Original Article

SALIVA AS A DIAGNOSTIC MEDIUM IN ORAL HEALTH SCIENCE: CONCEPTUALIZING ITS ROLE IN EARLY DETECTION OF ORAL AND SYSTEMIC DISEASES

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ABSTRACT

Saliva, an easily accessible biofluid, offers a non-invasive window into both oral and systemic health through its diverse molecular cargo. This conceptual diagnostic science article develops a unified model that positions saliva as a central medium for the early detection of oral diseases such as dental caries, periodontitis, and oral squamous cell carcinoma, as well as systemic conditions, including viral infections and certain malignancies. The model integrates the biological composition of saliva—encompassing proteins, metabolites, microbial communities, and nucleic acids—with advanced biomarker detection mechanisms and interpretive frameworks. Recent advances in proteomics, genomics, and metabolomics demonstrate that disease-specific alterations in salivary profiles precede clinical manifestations, enabling proactive screening. The proposed conceptual pathway progresses sequentially from salivary secretion and sample acquisition through technological detection, algorithmic signal interpretation, and clinical application. By conceptualizing these interconnected domains, the model eliminates reliance on invasive procedures while enhancing patient compliance and diagnostic equity. Challenges related to standardization and biomarker validation are addressed conceptually, with emphasis on the translational potential of point-of-care platforms. This framework underscores saliva's capacity to bridge oral and systemic medicine, fostering earlier intervention and improved outcomes across health domains.

Key words: Salivary biomarkers, Oral disease detection, Systemic disease screening, Saliva proteomics, Non-invasive diagnostics, Early detection pathway

Introduction

The global burden of oral diseases continues to rise, affecting billions and contributing to substantial healthcare costs and diminished quality of life. Traditional diagnostic approaches—ranging from visual-tactile examination to tissue biopsy—remain invasive, time-consuming, and dependent on specialist availability, often resulting in delayed detection until advanced stages. Saliva emerges as a compelling alternative because it is continuously produced, readily collected without trained personnel, and reflective of both local oral microenvironmental changes and distant systemic physiology [1-7].

Unlike blood or tissue sampling, salivary collection is painless, cost-effective, and repeatable, making it ideal for population-level screening and longitudinal monitoring. Its diagnostic utility stems from the fact that salivary constituents derive from multiple sources: major and minor salivary glands, gingival crevicular fluid, oral mucosa transudate, microbial communities, and even circulating molecules filtered from plasma [2, 6, 7]. These components undergo dynamic modulation in response to disease, providing measurable signals long before overt clinical signs appear [3, 4, 8-15].

Conceptual advances in salivary diagnostics have accelerated since the recognition that oral conditions share bidirectional pathways with systemic disorders. Periodontitis elevates inflammatory mediators that enter saliva and mirror systemic inflammation [15-19], while oral squamous cell carcinoma releases tumour-specific proteins and nucleic acids detectable in oral fluids [1, 20, 21]. Viral pathogens such as the hepatitis C virus alter salivary gland histology and composition, enabling non-invasive detection [6]. Similarly, metabolic shifts associated with lung cancer manifest in salivary glycopatterns [14], and radiation-induced salivary gland damage alters protein profiles [5].

The conceptual model presented here synthesises these insights into a cohesive diagnostic pathway. It avoids empirical datasets or statistical validation, focusing instead on mechanistic reasoning derived from established salivary biology [7, 10, 12]. By framing saliva as a liquid biopsy analogue, the model addresses key limitations of current oral health diagnostics: invasiveness, low sensitivity for early-stage disease, and poor integration of oral-systemic data [20-22]. Early detection through salivary signals could reduce progression to advanced oral lesions, lower systemic comorbidity risks, and support precision medicine approaches [1, 15].

This article is structured around two foundational domains. First, the biological composition of saliva and its inherent diagnostic potential are delineated, highlighting how specific molecular classes serve as disease indicators [8, 9,

19]. Second, a conceptual pathway is proposed that links saliva production to clinical application. The model is informed by peer-reviewed literature spanning salivary microbiome dynamics in caries and oral squamous cell carcinoma [1, 3, 4], proteomic and metabolomic alterations in periodontitis and systemic malignancies [10, 14, 19], and point-of-care technologies for active matrix metalloproteinase-8 [15]. Collectively, these sources underpin the rationale that saliva is not merely a diagnostic fluid but a conceptual bridge between oral health science and systemic medicine.

Results and Discussion

Biological composition of saliva and its diagnostic potential
Saliva is a complex biofluid whose composition reflects the integrated activity of salivary glands, oral microbiota, immune cells, and systemic circulation. Approximately 99% water, it contains electrolytes, proteins, peptides, metabolites, nucleic acids, and microbial elements that collectively encode health and disease states [7]. The three paired major salivary glands (parotid, submandibular, and sublingual) plus hundreds of minor glands secrete fluid modulated by autonomic innervation, hormonal signals, and local inflammation. Disease-induced changes in glandular function—such as those observed in viral infections [2, 6] or radiotherapy [5]—alter secretion rate, viscosity, and molecular cargo, creating diagnostic windows [7].

Proteins constitute the most abundant non-aqueous fraction and serve as primary biomarkers. Enzymes (α-amylase), mucins, proline-rich proteins, histatins, and statherin maintain homeostasis but exhibit quantitative and qualitative shifts in the context of pathology. In periodontitis, annexin A1 levels in saliva rise, reflecting neutrophil activation and tissue destruction [19]. Cytokines and matrix metalloproteinases, particularly active MMP-8, increase proportionally with disease severity, providing a measurable index of collagen degradation [15]. In oral squamous cell carcinoma, tumour-derived proteins and altered glycosylation patterns are detectable in saliva [1], whereas patients with burning mouth syndrome display distinct microbial and immune protein signatures [8]. Lung cancer induces changes in mannosylated glycopatterns recognised by specific lectins [14], demonstrating saliva's ability to capture distant neoplastic signals.

Metabolomics further expands diagnostic scope. Untargeted profiling of stimulated and unstimulated saliva reveals metabolite perturbations linked to caries risk, endocrine function, and immune status in children [10, 12]. Radiation-related caries onset correlates with longitudinal shifts in salivary protein composition even when high-fluoride regimens are employed [13]. These metabolic fingerprints precede clinical lesions, supporting the conceptual premise that saliva acts as an early-warning reservoir [10].

Genomic and microbiomic constituents add another layer. Cell-free DNA, microbial DNA, and RNA viruses are readily detectable [20]. The salivary microbiome in early childhood predicts future caries development through specific microbial indicators of dysbiosis [3, 4]. In oral squamous cell carcinoma, microbiome composition correlates with neoadjuvant immunotherapy response [1], while hepatitis C virus infection produces histologically verifiable glandular changes accompanied by compositional alterations [6]. Point-of-care detection of microbial shifts or host genomic markers thus becomes feasible without invasive sampling [15].

Immunoglobulins (secretory IgA), hormones, and growth factors complete the diagnostic repertoire. Activin-A and interleukin-1β concentrations in oral biofluids differentiate periodontitis stages [9], while histone deacetylase expression responds to non-surgical periodontal therapy [16]. These molecules link local oral pathology to systemic immune modulation, reinforcing saliva's role as an oral-systemic sentinel [7, 20].

Collectively, the biological complexity of saliva—its multi-source origin and dynamic responsiveness—confers exceptional diagnostic potential. Alterations occur at molecular, cellular, and microbial levels before macroscopic tissue damage, enabling conceptual models of pre-symptomatic detection [3, 15, 21]. The non-invasive nature of collection further amplifies utility for vulnerable populations, children, and repeated monitoring [4, 12]. By harnessing proteomics, genomics, and metabolomics, saliva transcends its traditional lubricating role to become a comprehensive diagnostic medium capable of flagging both localised oral diseases and systemic conditions with shared pathophysiological axes [1, 6, 14, 22].

Conceptual pathway for saliva-based disease detection
The conceptual diagnostic model organises saliva-based detection into four sequential yet interconnected domains: biological composition, biomarker detection mechanisms, diagnostic signal interpretation, and clinical screening applications. This pathway conceptualises saliva collection as the entry point to a non-invasive pipeline that culminates in actionable clinical decisions [15, 20].

Saliva production begins with glandular secretion modulated by neural and humoral inputs. Unstimulated whole saliva represents baseline physiology, while stimulated samples (chewing or citric acid) enrich certain analytes [10, 12]. Collection protocols—passive drooling or swab-based—preserve integrity for downstream analysis. The resulting fluid carries the full spectrum of biological components described earlier, providing the raw material for biomarker interrogation [7].

Biomarker detection mechanisms leverage diverse technologies tailored to the molecular class. Proteomic platforms (mass spectrometry, ELISA) quantify proteins such as annexin A1 [19] or active MMP-8 [15]. Genomic

approaches (next-generation sequencing, PCR) identify microbial signatures or host DNA mutations [1, 3]. Metabolomic techniques (NMR spectroscopy, mass spectrometry) capture small-molecule profiles [10, 12]. Point-of-care devices, exemplified by lateral-flow immunoassays for active MMP-8, enable chairside detection without laboratory infrastructure [15]. These technologies operate on microlitre volumes, supporting the model's emphasis on minimal invasiveness [20].

Diagnostic signal interpretation integrates raw data through threshold-based classification and pattern recognition. Conceptual algorithms correlate biomarker concentrations or microbial abundances with disease probability, incorporating patient-specific factors such as age, smoking status, and comorbidities [15, 17]. Machine-learning frameworks trained on multi-omics datasets refine risk stratification, distinguishing health from dysbiosis or early neoplasia [1, 17]. Feedback loops allow re-testing or adjunctive imaging when signals are equivocal.

Clinical screening applications translate interpreted signals into practice. In oral health, the pathway supports early caries risk assessment via microbiome profiling [3, 4], periodontitis staging through MMP-8 and annexin A1 [15, 19], and oral squamous cell carcinoma surveillance via proteomic and glycopattern markers [1, 14]. Systemically, salivary changes flag hepatitis C virus infection [6], radiation-induced glandular damage [5], and lung cancer-associated glycosylation shifts [14]. The model envisions integration into routine dental visits, community screening programmes, and telemedicine, thereby expanding access to early detection [20, 22].

Figure 1 illustrates the conceptual saliva-to-clinical diagnostic pathway linking salivary biological composition, biomarker detection technologies, algorithmic interpretation, and clinical disease screening applications.

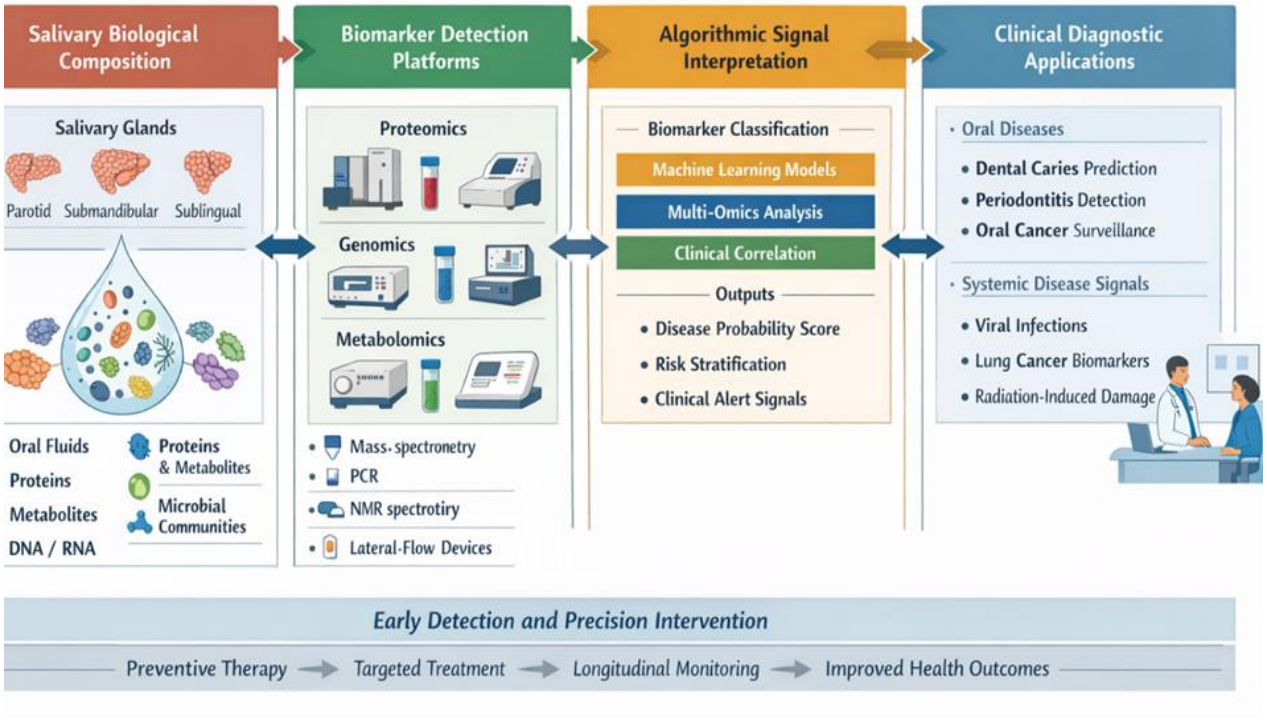

Figure 1. Conceptual saliva-to-clinical diagnostic pathway for early detection of oral and systemic diseases

This conceptual pathway therefore provides a coherent framework that unifies salivary biology with diagnostic technology and clinical utility, laying the foundation for saliva-centred oral and systemic disease detection.

Clinical diagnostic applications

The conceptual salivary diagnostic pathway finds practical expression across diverse clinical scenarios, where its non-invasive nature and early signal-capture capacity enable proactive management of both oral and systemic conditions. Because saliva integrates molecular signals from oral tissues, microbial communities, and the systemic circulation, it serves as a readily accessible diagnostic fluid that reflects ongoing pathophysiological processes in real time. Consequently, salivary diagnostics are increasingly conceptualized not merely as adjunctive tests but as integral components of preventive and predictive dental medicine [23- 32].

In periodontal disease screening, salivary biomarkers such as active matrix metalloproteinase-8 (aMMP-8) serve as reliable indicators of active tissue destruction and collagen breakdown within periodontal structures [15]. Point-of-care immunoassays can detect elevated aMMP-8 levels during routine dental examinations, allowing clinicians to stratify patients into biologically meaningful risk categories before radiographic bone loss becomes evident [15, 17]. Early identification of heightened proteolytic activity enables clinicians to initiate intensified preventive strategies, including targeted non-surgical periodontal therapy, localized antimicrobial delivery, or behavioral interventions to improve oral hygiene compliance. This application supports personalized periodontal therapy, where high-risk individuals receive intensified non-surgical interventions or adjunctive antimicrobials, potentially halting progression to advanced periodontitis [19]. Annexin A1, another salivary protein elevated in response to neutrophil degranulation and inflammatory signaling, complements aMMP-8 by providing additional confirmation of inflammatory status and host immune activation [19]. Integrating these markers into chairside testing protocols conceptualizes a shift from reactive periodontal treatment toward predictive periodontal care, reducing the incidence of tooth loss and potentially mitigating the systemic inflammatory burden associated with chronic periodontal infection [33-40].

For dental caries risk assessment, the salivary microbiome offers predictive power that surpasses traditional clinical indicators such as past caries experience or plaque indices [3, 4]. Microbial dysbiosis indicators in young children—particularly increased abundance of cariogenic species such as *Streptococcus mutans* and *Lactobacillus* spp.—can forecast future lesion development with sufficient lead time to implement preventive strategies including fluoride varnish applications, sealant placement, and dietary counseling [3, 4]. Stimulated and unstimulated saliva metabolomics further refine this application by revealing perturbations in carbohydrate metabolism, organic acid accumulation, and acidogenic profiles that precede clinically detectable enamel demineralization [10, 12]. These biochemical signatures provide insight into microbial metabolic activity and ecological imbalance within the oral biofilm. Together, microbial and metabolic salivary signals enable clinicians to tailor recall intervals, intensify preventive interventions, and implement targeted remineralization therapies. In this framework, caries management evolves from a restorative paradigm focused on repairing damage to a precision prevention model centered on early ecological correction and risk mitigation [41-50].

Oral squamous cell carcinoma (OSCC) surveillance is among the most transformative clinical applications of salivary diagnostics [1, 21, 22]. Salivary proteomic shifts—including tumour-derived proteins, extracellular vesicle components, and altered glycosylation patterns—can emerge during the earliest stages of carcinogenesis, often preceding overt clinical manifestations [1, 14]. These molecular alterations reflect both tumor cell activity and host immune responses, providing a multi-dimensional biomarker signature detectable through non-invasive sampling. Microbiome profiling in OSCC saliva has also demonstrated correlations with treatment response, suggesting that microbial community composition may serve as a dynamic indicator of therapeutic efficacy during neoadjuvant immunotherapy or targeted therapies [1]. Furthermore, glycopattern alterations detected in saliva have been associated not only with oral malignancies but also with distant cancers such as lung carcinoma, highlighting the systemic diagnostic potential of salivary glycomics [14]. The conceptual model, therefore, envisions routine salivary collection during dental visits for at-risk patients—such as tobacco users, heavy alcohol consumers, and individuals with premalignant oral lesions—with positive biomarker signals triggering referral for confirmatory imaging or histopathological evaluation. By enabling earlier detection of malignant transformation, this approach directly addresses the persistent challenge of late-stage OSCC diagnosis. It has the potential to significantly improve survival outcomes through timely intervention.

Beyond these primary applications, the broader integration of salivary diagnostics into dental practice supports the emergence of a continuous monitoring paradigm, in which molecular signals are periodically assessed to track disease trajectories over time. Such integration could allow dental clinics to function as frontline screening hubs for inflammatory, metabolic, and oncologic conditions, thereby expanding the role of oral healthcare providers in systemic disease surveillance.

Figure 2 presents a clinical workflow for integrating saliva-based screening into routine dental practice, from patient risk identification and sample collection to biomarker interpretation, intervention, referral, and longitudinal follow-up.

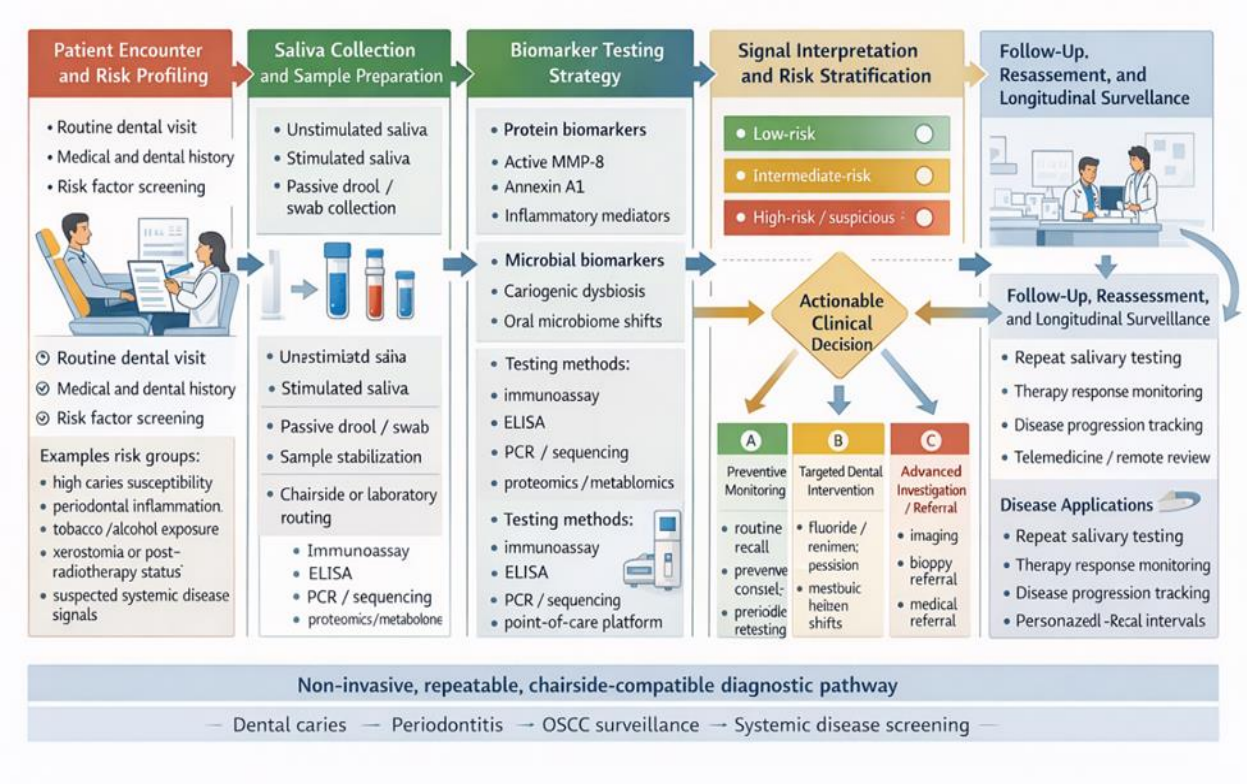

Figure 2. Clinical workflow for saliva-based screening and early diagnostic decision-making in oral health practice.

The figure illustrates a translational clinical pathway that begins with patient risk profiling and saliva collection, progresses through biomarker-specific testing and diagnostic interpretation, and culminates in preventive care, targeted intervention, referral, and longitudinal monitoring. The workflow emphasizes how saliva-based diagnostics can be embedded into routine dental care to support early detection of both oral and systemic diseases.

Systemic disease detection via saliva bridges oral and general health domains. Viral infections, such as hepatitis C, alter glandular histology and salivary composition, enabling non-invasive screening in dental settings [6]. Radiation-induced salivary gland dysfunction following head and neck cancer therapy manifests in protein profile changes, guiding supportive care and caries prevention protocols [5]. Emerging applications include metabolic and endocrine monitoring, where salivary metabolites reflect systemic shifts in burning mouth syndrome or pediatric endocrine function [8, 12]. The oral-systemic axis is particularly evident in periodontitis, where salivary cytokines and MMPs mirror vascular inflammation, supporting conceptual links to cardiovascular risk stratification [15, 19].

In pediatric and geriatric populations, salivary diagnostics enhance accessibility. Children tolerate drool-based sampling well, facilitating early caries and microbiome risk profiling [4, 12]. Older adults benefit from reduced invasiveness for monitoring xerostomia-related complications or systemic comorbidities [7]. Telemedicine integration allows remote saliva kit mailing, with results uploaded for virtual consultation, expanding reach in underserved areas [20].

These applications collectively demonstrate saliva's versatility: from point-of-care periodontal staging [15] to longitudinal OSCC surveillance [1] and systemic viral screening [6]. By embedding salivary testing into routine dental workflows, the model fosters interdisciplinary collaboration, with dentists serving as frontline diagnosticians for broader health surveillance. **Table 1** summarises major clinical applications of salivary diagnostics, highlighting representative biomarkers, detection technologies, and corresponding diagnostic outcomes across oral and systemic diseases.

Table 1. Clinical applications of salivary diagnostics across oral and systemic diseases

Clinical condition	Key Salivary biomarkers	Detection technology	Diagnostic purpose	Clinical outcome
Dental caries	Cariogenic microbiome indicators, acidogenic	Microbiome sequencing,	Early risk prediction before enamel	Targeted prevention and fluoride therapy

	metabolites	metabolomics profiling	demineralization	
Periodontitis	Active MMP-8, annexin A1, inflammatory cytokines	Immunoassay, ELISA, point-of-care tests	Detection of active periodontal tissue destruction	Personalized periodontal therapy and disease monitoring
Oral squamous cell carcinoma	Tumour-derived proteins, glycopattern alterations, and extracellular vesicle markers	Proteomics and glycomics profiling	Early detection and treatment monitoring	Earlier diagnosis and improved survival
Viral infections (e.g., hepatitis C)	Viral RNA, glandular inflammatory proteins	PCR, genomic sequencing	Non-invasive systemic disease screening	Referral for confirmatory testing and treatment
Lung cancer	Altered salivary glycopatterns	Lectin-based glycoprotein analysis	Early cancer signal detection	Trigger imaging or oncology referral
Radiation-induced salivary gland damage	Altered salivary protein composition	Proteomic profiling	Monitoring glandular dysfunction post-therapy	Preventive oral care and caries management

Future research opportunities in salivary diagnostics

Advancing the conceptual salivary diagnostic model requires targeted research to overcome current limitations and unlock full translational potential. Standardization of collection protocols remains a priority: variability in unstimulated versus stimulated sampling, time of day, and recent food intake influences biomarker stability [10, 12]. Future studies should establish consensus guidelines for pre-analytical handling, including storage temperature and centrifugation, to ensure reproducibility across laboratories and clinical sites.

Multi-omics integration presents a major opportunity. Combining proteomics, metabolomics, genomics, and microbiomics in single saliva samples could yield composite signatures with superior sensitivity and specificity [1, 3, 10, 15]. Machine-learning algorithms trained on these multi-layered datasets promise refined pattern recognition, distinguishing subtle disease transitions from normal variation [17]. Research should focus on validating such models in large, diverse cohorts to mitigate bias and enhance generalizability.

Point-of-care technology development is critical for real-world adoption. While lateral-flow assays for aMMP-8 demonstrate feasibility [15], expanding to multiplex platforms detecting panels of proteins, metabolites, and microbial DNA would enable comprehensive chairside profiling [20]. Nanotechnology-enhanced biosensors and microfluidic chips could achieve attomolar sensitivity for low-abundance biomarkers, such as tumour-derived microRNAs or glycans [14]. Portable, smartphone-integrated devices represent a promising direction, facilitating home-based monitoring and telemedicine integration.

Biomarker discovery for underrepresented conditions offers untapped potential. Beyond periodontitis and OSCC, salivary signals in autoimmune disorders (e.g., Sjögren's syndrome), neurodegenerative diseases, and metabolic syndromes warrant exploration [7, 22]. Longitudinal studies tracking salivary changes from preclinical to manifest stages could identify predictive markers for conditions like diabetes or rheumatoid arthritis, strengthening the oral-systemic diagnostic bridge.

Validation of salivary diagnostics against gold standards is essential. Comparative studies pitting saliva-based predictions against tissue biopsy, imaging, or blood assays will build evidentiary support for regulatory approval and insurance reimbursement [21, 22]. Cost-effectiveness analyses should quantify benefits in reduced invasive procedures, earlier interventions, and prevented complications.

Ethical and equity considerations merit a dedicated inquiry. Research must address accessibility in low-resource settings, cultural acceptability of saliva collection, and data privacy in AI-driven interpretation. Inclusive cohorts that reflect ethnic, socioeconomic, and geographic diversity will help prevent the exacerbation of health disparities.

Interdisciplinary collaboration—spanning dentistry, clinical pathology, bioinformatics, and engineering—will accelerate progress. Funding for consortium-based biobanking of annotated saliva samples could create shared resources for discovery and validation. Ultimately, these opportunities position salivary diagnostics as a cornerstone of precision oral and systemic medicine, evolving from conceptual promise to routine clinical reality.

Conclusion

Saliva stands as a uniquely accessible and information-rich medium that redefines diagnostic paradigms in oral health science. The conceptual model articulated here integrates its biological composition, detection mechanisms, interpretive frameworks, and clinical applications into a cohesive pathway for early disease identification. From microbiome-driven caries prediction and aMMP-8-guided periodontitis

management to proteomic surveillance of OSCC and systemic viral detection, saliva enables non-invasive, proactive strategies that transcend traditional limitations.

By conceptualizing saliva as a liquid biopsy for both local and distant pathologies, this framework highlights its capacity to bridge oral and systemic health domains. Routine dental encounters become opportunities for opportunistic screening, enhancing equity, compliance, and outcomes. Challenges in standardization, multi-omics integration, and point-of-care translation persist, yet ongoing advances in technology and biomarker discovery promise to surmount them.

The future envisions saliva-centric diagnostics embedded in personalized, predictive healthcare—where early salivary signals trigger timely interventions, reducing disease burden and fostering interdisciplinary collaboration. Realizing this vision requires sustained research commitment, but the foundational rationale is compelling: saliva, once viewed merely as a lubricant, now emerges as a powerful diagnostic ally in the pursuit of comprehensive health surveillance.

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