetes), deterioration of oral hygiene, or genetic predisposition, a cascade of dysbiosis is triggered, a process that has been shown to be causally linked to the initiation and progression of periodontitis[53]. The transition to inflammatory states coincides with subgingival microbiome restructuring, where the "red complex" (Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia) emerges as a keystone pathogen consortium driving tissue destruction in chronic periodontitis[54]. Advances in high-throughput DNA sequencing, particularly 16S ribosomal RNA (rRNA) gene amplicon sequencing, have revolutionized the characterization of microbial community structures and functional dynamics in periodontal niches. These techniques enable taxonomic resolution at the species level while uncovering microbial interactions governed by the polymicrobial synergy and dysbiosis model.

Comparative microbial analyses across periodontal health, gingivitis, and periodontitis reveal dynamic ecological transitions, with health-associated microbiomes dominated by commensals such as Rothia and Streptococcus, while inflammatory states progressively enrich Gram-negative anaerobic pathobionts like Porphyromonas and Treponema, underscoring the critical role of core pathogen consortia in disease progression[55]. Clinical interventions further validate these dynamics, as demonstrated by Jung et al., who identified significant post-treatment reductions in pathogenic taxa (Porphyromonas gingivalis, Tannerella forsythia, Filifactor alocis) through 16S rRNA sequencing and Spearman signed-rank tests. Ethnogeographic specificity emerges in microbiome studies, with Korean periodontitis patients exhibiting elevated Porphyromonas (32.2%), Fretibacterium (10.4%), Rothia (5.3%) and Filifactor (3.1%), while gingivitis microbiomes paradoxically show higher α-diversity, suggesting transitional dysbiosis preceding tissue destruction[56]. Collectively, these microbial fingerprints provide mechanistic insights into host-pathogen interplay, inform diagnostic biomarkers, and guide personalized antimicrobial strategies targeting keystone pathogens.

Metabolites are the end products of a complex network of biochemical reactions in an organism, usually endogenous small molecular compounds of low molecular weight (e.g., organic acids, amino acids, lipids, sugars, nucleotides and their derivatives). Metabolomics, on the other hand, is the science of systematic identification, quantification and analysis of all metabolites in a biological system, with the aim of comprehensively mapping metabolic phenotypes in specific physiological or pathological states, has emerged as a powerful tool for investigating periodontal pathogenesis.As metabolites represent terminal outputs of biochemical pathways driving periodontitis initiation and progression, mass spectrometry (MS)- and nuclear magnetic resonance (NMR)-based metabolomic profiling enables comprehensive characterization of disease-related metabolic shifts in tissues and biofluids. This approach holds promise for early disease detection, real-time activity assessment, and therapeutic monitoring[57,58].

Aimetti et al. pioneered salivary metabolomic analyses using NMR spectroscopy in 22 healthy controls and 32 periodontitis patients, achieving 84.1% diagnostic accuracy via pattern recognition algorithms. Significant alterations in periodontal disease-associated metabolites (including acetate, γ-aminobutyrate, butyrate, succinate, trimethylamine, propionate, phenylalanine, and valine) were identified, underscoring metabolomics' diagnostic potential[58]. Similarly, Kim et al. employed proton NMR to profile saliva from 129 periodontitis patients and 92 controls, establishing a five-metabolite panel (ethanol, taurine, isovalerate, butyrate, glucose) with discriminative power[59]. Romano et al. compared 33 chronic and 28 AgP cases using NMR metabolomics, revealing decreased pyruvate, *N*-acetyl groups, and lactate alongside elevated

Table 2 Proteomics.

Sample types	Method	Biomarkers	Conclusion	References
Saliva	2D-LC-MS/MS & ELISA	S100A8, S100A9	Elevated levels in periodontitis	[46]
GCF	LC-MS/MS	Galectin-10	Overexpression in CP	[47]
GCF	LC-MS/MS	26 dysregulated proteins	Potential diagnostic utility	[44]
Saliva	LC-MS/MS	MMP-8, MMP-9, alpha-2-macroglobulin, complement C3	Distinguishing periodontitis from healthy Individuals	[48]
GCF	proteomic analysis	DEFA-1	Superior diagnostic specificity	[49]
GCF	SWATH–MS	GAPDH, ZG16B, carbonic anhydrase 1, plasma protease inhibitor C1 and haemoglobin subunit beta	Excellent sensitivity/specificity as a diagnostic marker for periodontitis	[50]

proline, phenylalanine, and tyrosine in patients. Their model achieved 81% classification accuracy between healthy and diseased states, reinforcing metabolomics' sensitivity in biomarker discovery[21]. The information is detailed in Table 3.

Successful differentiation between healthy and diseased individuals also reaffirms the sensitivity of metabolomic analysis as a source of potential biomarker groups for molecular diagnostics. Nonetheless, the complex multifactorial etiology of periodontitis requires large clinical trials combining multicomponent assessments of saliva, GCF, etc. to better address this issue. Nonetheless, Advances in high-resolution MS and machine learning-driven data integration are poised to overcome current limitations, positioning metabolomics as a cornerstone of future precision periodontology.

2.4 Multi-omics integration and disease subtyping

While single-omics approaches effectively identify disease-associated molecular alterations and suggest potential biomarkers or pathogenic pathways[60], their inherent limitations in capturing systemic biological complexity persist. Recent breakthroughs in high-throughput technologies and enhanced capacity to decipher genotype-phenotype relationships have positioned multi-omics integration as a frontier methodology in systems biology. By synergistically analyzing genomic, proteomic, and metabolomic data, this approach elucidates the comprehensive landscape and dynamic interplay of multidimensional molecular networks[61]. In periodontology, multi-omics integration has emerged as a transformative strategy to systematically identify pivotal pathogenic mechanisms and develop precise diagnostic frameworks. Recent studies demonstrate its capacity to unravel molecular crosstalk between dysbiotic microbiomes, host immune responses, and metabolic reprogramming, enabling the discovery of novel diagnostic biomarkers and therapeutic targets[26]. Therefore, the integration of multi-omics not only provides a powerful systematic research framework for in-depth analysis of the molecular pathogenesis of periodontitis and the discovery of novel diagnostic markers and therapeutic targets, but also promotes the strategic transition from a single molecular description of periodontitis to a networked paradigm of medicine, which will ultimately accelerate the clinical realization of precision periodontics.

Marbach et al. pioneered the integration of genomics, epigenomics, and transcriptomics to systematically map tissue-specific regulatory networks across 394 human cell types. By deeply integrating GWAS data with these networks, they localized disease-associated genetic modules, offering novel insights into the molecular architecture of complex diseases[62]. In periodontology, Luo et al. combined transcriptomic and metabolomic profiling to identify three potential biomarkers (*PDGFD*, *NRTN*, and *IL2RG*) linked to periodontal pathogenesis. These markers not only elucidate disease mechanisms but also enable early detection through pathway-specific dysregulation patterns[63]. Ding et al. further advanced multi-omics applications by coupling 16S rRNA sequencing with targeted metabolomics in saliva. Their analysis revealed 93 differentially abundant microbial taxa and 103 altered metabolites in periodontitis patients, with functional enrichment highlighting upregulated pathways including ferroptosis, tryptophan metabolism, glutathione metabolism, and carbon metabolism. This dual microbial-metabolic profiling establishes a diagnostic framework for periodontitis while uncovering novel pathobiological networks[64]. Addressing pregnancy-associated periodontitis, Zhao et al. conducted subgingival plaque multi-omics analyses, identifying pathogen-enriched microbiomes alongside 87 dysregulated functional modules and 105 perturbed metabolites in affected individuals. Distinct metabolic signatures (including hyperactive pyruvate metabolism and elevated folate synthesis) contrasted sharply with the carbohydrate-dominated metabolism of healthy controls, providing actionable targets for early diagnosis and mechanistic intervention[65].

Collectively, the above systematic studies have depicted the highly coordinated multidimensional molecular event network in the pathological process of periodontitis, from the genetic regulation of susceptibility loci in the host genome, the dysfunction of key signaling pathway proteins, the kinetic fluctuation of characteristic metabolites, to the structural imbalance and ecological interactions in the oral microbial community, which have revealed the cross-scalar, multifactorial and interactions that drive the development of the disease. These findings not only confirm the systematic biology of periodontitis as a complex inflammatory disease, but also highlight the unique advantages of integrative genomics technologies (including genomics, proteomics, metabolomics, and microbiomics) in accurately capturing the molecular characteristics of the disease through high-dimensional, high-throughput data mining, which can be used for the screening of novel diagnostic markers. Through high-dimensional and high-throughput data mining, it provides an irreplaceable research paradigm for the screening of novel diagnostic markers, the optimization of individualized therapeutic strategies, and the analysis of deeper pathological mechanisms. Periodontitis exhibits pronounced heterogeneity, with conventional diagnosis typically confirming the disease only after overt tissue destruction has occurred. In contrast, multi-omics analysis not only enables precise disease subtyping and staging, but also detects subtle molecular alterations during early pathogenesis—including aberrant gene expression, dysregulation of inflammation-associated proteins or metabolites, and microbial dysbiosis—thereby facilitating early disease alert or diagnosis.

In particular, the multi-omics integration strategy provides a solid chain of molecular evidence for the construction of a systemic pathogenesis model of periodontitis by deeply deconstructing the dynamic crosstalk and feedback loops between different molecular

Table 3 Metabolomics.

Sample types	Method	Biomarkers	Conclusion	References
Saliva	NMR	acetate, γ-aminobutyrate, butyrate, succinate, trimethylamine, propionate, phenylalanine, valine	Differentiating between patients with CP and healthy individuals	[58]
Saliva	NMR	ethanol, taurine, isovalerate, butyrate, glucose	Differentiating between patients with different types of periodontitis and healthy individuals	[59]
Saliva	NMR	pyruvate, *N*-acetyl group, lactate, proline, phenylalanine, tyrosine	Provides specific biomarkers to enhance diagnostic accuracy	[21]

levels. Therefore, multi-omics integration further unveils cross-omics molecular crosstalk, providing robust evidence for disease mechanisms while pioneering novel pathways for precision diagnosis, prognostic evaluation, and treatment monitoring.

3 Data-driven technologies: advancing precision diagnostics in clinical periodontology

Data-Driven Medicine represents an emerging medical paradigm, the core of which lies in the systematic integration and analysis of massive, multi-source healthcare data (including clinical records, histological data, imaging data, electronic health records, real-time monitoring data, etc.), and relying on advanced computational algorithms and AI tools (e.g., machine learning, deep learning models) to realize the deep mining and modeling of the laws of disease occurrence and development. The method aims to provide objective and quantitative scientific basis for disease prediction, risk stratification, early prevention, precise diagnosis and individualized treatment plan development[66,67]. These data streams include longitudinal clinical records, multimodal imaging, multi-omics signatures, and behavioral biomarkers. The synthesis of these data streams is achieved via deep learning models such as convolutional neural networks (CNNs). Its essence is to drive a profound transformation of medical practice from experience-driven to evidence-driven, and from a group-based model to a highly individualized one[68-70]. The rise of data-driven medicine has directly catalyzed the revolutionary evolution of the clinical diagnosis and treatment model: diagnosis and intervention strategies are accelerating from the traditional "one-size-fits-all" model to a more comprehensive diagnosis and intervention model based on the patient's unique biological characteristics (genome, proteome, metabolome, etc.), clinical manifestations, environmental exposures, and lifestyle information. Tailor-made model based on patients' unique biological characteristics, clinical manifestations, environmental exposures, and lifestyles has significantly improved the precision and effectiveness of healthcare services.

In the field of periodontal diagnostics, data-driven approaches have been shown to possess the potential for transformative impact through the systematic integration of multidimensional datasets. These datasets encompass clinical periodontal parameters, such as probing depth and bleeding indices, imaging data pertaining to bone loss, host-microbiome interactomes, genetic susceptibility markers, and patient-reported outcomes. Recent validations demonstrate that machine learning architectures (e.g., random forests) processing integrated data show improvements in early detection rates compared to conventional diagnostic protocols[16]. Furthermore, these systems enable quantitative mapping of gingival inflammation dynamics and three-dimensional alveolar bone resorption trajectories, thereby providing robust support for the diagnosis, treatment, and clinical management of periodontal diseases[71,72], which are illustrated in Figure 2.

3.1 Data-driven traditional risk assessment tools in periodontal disease

The objective of periodontal risk assessment is to achieve long-term tooth preservation and functional maintenance through preventive strategies, early intervention, and personalized treatment planning. The utilization of this technology has the potential to assist clinicians in making objective assessments of the activity state and severity of periodontitis. It can facilitate the assessment of the risk of periodontal disease and the prediction of its progression based on various factors. Furthermore, it can guide the development of personalized treatment plans and provide accurate prognoses for individual affected teeth and the entire dentition. This enables the formulation of personalized diagnosis and treatment plans for patients.

Contemporary data-driven systems have revolutionized this paradigm, with the Page Risk Calculator (PRC)[73], representing a seminal innovation. This system dynamically quantifies disease progression risks and periodontal stability by integrating clinical parameters (including probing depth, BOP, bone loss), systemic factors (including age, smoking, diabetes), and treatment history, enabling risk-stratified intervention protocols[74]. It can record periodontal clinical indicators at different stages, monitor and assess the risk of periodontitis progression dynamically, and judge the progression of periodontitis based on the assessment results, so as to take graded interventions and individualized periodontal treatment plans. Its capacity to synergize full-mouth diagnostics with systemic health profiling enhances predictive accuracy, guiding both periodontal and prosthodontic rehabilitation strategies[75]. Furthermore, the Pre Viser Risk Assessment System further advances this field through evidence-based electronic questionnaires and clinical metrics, generating objective risk scores that inform personalized therapeutic regimens and longitudinal outcome monitoring[76].

Periodontal risk assessment (PRA) is to help dentists to predict the risk of recurrence of periodontitis after periodontal systemic treatment, so as to determine the time interval and content of the follow-up consultation, and to avoid under-treatment or over-treatment during periodontal supportive therapy. It uses several factors related to the progression of periodontitis. The outcome of the PRA is the individual risk stratification, divided into 3 categories

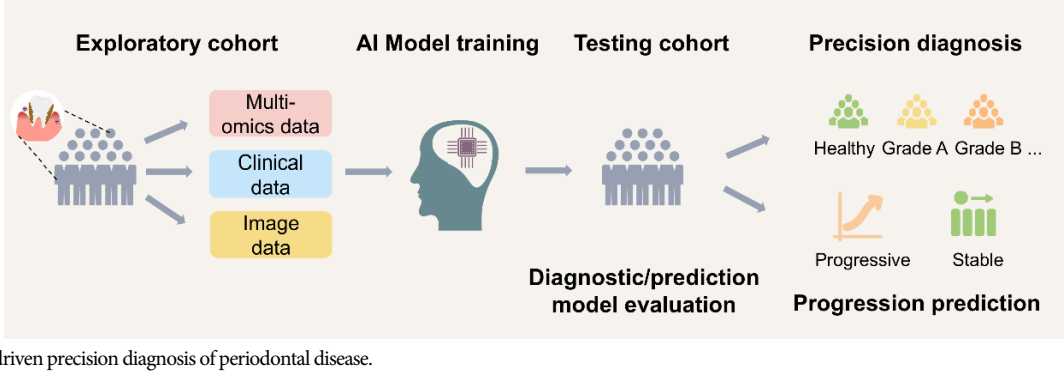

Figure 2 Data-driven precision diagnosis of periodontal disease.

(low, moderate, and high risk)[77]. Complementing these clinical tools, the Cumulative Risk Score (CRS) leverages salivary biomarkers and microbial diagnostics to predict periodontitis susceptibility[78,79]. Some researchers analyzed the diagnostic ability of salivary markers (including Porphyromonas gingivalis, IL-1β, and MMP-8) versus CRS in an adaptive design in detecting periodontal disease in 463 participants. The results showed that the area under the curve (AUC) of CRS was higher than any single biomarker threshold, with acceptable sensitivity and specificity and a strong correlation with at least two sites probed to a depth of 4-5 mm[80]. Similarly, Salminen et al. demonstrated CRS's superior diagnostic efficacy (OR=6.13; 95%CI=3.11-12.09) for moderate-to-severe periodontitis by combining MMP-8, IL-1β, and Porphyromonas gingivalis concentrations, outperforming single-marker approaches[81]. Demonstrating that the CRS exhibits greater capability in periodontal disease detection than a single biomarker with a fixed threshold.

While existing periodontal risk assessment tools incorporate validated predictors of disease progression with acceptable predictive accuracy, they remain constrained by reliance on single-biomarker analyses, static risk stratification incapable of capturing dynamic host-microbe interactions, and heterogeneity in disease classification criteria that complicates algorithmic generalizability. Addressing these limitations requires integrating novel predictive dimensions, including microbial consortia profiles, multiplex biomarker panels, and machine learning architectures (including random forests and graph neural networks), which are expected to make up for the shortcomings of the traditional methods, and provide more possibilities for personalized diagnosis and precise treatment of periodontitis.

3.2 Data-driven AI-enabled precision diagnosis of periodontal disease

AI-enhanced periodontal diagnostics leverage multiple data to overcome limitations of conventional methods, such as intraoral photographs for gingivitis detection via soft-tissue analysis and radiographic images for alveolar bone loss quantification and disease staging. Compared to traditional risk assessment tools, AI-powered systems demonstrate superior capabilities in alleviating repetitive clinical workloads, detecting subvisual pathological patterns, and deciphering complex diagnostic signatures across heterogeneous datasets[17,18,82]. By integrating AI with conventional diagnostic expertise, these systems enable intelligent large-scale screening for early intervention while augmenting clinicians' decision-making accuracy, thereby advancing precision treatment protocols and facilitating remote patient management through automated diagnostic workflows.

Gingivitis diagnosis relies heavily on clinicians' visual assessments of gingival color, texture, and morphology, a subjective process prone to inter-examiner variability[9]. AI-assisted systems address these limitations through standardized, quantitative assessments of gingival erythema and texture alterations. Chau et al. developed a DeepLabv3+ semantic segmentation model trained on 561 intraoral photographs pixel-level annotated for gingival margin status (healthy/suspect/diseased), achieving exceptional diagnostic performance (sensitivity=0.92, specificity=0.94) in localized inflammation detection[83]. Parallel advancements include You et al.'s CNN model for dental plaque detection. 102 photographs were evaluated separately by the AI model and the dentist, which demonstrated non-inferiority to clinicians (paired t-tests, $p>0.05$), demonstrating the potential for the clinical application of AI in plaque detection[84]. Furthermore, Alalharith et al. collected 134 intraoral color images of orthodontic patients, constructed Fast-R-CNN model for identifying gingival inflammation status, and diagnosed the presence of gingival inflammation in upper and middle incisors based on the criterion of gingival index, which had a diagnostic accuracy of 77.12%[71]. Li et al. uses a novel Multi-Task Learning CNN model designed for simultaneous detection and spatial localization of gingivitis and its irritants (dental calculus and soft deposits) through intraoral photographic analysis. Involving a cohort of 625 patients, the model demonstrated clinically relevant discriminative capacity with area under the curve values of 87.11%, 80.11%, and 78.57% for gingivitis, calculus, and soft deposit classification respectively. Meanwhile, the model can also localize the three types of findings on oral photos with moderate accuracy, which enables the model to explain the screen results. Comparative analyses against general-purpose CNNs revealed statistically superior performance across both categorical identification and anatomical localization tasks, substantiating the paradigm of multi-objective deep learning optimization in automated periodontal screening systems[85].

The deployment of these AI diagnostic models typically requires training on extensive datasets comprising hundreds to tens of thousands of clinical images to achieve robust predictive performance. In contrast to conventional gingivitis detection methods, which rely on subjective visual assessments of clinically apparent changes in gingival color, texture, and morphology, these methods are limited by human perceptual thresholds and the restricted sensitivity of conventional diagnostic criteria. AI systems trained on large-scale, high-resolution intraoral photographs demonstrate superior capability to identify subclinical gingival alterations that are imperceptible to clinicians[83,84].

Alveolar bone resorption, a hallmark of periodontitis, is quantified clinically using radiographic bone loss percentage (RBL%) relative to root length—a key diagnostic criterion in current periodontal classification[11]. Several studies have been conducted to construct AI models for recognizing alveolar bone resorption from imaging pictures. Chen et al. developed a Mask R-CNN model trained on 8000 periapical radiographs to identify tooth contours, cementoenamel junctions (CEJ), and bone levels, achieving ~90% accuracy in RBL% calculation[72]. Similarly, Chang et al. combined CNNs (InceptionV3 architecture) with computer-aided diagnosis (CAD) to analyze panoramic radiographs, automating periodontal staging with 87% accuracy in detecting mild-to-severe bone loss[23]. In addition, Li et al. propose an interpretable method called Deetal-Perio to predict the severity degree of periodontitis in dental panoramic radiographs. Deetal-Perio segmented and indexed individual teeth by Mask R-CNN combined with a novel calibration method, then segmented the alveolar bone contours and computed the ratio of individual teeth to represent alveolar bone loss, and finally predicted the severity of periodontitis based on the ratios of all the teeth, and the periodontitis prediction task yielded Macro F1-score and accuracy reached 0.894 and 0.896, respectively[86]. Kurt-Bayrakdar et al. develop a deep learning model based on the U-Net architecture for interpreting panoramic radiographs and evaluating its performance in detecting periodontal bone losses and furcation defects. The study demonstrated that this architecture not only quantitatively assesses total alveolar bone resorption, but also effectively

differentiates horizontal bone resorption (AUC = 0.91), vertical bone defects (AUC = 0.73), and furcation involvement (AUC = 0.87)[87]. The aforementioned studies exclusively employed radiographic as diagnostic determinants, but with the lack of clear criteria for the determination of alveolar bone resorption on two-dimensional images has resulted in learning limit of the AI being limited by the diagnostic level of the researcher.

The clinical probing metrics, particularly the percentage of BOP sites and clinical attachment loss (CAL), serve as sensitive and validated indicators of periodontal inflammation. The percentage of BOP sites is a key diagnostic criterion for gingivitis in the updated classification system, and CAL is an important marker to distinguish gingivitis from periodontitis. AI models integrating both probing data and radiographic analyses achieve enhanced diagnostic precision through multidimensional case definitions. Lee et al. developed a Deep Convolutional Neural Network (DCNN) to classify periodontal status (healthy/moderate/severe) on periapical radiographs based on CAL, achieving 76.7–81.0% accuracy[88]. Dai et al. combining CNN+ architectures with traditional machine learning to stage periodontitis using probing depths and radiographic bone loss patterns, attaining 84.2–96.8% classification accuracy[89]. Notably, in the study of Kearney et al., CAL data matched with radiographic imaging information and various deep learning algorithms were used to predict CAL from radiographic imaging information. At the same time, they developed an inpainting algorithm using generative adversarial networks coupled with partial convolutions to predict out-of-view anatomy to enhance CAL prediction accuracy and within the 1 mm clinician-determined measurement standard[90]. The information is detailed in Table 4.

The application of different models in periodontal disease diagnosis exhibits variations. For instance: CNNs serve as fundamental building blocks for image analysis tasks prevalent in periodontal diagnostics. They excel at extracting hierarchical features from images (intraoral photographs or radiographs) and are widely used for classification tasks[89]. U-Net is particularly suited for semantic segmentation tasks requiring pixel-wise labeling, such as delineating gingival margins[82] or alveolar bone contours[86,87]. For object detection tasks involving the identification and localization of multiple specific entities within images (e.g., detecting dental calculus, inflamed regions, or anatomical landmarks like the CEJ), variants of the R-CNN family, such as Faster R-CNN[71] and Mask R-CNN[72,86], are commonly employed. Multi-Task Learning CNNs[85] enable a single model to be trained for simultaneous execution of multiple related tasks (e.g., classifying gingivitis, calculus, and soft deposits while localizing them), thereby enhancing efficiency and leveraging shared features across tasks.

But, the output results of the models constructed by different research teams may vary depending on the diagnostic strategies used in training the models. The heterogeneity of design between these studies is large, and the external validation of AI-assisted diagnostic tools still suffers from small sample sizes and few evaluators, and large sample sizes are needed to validate the output results. Meanwhile, there is no clear criterion for the determination of "alveolar bone resorption" on 2D images, resulting in the learning of AI-assisted diagnostic tools being limited by the diagnostic level of the researchers. The integration of AI with multiple datasets, encompassing clinical parameters (e.g., probing pocket depth, CAL, BOP), radiographic imaging (e.g., periapical radiographs, intraoral photographs), and multi-omics signatures (e.g., inflammatory cytokines, matrix metalloproteinases, periodontal bacteria), demonstrates transformative potential for achieving precise and rapid classification of periodontitis. This data-convergent approach facilitates the development of AI-powered diagnostic systems, characterized by enhanced accuracy and operational efficiency. These advancements exemplify the potential of AI to personalize diagnostic procedures and enhance diagnostic precision.

3.3 Data-driven AI for periodontal risk prediction

AI has been demonstrated to enhance the diagnostic accuracy and efficiency of periodontal assessments. In addition, it has emerged as a transformative engine for predictive modeling in precision periodontology[91]. The assessment of the risk of periodontal disease progression is of crucial importance in the development of effective treatment plans and preventive strategies. The capacity of AI tools

Table 4 AI diagnostic models.

Disease	Data	Method	Purpose	Outcome	References
Gingivitis	561 intraoral photographs	DeepLabv3+	Identifying gingival margin status (healthy/suspect/diseased)	0.92 sensitivity and 0.94 specificity	[83]
	102 photographs	CNN	Potential for the clinical application of AI in plaque detection	non-inferiority to clinicians, paired t-tests, $p>0.05$	[84]
	134 intraoral color images	Fast-R-CNN	Identifying gingival inflammation status	77.12% accuracy	[71]
	625 intraoral photographs	Multi-Task Learning CNN	Gingivitis, calculus, and soft deposit classification respectively	AUC is 87.11%, 80.11% and 78.57%	[85]
Periodontitis	8000 periapical radiographs	Mask R-CNN	RBL% calculation	~90% accuracy	[72]
	panoramic radiographs	Combine CNNs with CAD	Detecting mild-to-severe bone loss	87% accuracy	[23]
	dental panoramic radiographs	Mask R-CNN	Detecting alveolar bone loss and predicted the severity of periodontitis	accuracy reached 0.894 and 0.896	[86]
	panoramic radiographs	U-Net architecture	Detecting horizontal bone resorption, vertical bone defects and furcation involvement	AUC is 0.91,0.73 and 0.87	[87]
	periapical radiographs	DCNN	Classify periodontal status (healthy/moderate/severe)	76.7–81.0% accuracy	[88]
	probing depths and radiographic bone loss patterns	CNN+	Stage periodontitis	84.2–96.8% classification accuracy	[89]

to analyze multiple risk factors, including demographic data, medical history, and clinical parameters, with a view to predicting the likelihood of future periodontal complications, is well-documented. The dynamic characterization of periodontal disease occurrence involves the integration of multiple levels of information, and achieving a comprehensive and holistic characterization from a single level of information is challenging due to the unique data structures present at different levels. In order to achieve a more comprehensive understanding of the disease and to reveal new biological and pathological connections between different interactors, a data-driven AI approach to analyze multi-source data has strong potential for disease risk prediction.

For instance, Woosun et al. developed a data-driven model based on a large-scale database (Korea National Health and Nutrition Examination Survey, n=10654). Through feature analysis, they identified 16 key risk factors (e.g., smoking, age, oral hygiene habits) and constructed predictive models using machine learning algorithms such as XGBoost and random forests. These models demonstrated high predictive performance in both internal validation (AUC = 0.823) and external clinical validation (AUC = 0.796), showing promise in predicting periodontitis risk, assessing bone loss, and evaluating clinical parameters such as gingival bleeding[92]. Furthermore，Deng et al. trained AI classifiers on nine non-invasive predictors (gingival disease, gingival/tooth health rating, dental cleanliness, tooth mobility symptoms, flossing habits, aMMP-8 point-of-care test, self-reported gingival bleeding on brushing, hemoglobin, and age) and achieved high accuracy (92.4%) in distinguishing different categories of periodontal conditions[16]. Ossowska et al. further advanced precision staging by integrating invasive clinical metrics (nicotinism approximal plaque index, probing depth, CAL, periodontal pocket depth) with demographic data, attaining 100% accuracy for predicting Grade C periodontitis classification and 80% for Grades A/B[93].

In addition, Kim et al. conducted a pioneering investigation evaluating machine learning models for periodontitis severity stratification using salivary bacteria. Their study analyzed 692 subjects (144 healthy controls, 548 generalized periodontitis cases), training classifiers on bacterial genomic signatures to differentiate disease stages. The optimal model demonstrated 93% accuracy (AUC = 0.96) in distinguishing healthy individuals from moderate/severe periodontitis，showing that ML models could potentially identify periodontitis severity, supporting early intervention strategies[94]. These computational architectures establish comprehensive diagnostic frameworks through AI-driven data fusion of non-invasive biomarkers (including self-reported questionnaires, imaging data, oral hygiene habits) and clinic-invasive parameters (including BOP, periodontal pocket depth, and CAL), demonstrating huge improvement in predictive performance compared to conventional diagnostic protocols. By combining non-invasive indicators with invasive indicators, these models provide efficient tools for personalized prevention and diagnosis.

The medical field is responsible for the generation of a wide array of data types, including but not limited to electronic health records (EHRs), medical imaging, genomic profiles, and physiological signals. The integration of these data can yield novel biological insights and reveal previously unknown molecular interactions. Recent studies indicate that the combination of AI and machine learning algorithms with big data (e.g., multi-omics data) enables refined molecular characterization of patients and facilitates personalized therapeutic strategies[95]. The application of omics technologies has facilitated the identification of a multitude of biomarkers in various biological systems, including the metabolome, microbiome, genome, and proteome. This has led to a significant advancement in our understanding of the pathophysiology of periodontal diseases. The substantial datasets generated by these technologies are well-suited for analysis using AI algorithms. By incorporating proteomic, genomic, microbiomics, and other multi-omics signatures into AI-driven analyses, researchers can identify novel biomarkers and achieve precise disease subtyping[96,97]. Data-driven technologies that integrate and analyze these multi-source data enhance understanding of disease mechanisms and individual differences. In the context of periodontal disease diagnosis, this approach demonstrates considerable promise. This approach has the potential to augment existing molecular mechanisms associated with periodontal disease, identify novel biomarkers, enhance the early prediction of periodontitis, facilitate personalized risk assessment, and furnish a more comprehensive information base for precision medicine.

4 Challenges and perspectives

Data-driven multi-omics studies of periodontal diseases and the identification of related biomarkers have provided novel tools for the precision diagnosis of periodontitis. To achieve optimal clinical utility, these biological features need to be integrated with traditional diagnostic indicators, such as clinical examination findings and imaging data. With the aid of AI, this integrative approach holds promise for more accurate diagnosis and prediction of disease progression. However, the clinical application of such data—particularly in omics-driven diagnostic strategies for periodontitis—still faces several challenges[98,99].

These challenges manifest in three critical dimensions. One of the primary challenges in this field pertains to the procurement of sufficient clinical samples. The issue of insufficient sample size is a common concern in contemporary genetic studies, particularly those investigating the extensive range of complex phenotypes present within human populations, due to the high degree of genetic diversity observed among individuals. For instance, the prevalence of AgP in the Japanese population is approximately 0.03%, which poses a significant challenge to the recruitment of a large number of affected individuals by a single research center[36]. Furthermore, the majority of multi-omics studies reveal only correlations rather than causative mechanisms, and the lack of longitudinal cohort studies to validate identified biomarkers further hinders clinical translation[100]. From an ethical perspective, significant challenges arise in striking a balance between individual data privacy and the broader benefits of public health[101]. The pervasive utilization of mobile health devices, wearables, and biosensors has significantly augmented the precision of health risk assessment through real-time monitoring and behavioral tracking. However, such data are often shared with service providers and third parties, thereby increasing the risk of data breaches. Cross-referencing data from multiple sources remains one of the most common practices that could lead to such breaches[102]. Addressing these ethical and privacy concerns is a prerequisite for any subsequent effort to standardize and share data across institutions. Moving forward, stronger data anonymization strategies and security measures must be implemented to address privacy and data protection concerns more effectively.

Secondly, issues related to data standardization limit the

comparability of studies. The quality of data processing and analytical algorithms largely depends on the reliability and validity of raw data[103]. Ethnic diversity across populations poses challenges for cross-center studies, often making horizontal comparisons difficult. Furthermore, variations in the resolution and distortion levels of imaging data—such as cone-beam computed tomography (CBCT) and panoramic radiographs—add another layer of complexity to data integration[104]. In addition, discrepancies in healthcare systems across regions result in heterogeneous standards for periodontal data collection, such as probing depth and attachment loss measurements, which further hinder the deep mining and cross-regional integration of periodontal datasets. Consequently, reducing the technological and financial barriers becomes the next logical step toward equitable clinical adoption.

In addition, the considerable expense associated with advanced omics technologies constitutes a significant impediment to their widespread clinical implementation. The implementation of techniques such as single-cell sequencing and spatial transcriptomics in primary care settings is hindered by the high cost of these methodologies. In the future, these challenges may be addressed through interdisciplinary collaboration. For example, the development of lightweight AI models could lower the threshold for multi-omics data interpretation. Alternatively, organoid models could be used to functionally validate candidate biomarkers, thereby accelerating the clinical translation of periodontal disease biomarkers. With technical hurdles and costs being mitigated, attention can now shift to building an integrated, clinician-friendly ecosystem.

Subsequent research endeavors will center on the integration of diverse biological characteristics with emerging technologies, such as AI. The overarching objective of these efforts is to establish a closed-loop system that encompasses risk prediction and precision intervention. Future research should also focus on creating decision-support systems that fuse patient-level data, evidence-based guidelines, and AI-driven predictions to recommend optimal, personalized treatment strategies. Its goal should be to strengthen, not replace, clinicians' decision-making. Investigations into the integration of AI with smart dental devices or home-use tools that continuously monitor periodontal health biomarkers will facilitate early detection of disease onset or recurrence. Enhancing the clinical integration of AI systems remains a pivotal area for future work. User-experience studies conducted with dental professionals are essential for optimizing the design and deployment of AI tools within existing clinical workflows. For instance, by incorporating multi-omics data, GCF metabolites, and oral microbiome profiles, dynamic models for risk prediction and diagnosis of periodontal disease can be developed. In the realm of technological advancement, AI-enabled multimodal-sensing toothbrushes (AI-MST)[105] and interactive telemonitoring toothbrushes (ITT)[106] are being developed to offer real-time guidance on oral hygiene practices. These toothbrushes facilitate the transmission of crucial behavioral and health data to clinicians, thereby enabling effective remote monitoring and personalized instruction. Furthermore, newly developed computational tools, including smart dental mirrors, have the capacity to analyze clinical and omics data in real time. Additionally, nano sensors, such as graphene-based electrochemical sensors, show promise in the real-time detection of subgingival plaque. Data-driven technologies are transforming the management of periodontal diseases. The primary value of these technologies lies in their ability to facilitate early intervention and precision medicine through the integration of multi-dimensional data.

In the future, it is imperative that research endeavors concentrate on the convergence of innovative AI algorithms, the acquisition of high-quality data, and the implementation of robust clinical validation. This strategic integration is crucial for accelerating the transition of these technologies from laboratory settings to clinical practice, thereby achieving a comprehensive intelligent upgrade across the domains of prevention, diagnosis, treatment, and monitoring.

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Author contribution

A.L. contributed conception and design of the study. H.S. and Z.C. contributed to writing-original draft. Z.C. and H.S. organized the figures. Y.Y. and Z.W. contributed to writing-review and editing. All the authors revised the manuscript and approved the final version.

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N/A

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