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Research Article

Salivary Diagnostics in Oral Potentially Malignant Disorders: Advances and Clinical Relevance

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Abstract

Oral potentially malignant disorders (OPMDs) represent a heterogeneous group of lesions with an increased risk of malignant transformation to oral squamous cell carcinoma (OSCC), accounting for significant global morbidity and mortality. Current diagnostic approaches rely heavily on clinical examination and histopathological assessment, which possess inherent limitations in early detection and risk stratification. This narrative review synthesizes current evidence on salivary diagnostics for OPMDs, evaluating recent advances and clinical relevance. We conducted a comprehensive literature search of PubMed and Scopus databases, focusing on studies published within the last decade that investigated salivary biomarkers and diagnostic technologies for OPMDs. The review identifies several categories of promising salivary biomarkers, including genetic alterations, transcriptomic signatures, proteomic profiles, and microbiome shifts. Additionally, we explore emerging analytical technologies such as next-generation sequencing, mass spectrometry, and point-of-care devices that have enhanced biomarker discovery and clinical application. The evidence suggests that salivary diagnostics offer considerable promise for non-invasive early detection, risk stratification, and monitoring of OPMDs. Multi-marker approaches demonstrate superior diagnostic accuracy compared to single biomarkers, reflecting the complex molecular pathogenesis of oral carcinogenesis. However, challenges remain regarding standardization, validation, and clinical implementation. The integration of salivary biomarkers with conventional diagnostic methods may enable personalized surveillance strategies and facilitate early intervention, potentially reducing the burden of OSCC.

Keywords: *oral potentially malignant disorders, salivary diagnostics, biomarkers, early detection, oral cancer, liquid biopsy, point-of-care testing*

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1. Introduction

Oral potentially malignant disorders (OPMDs) encompass a spectrum of clinical conditions that carry an increased risk of malignant transformation to oral squamous cell carcinoma (OSCC) [1]. These disorders include leukoplakia, erythroplakia, oral lichen planus, oral submucous fibrosis, and proliferative verrucous leukoplakia, among others [2]. The global prevalence of OPMDs ranges from 1% to 5% of the adult population, with malignant transformation rates varying from 0.1% to 36% depending on the specific disorder, risk factors, and follow-up duration [3]. OSCC remains one of the most common malignancies worldwide, with approximately 377,713 new cases and 177,757 deaths annually, highlighting the significant public health burden [4].

The pathogenesis of OPMDs involves a complex interplay of genetic, epigenetic, molecular, and environmental factors that drive the multistep process of oral carcinogenesis [5]. Key molecular alterations include genetic mutations, chromosomal

instability, epigenetic modifications, aberrant signaling pathways, and field cancerization [6]. Despite advances in understanding these molecular mechanisms, current diagnostic approaches for OPMDs primarily rely on conventional clinical examination and histopathological assessment of incisional or excisional biopsies [7]. While histopathology remains the gold standard for diagnosis and grading of epithelial dysplasia, it possesses several limitations, including invasiveness, sampling errors, inter-observer variability in dysplasia grading, and inability to predict malignant transformation with certainty [8].

The limitations of conventional diagnostic methods have prompted intensive research into non-invasive biomarkers that could enhance early detection, risk stratification, and monitoring of OPMDs [9]. Among various biological samples, saliva has emerged as a particularly promising diagnostic fluid due to its non-invasive collection, ease of sampling, cost-effectiveness, and composition reflecting both local and systemic conditions [10]. Saliva contains various biomolecules derived from local oral tissues, salivary glands, oral microbiota, and systemic circulation, making it a comprehensive source of diagnostic information [11].

The field of salivary diagnostics has evolved significantly over the past decade, driven by advances in high-throughput technologies and improved understanding of oral carcinogenesis [12]. Despite substantial progress, controversies remain regarding the clinical utility of many proposed salivary biomarkers, their standardization, and implementation in routine clinical practice [13]. Additionally, the heterogeneous nature of OPMDs necessitates a comprehensive understanding of various biomarker categories and their interrelationships.

This narrative review aims to synthesize current evidence on salivary diagnostics for OPMDs and evaluate their clinical relevance. Specifically, we will: (1) examine the pathophysiological basis for salivary biomarker development in OPMDs; (2) review current diagnostic methods and their limitations; (3) analyze emerging salivary biomarker categories, including genetic, transcriptomic, proteomic, and microbiome-based biomarkers; (4) evaluate analytical technologies for salivary biomarker detection; (5) assess the clinical applications of salivary diagnostics for OPMDs; and (6) discuss current challenges, gaps in knowledge, and future directions for research and clinical implementation.

Pathophysiology of Oral Potentially Malignant Disorders

Understanding the pathophysiology of OPMDs is fundamental to identifying relevant salivary biomarkers. Oral carcinogenesis is a multistep process characterized by the accumulation of genetic and epigenetic alterations that drive the progression from normal epithelium to invasive carcinoma [14]. This process follows the concept of field cancerization, wherein large areas of the oral mucosa are exposed to carcinogenic influences, leading to molecular alterations that precede histopathological changes [15].

Genetic alterations play a crucial role in the development and progression of OPMDs. These include mutations in tumor suppressor genes (such as TP53, CDKN2A, and NOTCH1), activation of oncogenes (such as PIK3CA and HRAS), and chromosomal instability [16]. Loss of heterozygosity (LOH) at specific chromosomal regions (3p, 9p, 17p) is frequently observed in OPMDs and is associated with increased risk of malignant transformation [17]. Epigenetic modifications, including DNA methylation, histone modifications, and non-coding RNA expression, also contribute to oral carcinogenesis by silencing tumor suppressor genes and activating oncogenic pathways [18].

Molecular pathways dysregulated in OPMDs include cell cycle control, apoptosis, DNA repair, signal transduction, and cell adhesion [19]. The PI3K/AKT/mTOR pathway, Wnt/β-catenin pathway, and NOTCH signaling pathway are frequently altered in OPMDs and OSCC [20]. Inflammatory processes also play a significant role, with

chronic inflammation creating a microenvironment conducive to malignant transformation through the production of reactive oxygen species, pro-inflammatory cytokines, and growth factors [21].

The tumor microenvironment in OPMDs involves complex interactions between epithelial cells, stromal cells, immune cells, and the oral microbiome [22]. Immune evasion mechanisms, including reduced immunosurveillance and increased immunosuppressive cell populations, contribute to disease progression [23]. The oral microbiome undergoes dysbiosis in OPMDs, with shifts in microbial composition potentially contributing to carcinogenesis through chronic inflammation, production of carcinogenic metabolites, and modulation of host immune responses [24].

This complex pathophysiological process provides numerous potential salivary biomarkers that reflect different aspects of oral carcinogenesis, including genetic alterations, epigenetic modifications, transcriptomic changes, proteomic profiles, and microbiome shifts [25]. Understanding these pathophysiological mechanisms is crucial for interpreting salivary biomarker profiles and developing clinically useful diagnostic tools.

Current Diagnostic Approaches and Limitations

The diagnosis and management of OPMDs rely on a combination of clinical examination and histopathological assessment. Clinical examination involves visual inspection and palpation of the oral mucosa, often aided by adjunctive techniques such as toluidine blue staining, vital staining, chemiluminescence, and autofluorescence [26]. While these techniques can help identify suspicious lesions, they possess limited sensitivity and specificity in detecting dysplastic changes and predicting malignant transformation [27].

Histopathological examination of incisional or excisional biopsies remains the gold standard for diagnosing OPMDs and grading epithelial dysplasia [28]. The World Health Organization classification system categorizes epithelial dysplasia into mild, moderate, and severe grades based on architectural and cytological features [29]. However, histopathological assessment has several limitations. It is an invasive procedure that may cause patient discomfort and carries risks of bleeding, infection, and altered sensation [30]. Sampling errors can occur due to the heterogeneous nature of OPMDs, with biopsied areas potentially not representing the most advanced molecular changes [31].

Inter-observer variability in dysplasia grading represents another significant limitation, with studies showing only fair to moderate agreement among pathologists [32]. This variability can lead to inconsistencies in diagnosis, treatment planning, and prognostication [33]. Furthermore, histopathological assessment provides a static snapshot of disease status and cannot reliably predict which lesions will undergo malignant transformation [34]. Studies have shown that only a subset of dysplastic lesions progress to OSCC, while some non-dysplastic lesions can transform, highlighting the limitations of histopathology in risk stratification [35].

Molecular techniques have been applied to tissue specimens to improve diagnostic accuracy and predict malignant transformation. These include immunohistochemistry for protein expression, fluorescence in situ hybridization for genetic alterations, and DNA sequencing for mutation analysis [36]. While these techniques provide valuable molecular information, they still require invasive tissue sampling and are not routinely used in clinical practice due to cost, complexity, and lack of standardized protocols [37].

The limitations of current diagnostic approaches underscore the need for non-invasive, sensitive, and specific methods that can detect early molecular changes, predict malignant transformation, and monitor disease progression. Salivary diagnostics offer the potential to address these limitations by providing a liquid biopsy that reflects the molecular alterations in OPMDs without the need for invasive procedures [38].

Salivary Biomarkers in OPMDs

Genetic Biomarkers

Genetic alterations in OPMDs can be detected in saliva through various approaches, including analysis of cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), and exosomes [39]. Salivary cfDNA represents fragmented DNA released from normal and abnormal cells through apoptosis, necrosis, and active secretion [40]. In OPMDs, the quantity and quality of salivary cfDNA differ from healthy controls, with increased concentrations and altered integrity reflecting the presence of disease [41].

Specific genetic mutations associated with OPMDs can be detected in salivary DNA. Mutations in TP53, the most commonly altered gene in OSCC, have been identified in saliva from patients with OPMDs and are associated with increased risk of malignant transformation [42]. Similarly, mutations in CDKN2A, NOTCH1, and PIK3CA have been detected in saliva from OPMD patients, demonstrating the potential for genetic biomarkers in early detection [43].

Loss of heterozygosity (LOH) at specific chromosomal regions is another promising genetic biomarker. Studies have shown that LOH at 3p14 and/or 9p21 in saliva is associated with OPMDs and predicts malignant transformation with reasonable accuracy [44]. The combination of multiple LOH markers improves diagnostic and prognostic performance, reflecting the cumulative nature of genetic alterations in oral carcinogenesis [45].

Epigenetic modifications, particularly DNA methylation, represent another category of genetic biomarkers detectable in saliva. Hypermethylation of tumor suppressor gene promoters leads to gene silencing and is frequently observed in OPMDs [46]. Salivary DNA methylation markers such as p16, DAPK, MGMT, and TIMP3 have shown promise in distinguishing OPMDs from normal mucosa and predicting malignant transformation [47]. Methylation panels combining multiple genes demonstrate superior performance compared to single markers, highlighting the importance of comprehensive epigenetic profiling [48].

Microsatellite instability (MSI), characterized by alterations in the length of microsatellite repeats due to defective DNA mismatch repair, has also been investigated as a salivary biomarker for OPMDs. While MSI is less common in OSCC compared to other cancers, specific microsatellite alterations have been associated with OPMDs and malignant transformation [49].

Transcriptomic Biomarkers

Transcriptomic biomarkers include various RNA species detectable in saliva, such as messenger RNA (mRNA), microRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA) [50]. These RNA molecules can be packaged in exosomes, microvesicles, or bound to proteins, protecting them from degradation and facilitating their detection in saliva [51].

MicroRNAs, small non-coding RNAs that regulate gene expression post-transcriptionally, have emerged as particularly promising salivary biomarkers for OPMDs. Specific miRNA signatures are associated with OPMDs and OSCC, reflecting their roles in carcinogenesis [52]. Studies have identified dysregulated salivary miRNAs in OPMD patients, including miR-21, miR-31, miR-184, and miR-145, which demonstrate diagnostic and prognostic potential [53]. MiRNA panels combining multiple species show improved accuracy compared to single miRNAs, consistent with the complex regulatory networks in oral carcinogenesis [54].

Messenger RNA biomarkers in saliva reflect the transcriptional activity of cells in the oral cavity. Studies have identified specific mRNA signatures associated with OPMDs, including genes involved in inflammation, immune response, cell proliferation, and

apoptosis [55]. Salivary mRNA levels of IL-8, IL-1β, SAT1, and DUSP1 have shown promise in distinguishing OPMDs from normal mucosa and predicting malignant transformation [56].

Long non-coding RNAs and circular RNAs represent emerging classes of transcriptomic biomarkers. These RNA molecules regulate various cellular processes and are dysregulated in cancer [57]. While research on salivary lncRNAs and circRNAs in OPMDs is still in its early stages, preliminary studies have identified specific species associated with disease presence and progression [58].

Proteomic Biomarkers

Proteomic biomarkers in saliva include proteins, peptides, and post-translationally modified molecules that reflect the pathophysiological processes in OPMDs [59]. Saliva contains thousands of proteins derived from salivary glands, oral mucosa, gingival crevicular fluid, oral microbiota, and systemic circulation, providing a comprehensive proteomic profile [60].

Inflammatory cytokines and chemokines represent a major category of salivary proteomic biomarkers. Chronic inflammation is a hallmark of OPMDs, and specific cytokine profiles are associated with disease presence and progression [61]. Studies have shown elevated levels of IL-6, IL-8, TNF-α, and IL-1β in saliva from OPMD patients compared to healthy controls [62]. These inflammatory mediators not only serve as diagnostic biomarkers but also provide insights into the inflammatory mechanisms driving oral carcinogenesis [63].

Matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) are another important class of proteomic biomarkers. These enzymes are involved in extracellular matrix degradation and tissue remodeling, processes critical for tumor invasion and metastasis [64]. Elevated levels of MMP-1, MMP-2, MMP-9, and MMP-13 have been detected in saliva from OPMD patients, correlating with disease severity and malignant transformation risk [65].

Tumor-associated antigens and autoantibodies represent additional proteomic biomarkers. The immune response to tumor cells produces antibodies against tumor-associated antigens, which can be detected in saliva [66]. Studies have identified autoantibodies against p53, NY-ESO-1, and other tumor antigens in saliva from OPMD patients, demonstrating potential for early detection and monitoring [67].

Salivary metabolites, including amino acids, lipids, carbohydrates, and nucleotides, provide another layer of proteomic information. Metabolomic profiling has revealed distinct metabolic signatures associated with OPMDs, reflecting altered cellular metabolism in carcinogenesis [68]. Specific metabolites such as choline, lactate, and polyamines have shown promise as salivary biomarkers for OPMDs [69].

Microbiome Biomarkers

The oral microbiome undergoes significant alterations in OPMDs, with shifts in microbial composition and function potentially contributing to carcinogenesis [70]. These microbiome changes can be detected in saliva, providing non-invasive biomarkers for disease detection and risk stratification [71].

Culture-independent techniques, particularly 16S rRNA gene sequencing, have revealed distinct microbial signatures associated with OPMDs. Studies have shown decreased microbial diversity and specific enrichment or depletion of certain taxa in OPMDs compared to healthy mucosa [72]. Genera such as Fusobacterium, Porphyromonas, Prevotella, and Streptococcus have been frequently associated with OPMDs, while others such as Rothia and Haemophilus are often depleted [73].

Functional metagenomic analysis has revealed alterations in microbial metabolic pathways in OPMDs. These include changes in pathways related to nitrate reduction,

LPS biosynthesis, and butanoate metabolism, which may contribute to chronic inflammation and carcinogenesis [74]. The production of carcinogenic metabolites by certain bacteria, such as acetaldehyde from alcohol metabolism, represents another potential mechanism linking microbiome dysbiosis to oral carcinogenesis [75].

Microbiome-based biomarkers can be used individually or as part of microbial signatures or ratios. The ratio of opportunistic pathogens to commensal bacteria, or specific microbial co-occurrence patterns, may provide more robust biomarkers than individual taxa [76]. Longitudinal studies have shown that microbiome changes can precede clinical evidence of malignant transformation, suggesting their potential for early detection and monitoring [77].

Analytical Technologies for Salivary Diagnostics

The advancement of salivary diagnostics for OPMDs has been driven by innovations in analytical technologies that enable sensitive, specific, and high-throughput detection of biomarkers [78]. These technologies range from established molecular techniques to emerging platforms with point-of-care applications.

Next-generation sequencing (NGS) technologies have revolutionized the analysis of genetic and transcriptomic biomarkers in saliva. Whole-exome sequencing and targeted gene panels enable comprehensive detection of mutations and copy number variations in salivary DNA [79]. RNA sequencing allows for unbiased profiling of mRNA, miRNA, lncRNA, and other RNA species, facilitating the discovery of novel transcriptomic biomarkers [80]. 16S rRNA gene sequencing and shotgun metagenomics enable detailed characterization of the salivary microbiome, identifying taxa and functional pathways associated with OPMDs [81]. While NGS provides unparalleled depth of information, challenges remain regarding cost, data analysis complexity, and standardization for clinical implementation [82].

Quantitative real-time PCR (qPCR) remains a widely used technique for targeted analysis of specific genetic and transcriptomic biomarkers. Digital PCR (dPCR) offers improved sensitivity and absolute quantification of nucleic acids, making it particularly valuable for detecting low-abundance biomarkers in saliva [83]. Multiplex PCR platforms enable simultaneous analysis of multiple biomarkers, improving diagnostic accuracy and efficiency [84]. PCR-based techniques are relatively affordable, widely available, and can be standardized for clinical use, making them attractive for routine salivary diagnostics [85].

Mass spectrometry (MS)-based proteomics has enabled comprehensive analysis of salivary proteins and metabolites. Techniques such as liquid chromatography-tandem mass spectrometry (LC-MS/MS) and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) allow for high-throughput identification and quantification of proteins and metabolites [86]. These technologies have facilitated the discovery of novel proteomic biomarkers and the development of multi-marker panels for OPMDs [87]. However, MS-based approaches require sophisticated instrumentation, specialized expertise, and complex data analysis, limiting their widespread clinical application [88].

Immunoassays, including enzyme-linked immunosorbent assay (ELISA), multiplex bead-based assays, and lateral flow assays, are widely used for protein biomarker detection in saliva. These techniques offer advantages of specificity, sensitivity, and relatively simple protocols [89]. Multiplex immunoassays enable simultaneous measurement of multiple proteins, providing comprehensive proteomic profiles with minimal sample volume [90]. Lateral flow assays and other point-of-care platforms offer rapid, equipment-free testing that could be implemented in clinical settings [91]. However, immunoassays are limited by the availability of high-quality antibodies and potential cross-reactivity issues [92].

Emerging technologies such as biosensors, microfluidics, and nanotechnology hold promise for advancing salivary diagnostics. Biosensors based on electrochemical, optical, or piezoelectric principles can detect biomarkers with high sensitivity and specificity [93]. Microfluidic devices enable miniaturization, automation, and integration of multiple analytical steps, reducing sample volume and processing time [94]. Nanotechnology-based approaches, including gold nanoparticles, quantum dots, and carbon nanotubes, enhance signal detection and enable novel assay formats [95]. These technologies are particularly promising for developing point-of-care salivary diagnostic devices that could be used in routine clinical practice [96].

Clinical Applications of Salivary Diagnostics in OPMDs

Early Detection and Diagnosis

Salivary biomarkers offer significant potential for the early detection and diagnosis of OPMDs, enabling intervention before malignant transformation occurs [97]. Several studies have demonstrated the ability of salivary biomarkers to distinguish OPMDs from normal mucosa with high sensitivity and specificity [98]. For instance, a panel of salivary miRNAs (miR-21, miR-31, and miR-200a) achieved 91% sensitivity and 87% specificity in discriminating OPMD patients from healthy controls [99]. Similarly, a combination of salivary proteins (IL-8, IL-1β, and SAT1) demonstrated 85% sensitivity and 83% specificity in detecting OPMDs [100].

The non-invasive nature of salivary testing makes it particularly suitable for screening high-risk populations, such as tobacco and alcohol users, betel quid chewers, and individuals with history of OPMDs or OSCC [101]. Screening programs incorporating salivary biomarkers could identify asymptomatic individuals with early molecular changes before clinical lesions become apparent, enabling preventive interventions [102]. This approach could significantly reduce the burden of OSCC by facilitating early detection and treatment of precursor lesions [103].

Salivary diagnostics also offer advantages for diagnosing lesions in difficult-to-access areas or in patients with comorbidities that make biopsy challenging [104]. Additionally, salivary testing can be repeated at regular intervals for monitoring suspicious lesions, providing dynamic assessment of disease status [105]. This longitudinal monitoring capability is particularly valuable for lesions with ambiguous clinical or histopathological features [106].

Risk Stratification and Prognosis

One of the most promising applications of salivary diagnostics is risk stratification of OPMDs, predicting which lesions are likely to undergo malignant transformation [107]. Current histopathological grading of dysplasia has limited predictive value, and molecular biomarkers could significantly improve risk assessment [108]. Several salivary biomarkers have been associated with malignant transformation risk, including specific genetic mutations, DNA methylation markers, miRNA signatures, and protein profiles [109].

For example, LOH at 3p14 and/or 9p21 in saliva has been shown to predict malignant transformation of OPMDs with a hazard ratio of 3.7, providing valuable prognostic information [110]. Similarly, a panel of salivary miRNAs (miR-21, miR-184, and miR-31) demonstrated 82% accuracy in predicting malignant transformation of oral leukoplakia [111]. Proteomic biomarkers such as MMP-9 and TIMP-1 have also shown prognostic value, with elevated levels associated with increased transformation risk [112].

Risk stratification based on salivary biomarkers could enable personalized surveillance strategies, with high-risk patients receiving more frequent monitoring and low-risk patients spared unnecessary interventions [113]. This approach would optimize resource allocation and reduce healthcare costs while improving patient outcomes [114].

Additionally, risk stratification could guide preventive interventions, such as chemoprevention with retinoids or other agents, for high-risk individuals [115].

Monitoring Treatment Response and Disease Progression

Salivary biomarkers offer a non-invasive means of monitoring treatment response and disease progression in OPMDs [116]. Current assessment of treatment efficacy relies on clinical examination and repeat biopsies, which are invasive and provide only limited information [117]. Salivary biomarkers can detect molecular changes before clinical or histopathological improvements become apparent, enabling early assessment of treatment response [118].

Studies have shown that salivary biomarker levels change following successful treatment of OPMDs. For instance, levels of miR-21 and IL-8 decrease significantly after surgical excision of dysplastic lesions, while levels of tumor suppressor miRNAs such as miR-145 increase [119]. Similarly, successful chemoprevention with retinoids or other agents is associated with normalization of salivary biomarker profiles [120]. These changes in biomarker levels can be detected earlier than clinical improvements, providing timely feedback on treatment efficacy [121].

Salivary biomarkers also enable monitoring of disease progression in patients under surveillance. Increasing levels of oncogenic biomarkers or decreasing levels of tumor suppressor biomarkers may indicate disease progression before clinical changes become apparent, enabling timely intervention [122]. This longitudinal monitoring capability is particularly valuable for patients with extensive or multifocal OPMDs, where clinical assessment alone may be insufficient [123

Discussion

The evidence reviewed in this article demonstrates the significant potential of salivary diagnostics for OPMDs across multiple clinical applications, including early detection, risk stratification, and monitoring. Saliva offers a unique diagnostic fluid that non-invasively captures the complex molecular alterations associated with oral carcinogenesis, providing a liquid biopsy of the oral cavity [124]. The diverse categories of salivary biomarkers—genetic, transcriptomic, proteomic, and microbiome—reflect the multifactorial nature of OPMD pathogenesis and offer complementary information for comprehensive assessment [125].

One of the key insights from this review is the superior performance of multi-marker approaches compared to single biomarkers. The complex and heterogeneous nature of OPMDs necessitates comprehensive biomarker panels that reflect various aspects of carcinogenesis [126]. Studies consistently demonstrate that combinations of biomarkers from different categories provide higher diagnostic and prognostic accuracy than individual markers [127]. For example, a panel combining genetic, transcriptomic, and proteomic biomarkers achieved 94% accuracy in discriminating OPMDs from normal mucosa, significantly outperforming individual biomarkers [128]. This highlights the importance of integrating multiple biological parameters for a more complete assessment of OPMDs [129].

The analytical technologies for salivary biomarker detection have evolved significantly, enabling sensitive, specific, and high-throughput analysis. Next-generation sequencing, mass spectrometry, and digital PCR have greatly enhanced biomarker discovery and validation [130]. At the same time, point-of-care technologies such as lateral flow assays and biosensors are making salivary testing more accessible for clinical use [131]. This dual advancement in both discovery and application technologies is driving the translation of salivary diagnostics from research to clinical practice [132].

Despite these advances, several challenges remain in implementing salivary diagnostics for OPMDs in routine clinical practice. Standardization of sample collection, processing,

and analysis protocols is essential for reliable and reproducible results [133]. Variability in salivary flow rates, diurnal variations in biomarker concentrations, and the influence of various systemic conditions and medications on salivary composition need to be addressed [134]. Additionally, large-scale longitudinal studies are needed to validate the prognostic utility of emerging biomarkers and establish clinically relevant thresholds for risk stratification [135].

The clinical implications of salivary diagnostics for OPMDs are substantial. Non-invasive early detection could significantly reduce the burden of OSCC by enabling intervention at precursor stages [136]. Risk stratification based on molecular profiles could personalize surveillance strategies and preventive interventions, optimizing resource allocation and improving patient outcomes [137]. Monitoring treatment response and disease progression with salivary biomarkers could enhance clinical decision-making and facilitate timely interventions [138]. Furthermore, the integration of salivary diagnostics with other diagnostic modalities could provide a comprehensive assessment of OPMDs, combining clinical, histopathological, and molecular information [139].

From a research perspective, salivary biomarker studies have provided valuable insights into the molecular mechanisms of oral carcinogenesis [140]. The identification of dysregulated pathways and networks in OPMDs has enhanced our understanding of disease pathogenesis and revealed potential therapeutic targets [141]. Additionally, the development of salivary biomarkers has contributed to the evolving concept of precision medicine in oral oncology, where interventions are tailored to individual molecular profiles [142].

Several gaps in the literature remain apparent. First, there is a need for large-scale prospective studies to validate the clinical utility of salivary biomarkers for OPMDs. Most current studies are cross-sectional or have limited sample sizes, restricting their generalizability [143]. Second, standardized protocols for sample collection, processing, and analysis need to be established and validated across different populations and settings [144]. Third, the cost-effectiveness of salivary diagnostics in routine clinical practice needs to be evaluated, considering the potential benefits in terms of early detection, personalized management, and improved outcomes [145]. Finally, the integration of salivary diagnostics with other diagnostic modalities and electronic health records needs to be explored to maximize their clinical utility [146].

Conclusion

Salivary diagnostics represent a promising frontier in the management of oral potentially malignant disorders, offering non-invasive, sensitive, and specific tools for early detection, risk stratification, and monitoring. The diverse categories of salivary biomarkers—genetic, transcriptomic, proteomic, and microbiome—reflect the complex molecular pathogenesis of OPMDs and provide complementary information for comprehensive assessment. Multi-marker approaches consistently demonstrate superior performance compared to single biomarkers, highlighting the importance of integrating multiple biological parameters.

Advances in analytical technologies, from next-generation sequencing to point-of-care devices, have enhanced both biomarker discovery and clinical application. These technologies are driving the translation of salivary diagnostics from research to clinical practice, with the potential to transform the management of OPMDs. The non-invasive nature of salivary testing makes it particularly suitable for screening high-risk populations, monitoring disease progression, and assessing treatment response.

Despite these advances, challenges remain regarding standardization, validation, and clinical implementation. Large-scale prospective studies are needed to establish the clinical utility of salivary biomarkers and define their role in routine practice.

Standardized protocols for sample collection, processing, and analysis must be developed and validated across different populations and settings.

Future research should focus on validating multi-marker panels, developing cost-effective point-of-care testing devices, and exploring the integration of salivary diagnostics with other diagnostic modalities. The implementation of salivary diagnostics in routine clinical practice has the potential to significantly reduce the burden of oral cancer by enabling early detection and personalized management of OPMDs. This biomarker-based approach represents a significant step toward precision medicine in oral oncology, where interventions are tailored to individual molecular profiles, ultimately improving patient outcomes and quality of life

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