

REVIEW ARTICLE

Salivary Biomarkers for Early Oral Cancer Diagnosis: Clinical Potential and Translational Challenges

Nayana Mohandas¹ | Padma K Bhat² | M Y Jayachandra³ | J Avinash⁴

¹Senior Lecturer, Department of Public Health Dentistry, Dayananda Sagar College of Dental Sciences, Bengaluru, India

²Professor, Department of Public Health Dentistry, Rajarajeshwari Dental College and Hospital, Bengaluru, India

³Professor, Department of Public Health Dentistry, Rajarajeshwari Dental College and Hospital, Bengaluru, India

⁴Professor and HOD, Department of Public Health Dentistry, Dayananda Sagar College of Dental Sciences, Bengaluru, India

Correspondence

Dr. Nayana M, Department of Public Health Dentistry, Dayananda Sagar College of Dental Sciences, Bengaluru, India.
Email: nayanam@dscds.edu.in

Abstract

Objective: To review the current advancements in identifying and refining a panel of soluble salivary biomarkers for the early detection and prognosis of oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMDs). **Methods:** A comprehensive literature search was conducted across the PubMed, Google Scholar, Web of Science, and Embase databases for articles published between 2014 and 2024. Combinations of specific medical subject headings (MeSH) and keywords—including "oral cancer", "biomarker", and "whole mouth saliva"—were applied using Boolean operators (AND/OR). Original studies, systematic reviews, and critical clinical resources were scrutinized. **Results:** Saliva serves as a highly reliable, non-invasive biofluid for liquid biopsy. Over 100 molecular candidates, categorized into proteomic, genomic, transcriptomic, and metabolomic targets, have demonstrated diagnostic significance. Combining single targets into a multi-biomarker panel (e.g., IL-1 β , IL-6, and IL-8) significantly increases diagnostic accuracy, though oral inflammatory conditions (e.g., periodontitis) remain a primary confounding factor causing false-positive results. **Conclusion:** Human whole mouth saliva (WMS) holds immense clinical utility for early diagnosis and treatment monitoring in oral oncology. High-sensitivity detection platforms show promise for transition into routine clinical dental practice, provided that standardized collection and pre-analytical protocols are globally implemented.

KEYWORDS

Oral Neoplasms, Biomarkers, Tumor, Saliva, Diagnosis, Oral

1 | INTRODUCTION

Oral malignancies present a profound clinical and economic challenge to healthcare infrastructure globally. Among these, oral squamous cell carcinoma (OSCC) represents more than 90% of all diagnosed oral malignant presentations¹. The Indian subcontinent bears a disproportionate share, accounting for roughly one-third of the global disease burden, largely driven by lifestyle dynamics and the extensive consumption of tobacco-related products¹. The primary determinant of long-term survival in OSCC remains early diagnosis. Currently, tissue biopsy paired with detailed histological evaluation is considered the diagnostic gold standard². Despite its clinical authority, conventional biopsy is limited by several drawbacks: it is invasive, painful, time-consuming, and expensive²; it carries sample site limitations, potentially omitting key neoplastic regions in presentations with multi-focal lesions³; it introduces clinical ambiguity when distinguishing early-stage OSCC from look-alike

oral potentially malignant disorders (OPMDs)³. To address these diagnostic challenges, contemporary translational research has shifted focus toward liquid biopsies. Whole mouth saliva (WMS) has emerged as a major diagnostic medium for applications in genomics, transcriptomics, proteomics, and metabolomics⁴. While analyte concentrations are frequently lower in saliva than in serum, the close anatomical proximity of saliva to developing oral lesions permits the direct shedding of tumor components. This review evaluates the utility, collection methodologies, and contemporary molecular landscape of salivary biomarkers configured for the early identification of oral malignancy.

2 | MATERIAL AND METHODS

An exhaustive review of published biomedical literature was conducted to assess the diagnostic accuracy and clinical feasibility of salivary biomarkers. Search Strategy and Database Selection: Electronic searches were executed across four primary databases: PubMed,

Google Scholar, Web of Science, and Embase. The search temporal window was restricted to a 10-year period (2014–2024) to prioritize contemporary technological and molecular advancements. Keyword Combinations and Logic: The search utilized explicit combinations of keywords and Medical Subject Headings (MeSH) coupled with Boolean operators (AND, OR): ("oral cancer" OR "oral squamous cell carcinoma" OR "OSCC") AND ("biomarker" OR "tumor marker" OR "salivary proteome") AND ("whole mouth saliva" OR "unstimulated saliva"). Inclusion and Exclusion Criteria: Articles selected for full-text screening included peer-reviewed original laboratory research, randomized controlled trials, diagnostic accuracy studies, cohort studies, systematic reviews, and meta-analyses. Non-peer-reviewed white papers, letters to the editor without primary data, and studies missing precise control cohorts were excluded.

3 | REVIEW AND DISCUSSION

Salivary Proteomics: Methodological Frameworks. Proteomics encompasses the large-scale analysis of proteins, which provide functional real-time data regarding gene expression and cellular pathway modulation during tumorigenesis⁵. In clinical saliva investigations, two distinct proteomic workflows are utilized⁶: 1. Top-Down Approach: Interrogates intact proteins and intact peptides directly from raw or minimally altered samples without prior chemical or proteolytic digestion. 2. Bottom-Up Approach: Employs enzymatic digestion (typically using trypsin) to convert complex protein mixtures into peptide fragments before performing Mass Spectrometry (MS) analysis. Salivary components can be structurally evaluated across the broader proteome or the smaller peptide fraction (peptidome)^{6,7}. Gel-based techniques (such as 2D Electrophoresis) resolve highly abundant proteins (e.g., mucins, statherins, histatins), whereas gel-free liquid chromatography-mass spectrometry (LC-MS) profiles low-abundance tumor-specific biomarkers. **Comparative Biological Characteristics of Human Saliva.** WMS is composed of secretions from the parotid, submandibular, sublingual, and minor salivary glands, combined with cellular debris, serum transudates (crevicular fluid), and local microflora. An adult healthy human maintains a mean unstimulated salivary flow rate of approximately 0.5 mL/min, secreting between 1.0 to 1.5 L daily. Saliva offers distinct biological and practical advantages compared to traditional blood or urine sampling: **Non-Invasive Collection:** Minimizes patient anxiety and coordinates safely with pediatric, geriatric, or needle-phobic patient groups. **Low Initial Complexity:** Contains significantly lower salt concentrations relative to urine, and lacks the overwhelming abundance of systemic masking proteins (like serum albumin and immunoglobulins) that often complicate blood-based proteomic profiling. **Direct Cargo Ingestion:** Neoplastic cells arising from the oral mucosal epithelium shed direct molecular cargo directly into the biological fluid environment, optimizing screening yield^{6,17}. **Standardization of Salivary Sample Collection.** The primary logistical limitation preventing regular clinical implementation of saliva-based diagnostics is a historical lack of pre-analytical standardization¹⁰.

Salivary profiles vary drastically depending on the collection mechanism: **Unstimulated Whole Saliva (USWS):** Collected via passive drooling or basic spitting. USWS contains an elevated concentration of serum-derived proteins and local inflammatory mediators, but spitting collection methods are prone to higher bacterial contamination¹⁰. **Stimulated Whole Saliva (SWS):** Collected following physiological induction (e.g., chewing on paraffin wax, gum, or citric acid application). SWS yields higher volumetric rates with elevated concentrations of glandular electrolytes (sodium, bicarbonate), but dilutes lower-abundance systemic and tumor-derived biomarkers⁶. To minimize biochemical variance, clinical sampling protocols must be strictly controlled: **Pre-collection Restrictions:** Patients must abstain from oral hygiene procedures, food ingestion, and fluid intake for a minimum of 1 hour prior to screening¹⁰. **Temporal Control:** Sampling should optimally occur between 8:00 AM and 10:00 AM to minimize the confounding effects of circadian rhythms on protein secretion. **Pre-cleansing:** A 1-minute oral rinse with distilled water must be executed 5 minutes before active collection. **Preservation Protocols:** Samples must undergo immediate chemical stabilization or biochemical processing within 1 hour to prevent rapid enzymatic degradation by local proteases. Chemical additions such as sodium azide () are commonly utilized to arrest bacterial overgrowth and stabilize fragile protein structures¹³. Several clinical devices have been validated to optimize pre-analytical recovery and room-temperature storage stability, including RNAPro™, SimpIOFy™, OraGene™, Salivette®, Quantisal®, and SuperSAL™^{6,10}. Furthermore, Direct Saliva Transcriptome Analysis (DSTA) enables direct room-temperature mRNA detection without requiring immediate isolation steps⁹. **Molecular Landscape of Salivary Biomarkers.** More than 100 molecular entities have demonstrated statistical significance as potential markers for oral oncogenesis. These candidates span multiple biomolecular tiers: 1. Tumor Markers and Cellular DNA Modifications. Somatic genetic alterations driven by carcinogens (tobacco, betel quid, alcohol, or viral vectors like HPV-16/18 and EBV) manifest as circulating tumor DNA (ctDNA) or mitochondrial DNA (mtDNA) variants in saliva^{18,35}. Mutations within the p53 tumor suppressor gene are detectable in up to 71% of saliva specimens collected from active OSCC patients¹⁸. Similarly, elevated concentrations of mitochondrial DNA fragments (specifically Cox I and Cox II genes) serve as indicators of cellular transformation, independent of confounding factors like age or smoking history³⁷. 2. Messenger RNA (mRNA) and MicroRNA (miRNA) Transcripts. Salivary transcriptomics represents a highly sensitive platform for detecting early malignant transformation. Key diagnostic mRNAs include³⁸: DUSP1 (Dual Specificity Phosphatase 1): Involved in the mitogen-activated protein kinase (MAPK) signaling pathway. Hypermethylation of the DUSP1 promoter frequently silences expression during early oral carcinogenesis³⁹. H3F3A (H3 Histone Family 3A): Functions as a nuclear structural marker reflecting rapid cell proliferation¹⁸. IL-8 and IL-1B: Cytokine transcripts regulating tumor angiogenesis and inflammatory signaling. Among small non-coding transcripts, microRNAs are remarkably stable targets due to their resistance to ribonuclease degradation. While miR-125a and miR-200a exhibit significant downregulation in OSCC cohorts, miR-31 displays

Salivary Proteomic Analysis

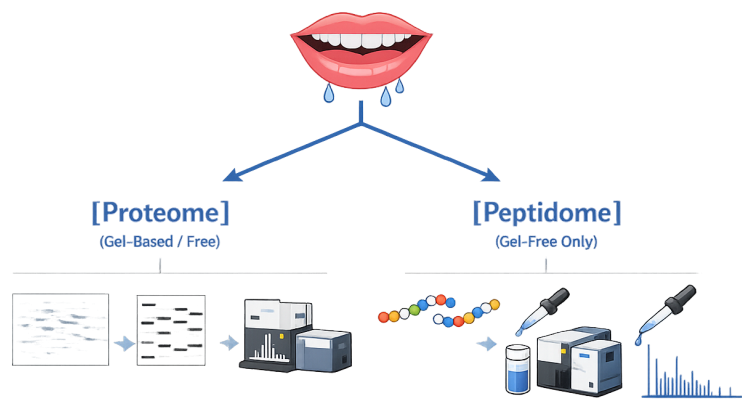


FIGURE 1 Methodological frameworks for salivary proteomic analysis.

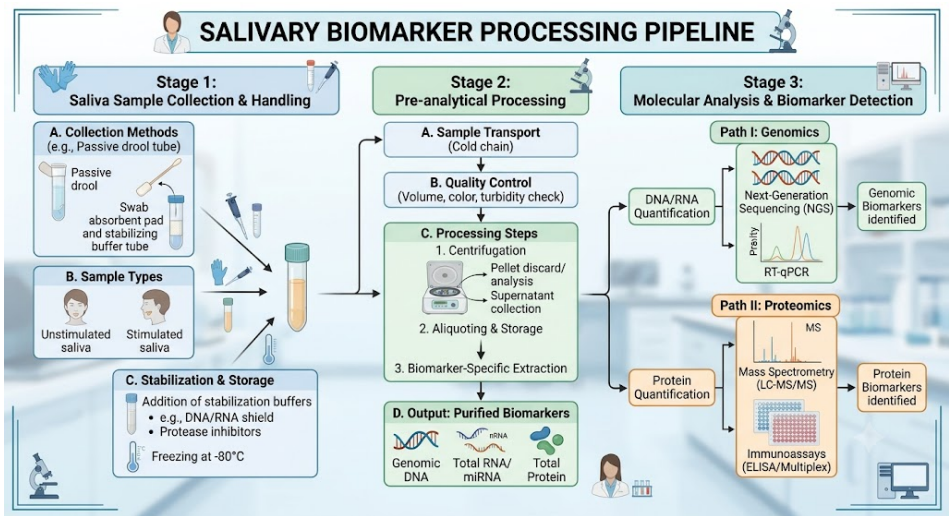


FIGURE 2 Salivary biomarker processing pipeline

marked upregulation across all progressive stages of squamous cell carcinoma, making it an excellent candidate for early-stage screening^{18,38}. 3. Soluble Proteins and Inflammatory Cytokines. The local inflammatory microenvironment of an oral tumor drives systemic and localized protein alterations. Pro-inflammatory cytokines, including Interleukins

(IL-1 β , IL-6, IL-8) and Tumor Necrosis Factor- α (TNF- α), are significantly elevated in both the saliva and serum of OSCC patients^{28,31}. These molecules track closely with increasing tumor volume and regional metastatic progression. Other critical proteomic markers include: Matrix Metalloproteinases (MMP-2, MMP-9): Enzymes responsible for

TABLE 1 Comparison of Salivary Biomarker Categories and Diagnostic Utility

Biomarker Category	Specific Molecular Targets	Primary Clinical Manifestation / Diagnostic Utility	References
Genomic / DNA	p53 Mutations, ctDNA, Cox I/II mtDNA	Early detection of genomic instability; tracks somatic mutation profiles and tumor heterogeneity.	[[REF:18, 34, 37]]
Transcriptomic (mRNA)	DUSP1, H3F3A, IL-1 β , IL-8, SAT	Identifies promoter hypermethylation, epigenetic silencing, and accelerated nuclear proliferation.	[[REF:9, 18, 38, 39]]
Transcriptomic (miRNA)	miR-31 (Upregulated), miR-125a / miR-200a (Downregulated)	Stage-independent screening; differentiates poorly differentiated carcinomas due to high transcript stability.	[[REF:18, 38, 40]]
Proteomic (Cytokines)	IL-1 β , IL-6, IL-8, TNF- α , VEGF	Correlates with local tumor burden, aggressive neoangiogenesis, and post-treatment recurrence tracking.	[[REF:28, 30, 31]]
Proteomic (Enzymes/Structural)	MMP-2, MMP-9, LDH, Soluble CD44, MRP14, Tetranectin	Indicates basement membrane degradation, metabolic shifts (glycolysis), and lymph node metastasis (Tetranectin downregulation).	[[REF:29, 32, 48, 50]]
Metabolomic / Inorganic	Altered Na, Ca, P, Mg ions; 57 distinct primary organic metabolites	Evaluates local oxidative stress status and shifted salivary electrolyte balances.	[[REF:27, 41, 44]]

extracellular matrix degradation, facilitating local invasion and vascular migration. CD44 (Soluble): Cell-surface glycoprotein involved in cell-to-cell adhesion and tumor metastasis, noted for its significant elevation in oral rinses of head and neck cancer cohorts²⁹. Mac-2-Binding Protein (M2BP) & MRP14: Calcium-binding proteins demonstrating a diagnostic sensitivity of 90% and specificity of 83% in targeted cancer detection trials³². Lactate Dehydrogenase (LDH): An enzyme involved in anaerobic glycolysis. Salivary LDH levels are consistently elevated in OPMDs (e.g., oral submucous fibrosis and leukoplakia) and OSCC, serving as an indicator of cellular injury and membrane breakdown^{48,49}. . Translational Challenges and Clinical Frameworks. While the scientific utility of salivary screening is clear, translating these findings into routine dental practice requires addressing key diagnostic challenges: The Confounding Role of Local Inflammation: The primary barrier to clinical validation of salivary oncology biomarkers is the overlapping molecular expression observed in common oral inflammatory pathologies. Chronic adult periodontitis, extensive dental caries, periapical infections, and oral lichen planus stimulate localized releases of IL-1 β , IL-6, IL-8, CRP, and MMPs^{10,15}. Because many diagnostic studies evaluate OSCC cohorts against perfectly healthy control groups, they often overlook these inflammatory overlaps. This lack of validation against benign inflammatory controls can result in false-positive outcomes in standard clinical settings. Transitioning to Biomarker Panels: Relying on a single isolated biomarker is insufficient to manage the spatial and intratumoral heterogeneity of oral squamous cell carcinoma. Diagnostic precision is significantly enhanced by utilizing multi-analyte validation matrices. For example, a combined panel featuring IL-1 β , IL-6, and IL-8 demonstrates excellent diagnostic sensitivity and specificity, providing a reliable strategy for distinguishing OPMDs from true malignant lesions⁵². Advanced Diagnostic Technologies: To transition these panels to point-of-care clinical tools, researchers are pairing them with high-throughput diagnostic platforms⁶: Proteomics: Multiplex ELISA arrays and quantitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) allow for the simultaneously absolute quantification of multiple low-abundance proteins⁶. Genomics/Transcriptomics: Quantitative polymerase chain reaction (qPCR) and high-density oligonucleotide microarrays (such as the Human Oral Microbe Identification Microarray - HOMIM) facilitate rapid transcriptomic and microbiome classification⁶. Metabolomics: Capillary electrophoresis time-of-flight mass spectrometry (CE-TOFMS) accurately identifies shifts in the metabolic profiles of oral cancers⁴⁴.

4 | CONCLUSION

Human saliva represents an exceptionally promising diagnostic biofluid for liquid biopsy, combining non-invasive collection with a rich array of real-time molecular data. For effective integration into routine clinical dental setups, future research must prioritize large-scale validation trials that test biomarker panels against benign oral inflammatory conditions. Establishing standardized, universally accepted pre-analytical collection

and stabilization frameworks will be essential to translate salivary diagnostics from a translational research platform into a reliable clinical tool for early oral cancer detection.

AUTHOR CONTRIBUTIONS

Conceptualization, Literature Search, Data Scrutiny, and Drafting of the Manuscript were performed collectively by all named authors. All authors have read and agreed to the published version of the manuscript. Author 1: Conceptualization, methodology, literature search, and writing – original draft preparation. Author 2: Data curation, literature screening, visual timeline/table formulation, and formal analysis. Author 3&4: Validation, critical review, editing of the final manuscript, and submission oversight.

FINANCIAL DISCLOSURE

This study received no specific financial support from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this manuscript.

REFERENCES

1. Reddy CU, Patil S, Singh S, Deora S, Sharma J, Sharma A. Oral health status of oral cancer patients seeking care from government hospital, Jaipur, Rajasthan. *Int J Oral Care Res.* 2014; 2:7-10.
2. Kaur J, Jacobs R, Huang Y, Salvo N, Politis C. Salivary biomarkers for oral cancer and pre-cancer screening: a review. *Clin Oral Investig.* 2018; 22(2):633-640.
3. Chu HW, Chang KP, Hsu CW, Chang IY, Liu HP, Chen YT, et al. Identification of salivary biomarkers for oral cancer detection with untargeted and targeted quantitative proteomics approaches. *Mol Cell Proteomics.* 2019; 18(9):1796-1806.
4. Zhang A, Sun H, Wang P, Wang X. Salivary proteomics in biomedical research. *Clin Chim Acta.* 2013; 415:261-265.
5. Aslam B, Basit M, Nisar MA, Khurshid M, Rasool MH. Proteomics: technologies and their applications. *J Chromatog Sci.* 2016; 54(10):1765-1781.
6. Khurshid Z, Zafar MS, Khan RS, Najeeb S, Slowey PD, Rehman IU. Role of salivary biomarkers in oral cancer detection. *Adv Clin Chem.* 2018; 86:23-70.
7. Amado FM, Ferreira RP, Vitorino R. One decade of salivary proteomics: current approaches and outstanding challenges. *Clin Biochem.* 2013; 46(6):506-517.
8. Dodds MW, Johnson DA, Yeh CK. Health benefits of saliva: a review. *J Dent.* 2005; 33(3):223-233.
9. Lee YH, Zhou H, Reiss JK, Yan X, Zhang L, Chia D, et al. Direct saliva transcriptome analysis. *Clin Chem.* 2011; 57(9):1295-1302.
10. Khurshid Z, Zohaib S, Najeeb S, Zafar MS, Slowey PD, Almas K. Human saliva collection devices for proteomics: an update. *Int J Mol*

Sci. 2016; 17(6):846.

11. Gröschl M, Köhler H, Topf HG, Rupprecht T, Rauh M. Evaluation of saliva collection devices for the analysis of steroids, peptides and therapeutic drugs. *J Pharm Biomed Anal.* 2008; 47(3):478-486.
12. Denny P, Hagen FK, Hardt M, Liao L, Yan W, Arellano M, et al. The proteomes of human parotid and submandibular/sublingual gland salivas collected as the ductal secretions. *J Proteome Res.* 2008; 7(5):1994-2006.
13. Whembolua GL, Granger DA, Singer S, Kivlighan KT, Marguin JA. Bacteria in the oral mucosa and its effects on the measurement of cortisol, dehydroepiandrosterone, and testosterone in saliva. *Horm Behav.* 2006; 49(4):478-483.
14. Sannam Khan R, Khurshid Z, Akhbar S, Faraz Moin S. Advances of salivary proteomics in oral squamous cell carcinoma (OSCC) detection: an update. *Proteomes.* 2016; 4(4):41.
15. Nagler RM. Saliva as a tool for oral cancer diagnosis and prognosis. *Oral Oncol.* 2009; 45(12):1006-1010.
16. Xiao H, Langerman A, Zhang Y, Khalid O, Hu S, Cao CX, et al. Quantitative proteomic analysis of microdissected oral epithelium for cancer biomarker discovery. *Oral Oncol.* 2015; 51(11):1011-1019.
17. Zimmermann BG, Park NJ, Wong DT. Genomic targets in saliva. *Ann N Y Acad Sci.* 2007; 1098(1):184-191.
18. Radhika T, Jeddy N, Nithya S, Muthumeenakshi RM. Salivary biomarkers in oral squamous cell carcinoma—An insight. *J Oral Biol Craniofac Res.* 2016; 6:S51-S54.
19. Malhotra T, Sachdeva A, Bhateja S, Arora G. Salivary biomarkers as a diagnostic tool. *J Surg Allied Sci.* 2019; 1(1):1-4.
20. Rajkumar K, Kumar AR, Ramyalini V, Nandhini G, Kumar TD, Ashwini BK, et al. Estimation of serological and salivary biomarkers in patients with Oral Squamous cell carcinoma, premalignant lesions and conditions. *SRM Univ J Dent Sci.* 2010; 1(1):14-19.
21. Sudbø J, Kildal W, Risberg B, Koppang HS, Danielsen HE, Reith A. DNA content as a prognostic marker in patients with oral leukoplakia. *N Engl J Med.* 2001; 344(17):1270-1278.
22. Zhang L, Rosin MP. Loss of heterozygosity: a potential tool in management of oral premalignant lesions?. *J Oral Pathol Med.* 2001; 30(9):513-520.
23. Szanto I, Mark L, Bona A, Maasz G, Sandor B, Gelencser G, et al. High-throughput screening of saliva for early detection of oral cancer: a pilot study. *Technol Cancer Res Treat.* 2012; 11(2):181-188.
24. Wong DT. Salivary diagnostics powered by nanotechnologies, proteomics and genomics. *J Am Dent Assoc.* 2006; 137(3):313-321.
25. Markopoulos AK, Michailidou EZ, Tzimagiorgis G. Salivary markers for oral cancer detection. *Open Dent J.* 2010; 4:172-178.
26. Cheng YS, Rees T, Wright J. A review of research on salivary biomarkers for oral cancer detection. *Clin Transl Med.* 2014; 3:1-10.
27. Shpitzer T, Bahar G, Feinmesser R, Nagler RM. A comprehensive salivary analysis for oral cancer diagnosis. *J Cancer Res Clin Oncol.* 2007; 133:613-617.
28. Panta P, Wong DT. Salivary biomarkers in oral cancer. In: *Oral Cancer Detection: Novel Strategies and Clinical Impact.* Cham: Springer; 2019:265-295.
29. Franzmann EJ, Reategui EP, Pedrosa F, Pernas FG, Karakullukcu BM, Carraway KL, et al. Soluble CD44 is a potential marker for the early detection of head and neck cancer. *Cancer Epidemiol Biomarkers Prev.* 2007; 16(7):1348-1355.
30. Russo N, Bellile E, Murdoch-Kinch CA, Liu M, Eisbruch A, Wolf GT, et al. Cytokines in saliva increase in head and neck cancer patients after treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2016; 122(4):483-490.
31. St John MA, Li Y, Zhou X, Denny P, Ho CM, Montemagno C, et al. Interleukin 6 and interleukin 8 as potential biomarkers for oral cavity and oropharyngeal squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg.* 2004; 130(8):929-935.
32. Hu S, Arellano M, Boontheung P, Wang J, Zhou H, Jiang J, et al. Salivary proteomics for oral cancer biomarker discovery. *Clin Cancer Res.* 2008; 14(19):6246-6252.
33. Almadori G, Bussu F, Galli J, Limongelli A, Persichilli S, Zappacosta B, et al. Salivary glutathione and uric acid levels in patients with head and neck squamous cell carcinoma. *Head Neck.* 2007; 29(7):648-654.
34. Yamanishi Y, Boyle DL, Rosengren S, Green DR, Zvaifler NJ, Firestein GS. Regional analysis of p53 mutations in rheumatoid arthritis synovium. *Proc Natl Acad Sci U S A.* 2002; 99(15):10025-10030.
35. Cristaldi M, Mauceri R, Di Fede O, Giuliana G, Campisi G, Panzarella V. Salivary biomarkers for oral squamous cell carcinoma diagnosis and follow-up: current status and perspectives. *Front Physiol.* 2019; 10:1476.
36. Ignatiadis M, Lee M, Jeffrey SS. Circulating tumor cells and circulating tumor DNA: challenges and opportunities on the path to clinical utility. *Clin Cancer Res.* 2015; 21(21):4786-4800.
37. Jiang WW, Masayeva B, Zahurak M, Carvalho AL, Rosenbaum E, Mambo E, et al. Increased mitochondrial DNA content in saliva associated with head and neck cancer. *Clin Cancer Res.* 2005; 11(7):2486-2491.
38. Liu J, Duan Y. Saliva: a potential media for disease diagnostics and monitoring. *Oral Oncol.* 2012; 48(7):569-577.
39. Khor GH, Froemming GR, Zain RB, Abraham MT, Omar E, Tan SK, et al. DNA methylation profiling revealed promoter hypermethylation-induced silencing of p16, DDAH2 and DUSP1 in primary oral squamous cell carcinoma. *Int J Med Sci.* 2013; 10(12):1727-1733.
40. Lajer CB, Nielsen FC, Friis-Hansen L, Norrild B, Borup R, Garnæs E, et al. Different miRNA signatures of oral and pharyngeal squamous cell carcinomas: a prospective translational study. *Br J Cancer.* 2011; 104(5):830-840.
41. Bahar G, Feinmesser R, Shpitzer T, Popovtzer A, Nagler RM. Salivary analysis in oral cancer patients: DNA and protein oxidation, reactive nitrogen species, and antioxidant profile. *Cancer.* 2007; 109(1):54-9.
42. Agha-Hosseini F, Mirzaei-Dizgah I, Farmanbar N, Abdollahi M. Oxidative stress status and DNA damage in saliva of human subjects

- with oral lichen planus and oral squamous cell carcinoma. *J Oral Pathol Med*. 2012; 41(10):736-740.
43. Vajaria BN, Patel KR, Begum R, Shah FD, Patel JB, Shukla SN, et al. Evaluation of serum and salivary total sialic acid and α -l-fucosidase in patients with oral precancerous conditions and oral cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013; 115(6):764-771.
 44. Sugimoto M, Wong DT, Hirayama A, Soga T, Tomita M. Capillary electrophoresis mass spectrometry-based saliva metabolomics identified oral, breast and pancreatic cancer-specific profiles. *Metabolomics*. 2010; 6:78-95.
 45. Schaaij-Visser TB, Brakenhoff RH, Leemans CR, Heck AJ, Slijper M. Protein biomarker discovery for head and neck cancer. *J Proteomics*. 2010; 73(10):1790-1803.
 46. Ludwig JA, Weinstein JN. Biomarkers in cancer staging, prognosis and treatment selection. *Nat Rev Cancer*. 2005; 5(11):845-856.
 47. Onda T, Uzawa K, Nakashima D, Saito K, Iwadata Y, Seki N, et al. Lin-7C/VELI3/MALS-3: an essential component in metastasis of human squamous cell carcinoma. *Cancer Res*. 2007; 67(20):9643-9648.
 48. Patel S, Metgud R. Estimation of salivary lactate dehydrogenase in oral leukoplakia and oral squamous cell carcinoma: a biochemical study. *J Cancer Res Ther*. 2015; 11(1):119-123.
 49. Kallalli BN, Rawson K, Muzammil, Singh A, Awati MA, Shivhare P. Lactate dehydrogenase as a biomarker in oral cancer and oral submucous fibrosis. *J Oral Pathol Med*. 2016; 45(9):687-690.
 50. Arellano-Garcia ME, Li R, Liu X, Xie Y, Yan X, Loo JA, et al. Identification of tetranectin as a potential biomarker for metastatic oral cancer. *Int J Mol Sci*. 2010; 11(9):3106-3121.
 51. Yoshizawa JM, Schafer CA, Schafer JJ, Farrell JJ, Paster BJ, Wong DT. Salivary biomarkers: toward future clinical and diagnostic utilities. *Clin Microbiol Rev*. 2013; 26(4):781-791.
 52. Piyarathne NS, Rasnayake RM, Angammana R, Chandrasekera P, Ramachandra S, Weerasekera M, et al. Diagnostic salivary biomarkers in oral cancer and oral potentially malignant disorders and their relationships to risk factors-A systematic review. *Expert Rev Mol Diagn*. 2021; 21(8):789-807.

How to cite this article:

Mohandas N, Bhat PK, Jayachandra MY, Avinash J. Salivary Biomarkers for Early Oral Cancer Diagnosis: Clinical Potential and Translational Challenges. *World J Dent Excell*. 2026;2(1):35.