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BIOANALYTICAL BIOMARKERS IN ORAL CANCER DETECTION AND THERAPEUTIC MONITORING

Dr. Deepak Kolte[1], Dr Rajendra Sadashiv Patil[2], Dr Kumarjyoti Chatterjee[3], Dr. Dipti Chandrakar[4], Dr Tufail Ahmed[5], Deepti Rawat[6]

[1]Assistant Professor, Oral and Maxillofacial Surgery, Bharati Vidyapeeth Deemed to be University Dental College and Hospital, Navi Mumbai, deepakolte79@gmail.com, Orcid I'd: - 0000-0002-8857-0803
[2]Associate Professor, Department of Pathology, Dr. D. Y. Patil Medical College Hospital and Research Institute Kolhapur. D.Y. Patil Education Society (Deemed to be University) Kolhapur, drrspatil18@gmail.com Orcid I'd: - 0009-0001-7636-1430
[3]PHD (Research Scholar), Dept of Oral Pathology & Microbiology, DMIHER, Wardha, Maharashtra (India), kjyoti931@gmail.com
[4]Assistant Professor, Department of Biotechnology, Anjaneya University, Raipur, Chhattisgarh, ORCID ID: 0009-0002-3648-4740, drdiptichandrakar@gmail.com
[5]Assistant Professor, Department of Microbiology, Government Medical College Anantnag, tufailwani@gmail.com, ORCID ID: 0000-0002-8083-1116
[6]Assistant proffesor, community health nursing, graphic era deemed to be University college of nursing, deeptirawat.nurs@geu.ac.in, ORCId id-0009-0007-2739-6841

ABSTRACT:
Oral cancer remains a significant clinical problem, and prognosis is heavily dependent on the stage at diagnosis and the capacity to track the evolution of the disease during and after treatment. Bioanalytical biomarkers can provide additional information to traditional examination and histopathology and provide contemporisation of molecular alterations occurring during the process of carcinogenesis, tumor behavior, treatment response, residual disease, and recurrence. This review synthesizes current evidence on genomic, epigenomic, transcriptomic, proteomic, metabolomic, inflammatory, immune, and circulating biomarkers relevant to oral cancer. This also explores the diagnostic uses of saliva, blood, tissue, cytological and emerging matrices and analytical platforms such as PCR-based assays, sequencing, immunoassays, mass spectrometry, biosensors, microfluidics and lab-on-a-chip systems. A special focus is given to the use of longitudinal applications, like therapeutic-response assessment, minimal residual disease detection, recurrence surveillance, and personalized monitoring. Other novel methods such as multi-omics integration, spatial profiling, extracellular-vesicle analysis, nanotechnology and artificial intelligence are also reviewed for their translation potential. Even with the advancement of technology, there are still challenges to its routine clinical use due to tumor heterogeneity, preanalytical variability, limited assay standardization, limited external validation, and regulatory challenges. Further advances will rely upon prospective multicenter studies, harmonized workflows and clinically interpretable multimarker models that will help in earlier diagnosis and more accurate therapeutic monitoring.

KEYWORDS: Oral cancer, Bioanalytical biomarkers, Liquid biopsy, Therapeutic monitoring, Multi-omics

1. INTRODUCTION

Oral cancer continues to be a significant oral health problem in the world, due to its high morbidity, mortality, functional impairment, and geographical inequalities in oral cancer burden. While significant progress has been made in prevention and oncological treatment, it is noteworthy that cancer's burden has not been reduced significantly in the last few decades and varies widely by region and population (Wu et al., 2025). With its large population and common exposures to known behavioral and environmental risk factors, exposure is especially high in Asia (Xie & Shang, 2022). Tobacco use, alcohol consumption, betel-quid and areca-nut use, and demographic and socioeconomic factors that affect disease occurrence and outcomes are all closely linked to the epidemiology of oral cancer (Sarode et al., 2020). Long-term analyses also show that temporal and regional trends of oral cancer are influenced by changing distributions of risk factors in populations and population structures, which further underscores the importance of developing more effective strategies to prevent, detect and manage oral cancer (Ren et al., 2020).

The treatment of oral cancer continues to be difficult due to the impact of the stage at diagnosis on the complexity and prognosis of the disease. Routine assessment is primarily based on clinical examination and subsequently on the pathological confirmation of suspicious lesions, and the treatment is based on the stage of the tumour, together with its anatomical site and the patient-related factors (D'Cruz et al., 2018). Oral carcinogenesis is also molecularly heterogeneous and is mediated by a series of genetic changes that affect the proliferation, differentiation, apoptosis, genome stability and malignant transformation of cells (Ali et al., 2017). It makes sense to search for measurable biological indicators which can reflect the early events of malignant transformation and clinically relevant disease behavior, given this molecular complexity. While preventive measures such as modification of the risk factors, public awareness, screening and identification of potentially malignant lesions have been found to be essential, these measures alone cannot compensate for the shortcomings of late diagnosis and the variable nature of disease progression (D'souza & Addepalli, 2018).

The study of bioanalytical biomarkers is an important opportunity to complement the traditional diagnostic route, allowing measurable molecular information to be gained relating to the initiation and progression of a tumour. It is important to

note that saliva is an ideal source for oral cancer diagnosis since it can be collected without any invasive procedure and contains different molecular components which may hold diagnostic value and is also considered as a useful medium for the early detection of oral cancer (Saxena et al., 2017). Therapeutic monitoring could also go beyond diagnosis with the potential of molecular changes to help define the response to treatment, residual disease, recurrence, and emerging resistance. With the evolution of oral cancer treatment from traditional surgery, chemotherapy and radiotherapy to novel and more personalized therapeutic strategies, this application is gaining more relevance (Nandini et al., 2020).

One critical research need, however, remains from discovery to reliable clinical use of biomarkers. There is not enough consistency across studies or between different types of biological matrices, analytical platforms, sampling methods, biomarker thresholds, tumor heterogeneity, and validation strategies for cross-study comparability and translation. There is also limited evidence linking diagnostic biomarkers to the longitudinal monitoring of therapy, and very limited evaluation of new bioanalytical technologies integrated.

The purpose of this review is to critically assess the molecular basis and the most relevant classes of bioanalytical biomarkers in relation to oral cancer, to evaluate the types of biological matrices and platforms available for their detection, as well as the use of these markers for early diagnosis, prognosis, assessment of therapeutic response and for disease surveillance, and to analyze new technologies, potential translation hurdles and future priorities for the development of clinically actionable biomarker strategies.

2. Molecular Landscape and Biological Basis of Biomarkers in Oral Cancer

Oral carcinogenesis is a multistep biological process that involves progressive molecular and phenotypic changes of the normal oral epithelium that may eventually lead to the development of an invasive oral squamous cell carcinoma (OSCC). The risks of malignant transformation of oral potentially malignant disorders are variable; leukoplakia, erythroplakia, oral submucous fibrosis and oral lichen planus are examples of these disorders. Ongoing exposure to carcinogens leads to genomic damage and oxidative stress, chronic inflammation, epithelial dysplasia, and impairment of the mechanisms regulating proliferation and apoptosis, which makes conditions favorable for clonal evolution (Kumari et al., 2022). The transition to invasive malignancy is characterized by a series of interrelated changes in oncogenic signaling, tumor suppressor mechanisms, cell cycle control, immunity and stromal interactions. The progressive molecular alterations represent the biological continuum from pre-malignancy to invasive disease and serve as a basis for identification of biomarkers associated with the stages (Tarle & Lukšić, 2024). Genomic instability is one of the hallmarks of oral cancer, and it creates molecules that can be used as markers for diagnosis and prognosis. Malignant transformation and tumor evolution are due to somatic mutations, chromosomal abnormalities, copy-number alterations, loss of heterozygosity and the disruption of pathways of DNA repair, apoptosis, proliferation and differentiation. These abnormalities can be characterized to give a molecular signature in terms of development of disease, biological aggressiveness, and maybe therapeutic susceptibility (Karunakaran & Muniyan, 2020). Epigenomic dysregulation further alters the behaviour of the tumour, but does not change the DNA sequence. DNA methylation changes, histone modifications and chromatin remodeling can lead to suppression of tumour suppressor genes or to the recruitment of oncogenic transcription programs. Their incidence as alterations during oral carcinogenesis and the possibility of their detection in clinical samples make them good candidates for use as biomarkers (Irimie et al., 2018).

Oral tumor transcriptomic changes provide a dynamic view of molecular activity in these tumors. Transcriptome profiling can be used to identify differentially expressed genes and pathway-level signatures associated with malignant transformation, tumor progression, metastatic potential and treatment response, as well as molecular heterogeneity of OSCC (Natarajan & Umapathy, 2025). These are not the only regulatory genes; there are additional non-coding RNAs. Long non-coding RNA, circular RNA and microRNAs regulate the expression of genes at the transcriptional, post-transcriptional and epigenetic levels, and can also modulate growth, cell death, invasion, metastasis and therapeutic resistance. They can also be measured in tissues and biological fluids, and their expression is altered, which has led to their development as disease diagnostic, prognostic and predictive biomarkers (Dey et al., 2023). Proteomic changes represent a functional view of cancer-associated molecular activity, as it is proteins that act directly in the mediation of signaling, enzymatic reactions, immune responses, the architecture of the cell, and intercellular communication. A proteomic analysis of OSCC has revealed the presence of proteins that are differentially expressed, which can be used for early detection, diagnosis, prognosis, and monitoring of therapy. However, a lot of the candidate biomarkers have not been adequately validated independently, and there is methodological heterogeneity in clinical translation (Pillai et al., 2021). Metabolic reprogramming is also a crucial step in oral carcinogenesis. Changes in amino acid, carbohydrate, lipid and related metabolites are the result of altered energy requirements, biosynthetic activity, oxidative balance and nutrient utilization. These metabolic signatures might be indicative of tumour phenotype and serve as complementary markers of malignant biochemical activity (Vitorio et al., 2020).

Oral cancer biomarker profiles are further enriched with biological information provided by the tumor microenvironment. Malignant epithelial cells are in constant contact with cancer-associated fibroblasts (CAFs), endothelial cells, immune cells, extracellular matrix elements, cytokines, chemokines and growth factors. These interactions allow for chronic inflammation, immune escape, angiogenesis, matrix remodeling, invasion and metastatic progression. Both tumour cells and the tumour microenvironment can thus provide biomarkers of tumour burden and biological aggressiveness, paving the way for a multidimensional approach including tumour-intrinsic, inflammatory, angiogenic and immune-associated signals (Radaic et al., 2024). Accessibility of these molecular signals and their reliable detection in clinical specimens are also important for their clinical usefulness. Nucleic acids, proteins, metabolites, inflammatory mediators, and other molecular components can be secreted, shed, leaked from tissues, released from cells, and transported outside the cell into biological fluids to contribute to the composition of oral tumors. Oral saliva is of special interest since it comes in direct

contact with oral lesions, can be easily collected, can be sampled repeatedly, and contains a wide variety of tumor associated molecules. However, oral inflammation, systemic diseases, collection methods and analytical variation may affect its biomarker composition, making it crucial to have standardized bioanalytical workflows (Kaur et al., 2018).
The molecular basis of oral cancer is thus a multi-faceted one that involves the interwoven changes in the genome, epigenome, transcriptome, proteome, metabolism, immune system and microenvironment. These changes can be mapped onto measurable signatures within easily accessed biological matrices that can serve as a mechanistic basis for the development of biomarkers that can aid in early detection, characterization, and longitudinal monitoring of disease in therapy. The relationship between carcinogenic exposure, molecular changes, malignant transformation, biomarker release and clinical utility is depicted in Figure 1.

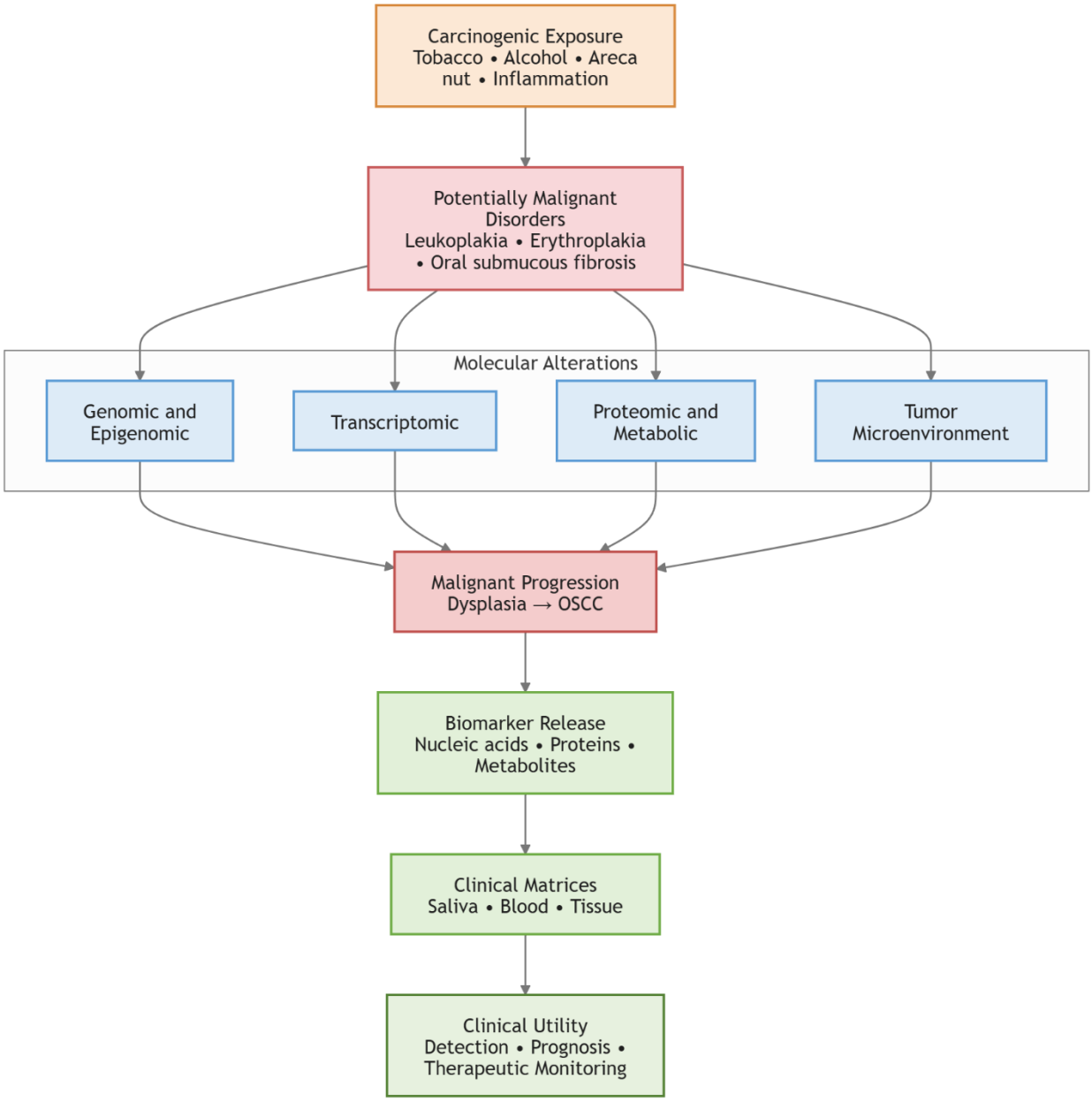

Figure 1. Molecular landscape and biological basis of biomarkers in oral cancer

3. Bioanalytical Biomarkers for Early Detection and Diagnosis

Early detection of oral cancer is dependent on the ability to detect the molecular changes that occur before significant morphological and clinical changes. Genomic markers are of special interest because they not only include those that are inherited, but also those that are acquired, such as mutations in oncogenes, tumor suppressor genes, DNA repair genes, and regulatory pathways that participate in oral carcinogenesis. Genetic association studies have identified variations associated with oral cancer susceptibility, but there are issues of population heterogeneity and variation in environmental exposures that make it difficult to develop a genetic signature for oral cancer that is applicable across the whole population (Sharma et al., 2017). In addition, molecular characterization of oral leukoplakia further illustrates that pockets of potentially malignant lesions may contain genomic and mutational abnormalities that correlate with the risk of progression, which makes cancers more likely to develop from leukoplakia than not, and provides the possibility to distinguish potentially high-risk lesions from not so high-risk lesions for progression (Farah, 2021). Epigenetic biomarkers are important as complementary markers since DNA methylation, histone modification, chromatin remodeling and

associated regulatory mechanisms may be aberrant during malignant transformation. Epigenetic changes impact both the tumor cells and the microenvironment, including the activity of tumor suppressor genes, oncogenic signaling, immune regulation and cell plasticity. Epigenetic signatures are promising targets for early detection and molecular stratification of oral squamous cell carcinoma (OSCC) because they are potentially reversible and can be easily measured at the molecular level (Mesgari et al., 2023).

Transcriptomic biomarkers bring to diagnostic assessment the dynamic changes in expression of RNA. Multiple processes contributing to oral carcinogenesis, such as proliferation, apoptosis, epithelial–mesenchymal transition, invasion, metastasis and treatment resistance, are regulated by non-coding RNAs, which could be used as part of molecular diagnostic panels (Umapathy et al., 2024). MicroRNAs are particularly promising given that expression patterns can be identified in specimens from patients with disease and that these patterns could help to distinguish malignant and non-malignant states (Osan et al., 2021). Circular RNAs create an additional layer of regulation by binding with microRNAs and downstream networks of genes. Thus, dysregulation of the circRNA–miRNA axis in OSCC has become a new source of molecular signatures in the form of RNA in the early diagnosis of OSCC (Saikishore et al., 2020). Protein biomarkers can offer a direct measurement of changes to cellular function and are especially appropriate to be analyzed in minimally invasive saliva samples. Salivary protein signatures, which have been identified by proteomic profiling, show that the changes in the proteome of tumors can be translated into early detection assays that can distinguish OSCC from non-cancer controls, highlighting the potential for diagnostic applications in early detection (Shan et al., 2019). Finally, more comprehensive proteomic approaches that involve discovery-based screening followed by targeted validation can reveal protein signatures linked to clinically important tumor phenotypes, highlighting proteins that can be measured in multiple combinations rather than singly (Carnielli et al., 2018).

The metabolomic and lipidomic markers reflect late-stage biochemistry of the transformed cells. Metabolic reprogramming associated with tumors changes lipid biosynthesis, membrane turnover, energy metabolism and signaling mechanisms, which results in measurable changes in circulating molecular profiles. Lipidomics has been found to be a promising diagnostic tool for OSCC, as lipid species and composite patterns have been identified that differentiate patients from controls, and can be used to complement the genomic and proteomic assessment (Wang et al., 2017). Biomarkers of inflammation and of oxidative injury are markers of the biological environment associated with oral carcinogenesis. Cytokines and other inflammatory mediators are potentially informative markers of OSCC development and progression, as they can lead to persistent inflammation, cytokine signaling, tissue remodeling, angiogenesis, and tumor supporting immune responses (Tampa et al., 2018). Oxidative imbalance can simultaneously produce an increase in the levels of ROS, lipid peroxidation, damage to proteins and alterations in DNA, which all play their part in the oral pathological processes. As such, oxidative-stress markers can perhaps be used together with tumor-specific markers, but with caution in the context of multimarker approaches due to their low specificity (Kumar et al., 2017).

Liquid biopsy also extends early diagnostic opportunities as it allows the analysis of material circulating in the blood that is derived from the tumour. The molecular information can come from the circulating tumor DNA, circulating tumor cells, extracellular vesicles, cell-free RNA, proteins, and other types of circulating components without the need for repeated invasive tissue sampling. Their potential applications range from early detection to molecular characterization, risk assessment, and longitudinal evaluation; however, low abundance of the analytes and variability in the methods pose challenges in analysis (Prakash & Pradeep, 2022). It seems unlikely that a single biomarker will be diagnostic of the wide spectrum of oral cancer's biological heterogeneity with much diagnostic power. Combining genomic, epigenetic, transcriptomic, proteomic, metabolic and circulating biomarkers provides a more detailed picture of the biology of the malignancy and could enhance the sensitivity and specificity of diagnosis. Many emerging molecular diagnostic strategies focus on multimodal assessment and individualized characterization that provide a basis for the integration of biomarker panels with contemporary oral cancer diagnostic and treatment pathways (Hsu et al., 2025).

The most promising approach to achieving clinically relevant early detection is to move away from single biomarker detection to analytically validated molecular signatures that represent complementary aspects of oral carcinogenesis. In the future, multi-analyte and multi-omics technologies might be needed to start making better diagnoses and risk stratify high-risk lesions before they become a clinical malignancy. Oral cancer biomarkers are being explored in various classes, and each class has key analytical properties, as summarized in Table 1.

Table 1. Major bioanalytical biomarker classes for early detection and diagnosis of oral cancer

Biomarker class	Representative signal	Common matrix	Primary utility	Main limitation
Genomic	Mutations, genetic variants	Tissue, saliva, plasma	Risk and early detection	Population variability
Epigenomic	DNA methylation patterns	Tissue, saliva, blood	Early molecular change	Assay standardization
Transcriptomic	mRNA, miRNA, lncRNA, circRNA	Tissue, saliva, plasma	Molecular classification	Expression variability
Proteomic	Differential protein signatures	Saliva, tissue, plasma	Early diagnosis	Validation inconsistency
Metabolomic/lipidomic	Metabolites, lipid profiles	Plasma, saliva	Metabolic discrimination	Limited specificity
Inflammatory/oxidative	Cytokines, oxidative markers	Saliva, serum	Complementary detection	Confounding inflammation

Liquid biopsy	ctDNA, CTCs, extracellular vesicles	Plasma, saliva	Minimally invasive detection	Low analyte abundance
Multi-omics panels	Integrated molecular signatures	Multiple matrices	Improved classification	Analytical complexity

4. Biological Matrices and Bioanalytical Platforms for Oral Cancer Biomarker Assessment

Detection of an oral cancer biomarker is also dependent on the matrix in which the biomarker is measured, as well as on the analytical platform used for detection, in addition to its biological relevance. Saliva is especially beneficial due to its non-invasive characteristics, easy accessibility, low cost to collect, and ability to be sampled repeatedly. It can be used to detect locally released proteins, nucleic acids, metabolites, cytokines and other tumor-associated molecules, due to direct contact with the oral lesions. Saliva thus has many features that make it an ideal specimen for screening and point-of-care (PoC) applications, but the flow rate, collection method, circadian rhythm, oral hygiene and inflammatory conditions may all affect the analytical reproducibility of saliva. (Goldoni et al., 2021) Blood matrices are an alternative systemic representation of tumour biology. Cytokines, circulating nucleic acids, proteins, EVs and other tumor-associated factors in plasma/serum may be related to local disease and systemic host response. The performance of the biomarkers in OSCC varies significantly between matrices, suggesting that the diagnostic information or performance of each will depend on the matrix, which is why it is important to validate them in each matrix before using them for clinical diagnosis (Lee et al., 2018). The tissue biopsy is the definitive histopathological specimen and also highly localised material for molecular profiling but is not suitable for population screening or for the repeated sampling of longitudinal studies. A less invasive alternative to taking epithelial samples of suspicious oral lesions is cytological specimens. Oral brush cytology can be used to aid early diagnosis of oral cancer and oral potentially malignant disorders, and to obtain oral cells that can be used for morphological or molecular analysis. However, due to the differences in the level of sampling and the diagnostic interpretation, integration with suitable confirmatory methods is required (Alsarraf et al., 2018).

Other matrices could be used to further the non-invasive assessment of oral cancer. The gas-rich portion of the breath (exhaled breath) consists of VOCs, formed endogenously during metabolic and oxidation processes, and metabolic changes in cancer can lead to a characteristic VOC profile. Breath cancer detection is becoming more feasible due to the development of sensitive chemical sensors and detection using nanotechnology, but standardization of breath collection conditions, environmental factors, identification of analytes, and disease-specific validation are still needed before the technique can be widely used in clinical practice (Jia et al., 2025). Bioanalytical platforms assess the efficacy of the conversion of the molecular signals to clinically interpretable measurements in these matrices. The use of molecular techniques like PCR, quantitative PCR, digital PCR and next-generation sequencing allows for sensitive interrogation of mutations, methylation patterns, transcripts and circulating nucleic acids. Immunoassays and mass-spectrometry-based workflows can be used for protein analysis, whereas targeted and untargeted proteomics can complement each other to support the discovery of new biomarkers and to verify them quantitatively. The integrated salivary proteomic approaches have proved to have potential for moving beyond the discovery of large numbers of proteins to the measurement of proteins that are relevant to oral cancer detection (Chu et al., 2019).

The potential for using biosensors to convert molecular biomarkers to fast, and potentially decentralized diagnostic tests is an attractive pathway. Sensors with electrochemical, optical and nanomaterial-based sensing capabilities can detect biomolecular recognition events and generate signals in a relatively small volume of sample. Surface area expansion, molecular capture, signal amplification, and detection sensitivity can be improved with nanodiagnostic methods that can aid in the analysis of the low-abundance oral cancer biomarkers. Unlike the proof-of-concept sensitivity, they also need to be assessed for their selectivity, reproducibility, analytical stability, fabrication consistency, and performance in a heterogeneous patient population (Chakraborty et al., 2023). Sample handling, analyte processing, detection, and data acquisition are other sub-processes integrated as miniaturized systems, such as microfluidic and lab-on-a-chip technologies. In such platforms, reagent consumption and analysis time can be minimized, small volume specimens can be manipulated, and potential multiplex measurement of biomarkers can be achieved. One example of how on-chip sample processing can be tailored for oral cancer diagnostic applications is presented by the SMILE microfluidic platform, which shows the potential to integrate microfluidics with powerful and sensitive detection technologies for creating compact workflows at the point of care (Zoupanou et al., 2021).

It is therefore crucial to deliberately match the biological matrix to the analytical platform appropriate for the detection of the biomarker in a cancer diagnosis. Sampling, molecular analysis, biosensing, and microfluidics technologies are all being combined in a way that provides a plausible pathway to the discovery of a biomarker in the lab to a reproducible, quick, and clinical oral cancer test. The biological matrices and platforms suitable for oral cancer biomarker assessment are summarized in Table 2.

Table 2. Biological matrices and bioanalytical platforms used in oral cancer biomarker assessment

Matrix	Major analytes	Suitable platforms	Key advantage	Key limitation
Saliva	RNA, proteins, cytokines, metabolites	PCR, immunoassays, biosensors	Non-invasive sampling	Pre-analytical variability
Plasma/serum	ctDNA, cytokines, proteins, EVs	dPCR, NGS, ELISA	Systemic assessment	Low tumor-derived signal
Tissue	DNA, RNA, proteins	NGS, PCR, proteomics	High tumor specificity	Invasive collection
Brush cytology	Cellular DNA/RNA	Cytology, PCR	Minimally	Sampling variability

			invasive	
Exhaled breath	Volatile organic compounds	Chemical/nanosensors	Fully non-invasive	Environmental confounding
Multiple matrices	Multiplex biomarkers	Microfluidics, lab-on-chip	Integrated analysis	Platform complexity

5. Biomarkers for Prognosis, Therapeutic Response, and Disease Monitoring

In the field of oral squamous cell carcinoma (OSCC), the use of prognosis biomarkers is becoming more and more common to improve the risk assessment of OSCCs beyond the usual clinicopathological factors including tumour size, node involvement, histological grade and stage. A number of molecular markers relating to proliferation, invasion, EMT, angiogenesis, apoptosis, stemness and metastatic potential could be used to obtain additional data regarding tumor aggressiveness and survival. Their main significance is in the determination of those patients with apparently similar clinical staging who might need more intense observation or a treatment strategy for their biologically high-risk disease (Sasahira & Kirita, 2018). In addition, circulating and histological biomarkers can be used to aid prognosis, which involves individualizing the prognosis based on tumor morphology and measurable systemic signals. Complementary to the pathological assessment, serological proteins, inflammatory mediators, tissue markers and molecular signatures can add to the stratification of the risk of recurrence, metastatic potential and therapeutic sensitivity. The incorporation of these markers into individualized treatment strategies could lead to better decisions for the intensity of treatment and post-treatment surveillance regimens, but reproducibility and prospective validation are still necessary for clinical use (Pekarek et al., 2023).

The highly relevant predictive biomarkers are those that are relevant in the expanding treatment paradigms involving targeted and immune-based therapies. The PD-1/PD-L1 axis has emerged as a therapeutic target in OSCC, and biomarkers of immune checkpoint expression, tumor immune status and molecular signaling could prove useful in selecting patients for whom immunotherapy is likely to be more effective. However, PD-L1 expression is not sufficient to define treatment responsiveness, and using composite models of biomarkers, which integrate tumor genetics, immune contexture, and other molecular features of resistance or sensitivity, is essential to understanding treatment responsiveness (Cheng et al., 2024).

Another avenue of potential pharmacodynamic assessment and real-time therapeutic monitoring is provided by minimally invasive biomarkers. Salivary or blood analysis can be repeated during treatment, providing a way to monitor changes in the nucleic acids, proteins, EVs, metabolites, and immunes associated with the tumor. These longitudinal samples can also provide dynamic information about tumor response that could be earlier than radiological and/or clinical signs of progression. Thus, the shift from single-marker testing towards a personalized molecular profile could benefit adaptations and surveillance of OSCC (Suri et al., 2024).

The use of circulating tumor DNA (ctDNA) is a very promising application for the detection of minimal residual disease. Plasma DNA from the residual tumor after definitive treatment could be considered as evidence of microscopic disease even in the absence of conventional imaging evidence of tumor. In the context of a tumor-agnostic approach, ctDNA has been found to be able to detect molecular residual disease and adverse outcomes in locally advanced squamous cell carcinoma of the head and neck, and could prove useful for early risk stratification post-therapy using plasma-based assays (Honoré et al., 2023). Longitudinal molecular surveillance can also help to identify the occurrence of recurrence and treatment resistance. Repeated molecular analyses of saliva and plasma allow for monitoring of tumor-associated somatic mutations over time and could provide insights into tumor recurrence prior to clinical recurrence. Besides being a convenient source from which to obtain information from the tumor, saliva may be more valuable in providing information on local disease, while plasma may be more useful in providing information on systemic disease burden. Longitudinal monitoring of both matrices can be in combination, which may enhance post-treatment surveillance by identifying patterns of residual/recurrent disease at different spatial locations (Cui et al., 2021).

Many of the most clinically useful biomarkers for prognosis and therapeutic monitoring are likely to be ones that will give more dynamic, longitudinal information than static markers. Tissue-based prognostic markers, when combined with circulating and salivary markers, may facilitate risk-tailored treatment, early detection of residual disease, early detection of recurrence and more individualised treatment decision-making. The main uses of biomarkers in prognosis, therapeutic response assessment, minimal residual disease and post-treatment surveillance are summarized in Table 3.

Table 3. Biomarker applications in prognosis, therapeutic response, and disease monitoring

Clinical application	Biomarker approach	Matrix	Clinical value	Current challenge
Prognosis	Molecular and histological markers	Tissue, serum	Risk stratification	Variable validation
Treatment prediction	PD-1/PD-L1 and immune markers	Tissue, blood	Therapy selection	Incomplete predictive power
Response monitoring	Dynamic molecular profiles	Saliva, blood	Early response assessment	Threshold definition
Minimal residual disease	ctDNA	Plasma	Detect occult disease	Low post-treatment levels
Recurrence surveillance	Somatic mutations	Saliva, plasma	Earlier relapse detection	Longitudinal standardization
Personalized	Multimarker profiles	Multiple	Individualized	Clinical integration

monitoring		matrices	follow-up	

6. Emerging Technologies and Integrated Approaches in Oral Cancer Biomarker Research

Oral cancer biomarker research is changing from the traditional single biomarker detection paradigm to molecularly heterogeneous systems and clinically actionable assessment. Modern methods integrate powerful molecular characterization with highly sensitive detection platforms, computational analysis and utilize minimally invasive sampling techniques. New screening and diagnostic technologies are increasingly being developed that utilize optical approaches, molecular assays, biosensing and point-of-care strategies to enhance detection of a malignant change at an early stage. Their value is based on the possibility of obtaining a good level of diagnostic accuracy and having good reproducibility, accessibility, and practicality for clinical workflows and screening at the population level (Bisht et al., 2021). However, multi-omics integration can be used to understand oral squamous cell carcinoma (OSCC) at the omics level and by integrating all the omics information, instead of analyzing each omics level individually, one can get a systems-level understanding of OSCC. This integration can uncover interactions leading to cellular networks that would not be apparent in a single-omics approach. Multi-omics investigation has shown that there are connections between intercellular communication, oxidative-stress regulation and the progression of OSCC, highlighting the power of combined molecular datasets to find mechanistically linked biomarker combinations. These strategies could allow for the development of panels of biomarkers that encompass both alterations intrinsic to the tumor and tumor dynamic interactions. (Zhang et al., 2024)

The ability of single-cell and spatially resolved technologies remains to capture information that is lost when performing bulk molecular profiling, addressing the intratumoral heterogeneity. Spatial transcriptomics can directly characterize gene-expression programs in the context of tissue architecture, facilitating the characterization of malignant cells, stromal populations, immune compartments and their localized interactions. Spatial analysis of OSCC has identified relationships between metabolic profiles and immunosuppressive microenvironment and transformation of inflammatory cancer-associated fibroblasts, revealing how spatially defined molecular states can provide biomarkers of tumour behaviour and immune dysfunction (Liu et al., 2024a). In addition to circulating tumour DNA and circulating tumour cells, advanced liquid biopsy is also evolving to encompass extracellular vesicles (EVs). The proteins, lipids, DNA, messenger RNA, microRNAs and other cargoes carried by EVs reflect the physiological state of their cells of origin. They are present in easily accessible biofluids, and are relatively stable, making them ideal candidates for minimally invasive oral cancer detection and longitudinal monitoring. Repeated characterization of tumor-associated molecular changes may be possible with EV-based liquid biopsy; however, standardised isolation, characterization, quantification, and analytical validation of EVs is required to allow for reliable clinical implementation (Minami et al., 2023).

Another approach to improving the detection of biomarkers is the use of engineered materials that have high surface-to-volume ratios, tunable physicochemical properties and signal amplification. Nanoparticles and nanostructured sensing interfaces will be used to enhance the ability to capture molecules and detect low abundance cancer associated molecules. AI could further enhance diagnostics, with the potential for automated interpretation of intricate molecular or imaging patterns. Oral and maxillofacial oncology is witness to nanotechnology-based applications integrating with AI, with the translational potential of these applications remaining to be determined, contingent on biosafety, fabrication reproducibility, external clinical validation, and superior performance compared to existing parts of the diagnostic pipeline (Sadeghzade et al., 2025). Machine learning and deep learning are a set of computational methods that can help to find clinically relevant patterns in highly dimensional oral cancer data sets. Molecular profiling could be combined with other molecular data from histopathology, imaging, clinical variables, and potentially multimodal biomarkers in algorithms to aid classification, risk prediction, and diagnostic decision-making. However, existing models have significant promise for automated oral cancer diagnosis, but there are challenges such as small or imbalanced datasets, inconsistent preprocessing, overfitting, limited external validation, and lack of interpretability that limit generalizability. More diverse multicenter datasets, reporting, robust validation and explainable models for clinical decision support and not just algorithmic performance, are needed for future development (Dixit et al., 2023).

Oral cancer biomarkers of the future will not be a single technology, but rather will be a result of convergence. Combining multi-omics, spatial profiling, liquid biopsy, nanobiosensing, and interpretable AI could revolutionize the ability to convert complex molecular signals into individualized signatures for early detection and therapeutic monitoring, but only if technology is sufficiently sophisticated and validated in the clinic and is practically deployable. The integration of new technologies into a single oral cancer biomarker platform along with their possible clinical applications is depicted in Figure 2.

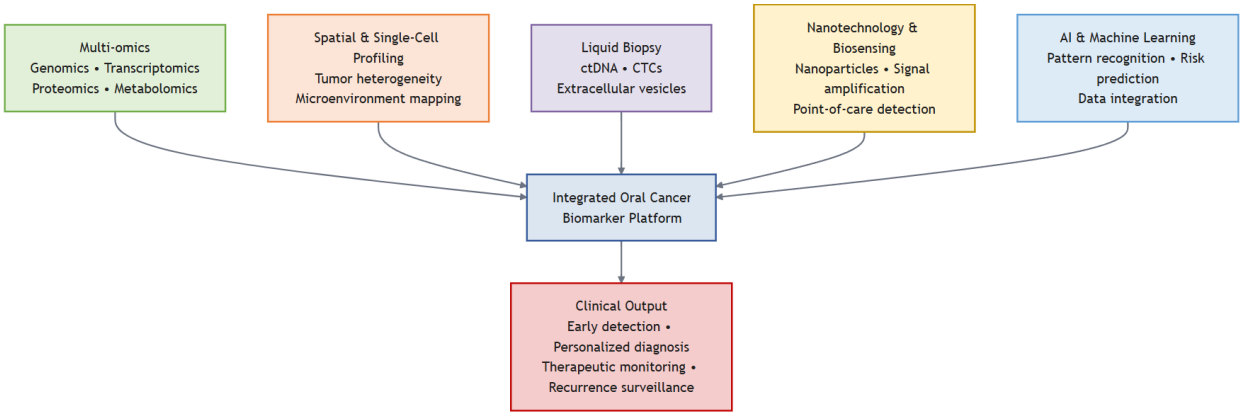

Figure 2. Emerging technologies and integrated approaches in oral cancer biomarker research

7. Clinical Translation, Current Challenges, and Future Perspectives

For clinical translation of oral cancer biomarkers, analytical, clinical, and analytical accuracy, reproducibility and utility beyond conventional examination and histopathology are needed. Presently, the available evidence is limited by the different study designs, the use of inconsistent diagnostic criteria and the lack of external validation, and there is a deficiency in translating biomarker discovery to clinical use (González-Moles et al., 2022). Another factor of major concern is pre-analytical variation, especially in the case of salivary markers. The stability and measured concentrations of biomarkers can be affected by the collection conditions, processing delay, storage, freeze–thaw cycles, and extraction procedures. Sample-associated factors, such as collection, processing, storage and quality controls, are important and should all be standardized when collecting and processing salivary miRNAs (Romani et al., 2024). Additionally, the molecular profile of a tumor is variable depending on the subsite, stage, microenvironment and treatment history, adding to the challenge of biomarker interpretation. Biological or prognostic relationships are not always therapeutically relevant, as indicated by the example of the fibroblast activation protein (Liu et al., 2024b), which has a prognostic value but is not a therapeutic target. Beyond the challenges with isolation, characterization, quantification, reproducibility, scalability, and regulatory standardization, emerging extracellular-vesicle biomarkers are further complicated by these challenges (Cheng & Kalluri, 2023). To make sure the clinical data is representative, population heterogeneity should be taken into account. Oral and oropharyngeal cancer epidemiology and performance of biomarkers may vary between population, due to changing patterns of tobacco and alcohol exposure, HPV-associated disease, demographics and tumor distribution (Chaturvedi et al., 2022). In addition, there are clear regulatory and diagnostic pathways to be included in the clinical adoption as delayed, missed diagnosis of OSCC has severe clinical and medico-legal implications. Therefore, biomarker assays should be used in addition to standard diagnostics until they have been proven more reliably for use in the clinic (Albano et al., 2024).

Prospective multicenter validation, harmonization of biobanking, analytical protocols, and longitudinal sampling should be the focus of future studies. Combined models, which combine genomic, transcriptomic, proteomic, metabolic, immune, and liquid-biopsy signals in a multimarker approach may be more clinically robust than individual biomarkers. Fast and minimally invasive assessment could further be made possible by integrating with explainable artificial intelligence, biosensors and microfluidic platforms. This is to be achieved with an optimal approach towards a clinically useful bioanalytical framework linking early detection to therapeutic response assessment, minimal residual disease detection and recurrence surveillance in the long term. The key to success will be transforming promising molecular signatures into affordable, reproducible, scalable and clinically interpretable tests. The main priority of translation is thus not the ongoing development of candidate biomarkers, but their robust validation as integrated signatures that can effectively and meaningfully contribute to the diagnostic and therapeutic process in oral cancer. The summary of the major challenges, clinical translation pathway and future considerations for oral cancer biomarkers is shown in Figure 3.

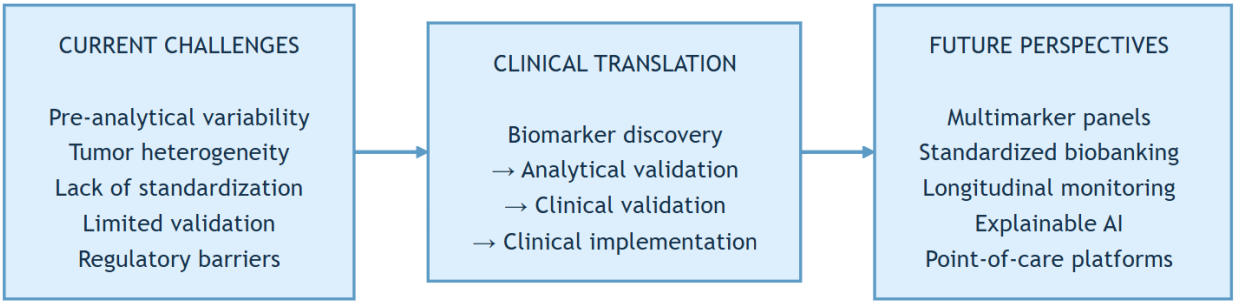

Figure 3. Clinical translation, current challenges, and future perspectives of oral cancer biomarkers

8. CONCLUSION

Adding to the traditional clinical and histopathological assessment, bioanalytical biomarkers are changing the oral cancer detection and therapeutic monitoring arena by providing a molecular evaluation. Biomarkers (genomic, epigenomic, transcriptomic, proteomic, metabolomic, immune and circulating) offer complementary information about the

development and biological behavior of the tumor, as well as its response to treatment and tumor recurrence. Saliva and blood provide exclusive benefits in the field of minimally invasive and longitudinal evaluation, and integrated biomarker analysis has gained more traction thanks to developments in liquid biopsy, biosensors, microfluidics, multi-omics, spatial profiling, and artificial intelligence. Although there is progress, clinical use is hampered by tumor variability, pre-analytical variation, the use of inconsistent methods, poor external validation, and the absence of standardized thresholds. Going forward, further advances should be directed towards validated multimarker signatures, not individual candidate biomarkers. Future multi-center studies, consistent analytical procedures, prospective sampling, and clinically related computational processes will be crucial for bringing biomarker discoveries to reliable practice. Finally, there are possibilities of integrated bioanalytical strategies for earlier diagnosis, personalized therapy choice, real-time therapeutic monitoring and better monitoring of oral cancer.

REFERENCES

1. Albano, D., Argo, A., Bilello, G., Cumbo, E., Lupatelli, M., Messina, P., ... & Scardina, G. A. (2024). Oral squamous cell carcinoma: features and medico-legal implications of diagnostic omission. Case Reports in Dentistry, 2024(1), 2578271.
2. Ali, J., Sabiha, B., Jan, H. U., Haider, S. A., Khan, A. A., & Ali, S. S. (2017). Genetic etiology of oral cancer. Oral oncology, 70, 23-28.
3. Bisht, S. R., Mishra, P., Yadav, D., Rawal, R., & Mercado-Shekhar, K. P. (2021). Current and emerging techniques for oral cancer screening and diagnosis: a review. Progress in Biomedical Engineering, 3(4), 042003.
4. Carnielli, C. M., Macedo, C. C. S., De Rossi, T., Granato, D. C., Rivera, C., Domingues, R. R., ... & Paes Leme, A. F. (2018). Combining discovery and targeted proteomics reveals a prognostic signature in oral cancer. Nature communications, 9(1), 3598.
5. Chakraborty, D., Ghosh, D., Kumar, S., Jenkins, D., Chandrasekaran, N., & Mukherjee, A. (2023). Nano-diagnostics as an emerging platform for oral cancer detection: Current and emerging trends. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology, 15(1), e1830.
6. Chaturvedi, A. K., Freedman, N. D., & Abnet, C. C. (2022). The evolving epidemiology of oral cavity and oropharyngeal cancers. Cancer Research, 82(16), 2821-2823.
7. Cheng, K., & Kalluri, R. (2023). Guidelines for clinical translation and commercialization of extracellular vesicles and exosomes based therapeutics. Extracellular Vesicle, 2, 100029.
8. Cheng, Y., Song, Z., Chen, J., Tang, Z., & Wang, B. (2024). Molecular basis, potential biomarkers, and future prospects of OSCC and PD-1/PD-L1 related immunotherapy methods. Heliyon, 10(4).
9. Chu, H. W., Chang, K. P., Hsu, C. W., Chang, I. Y. F., Liu, H. P., Chen, Y. T., & Wu, C. C. (2019). Identification of salivary biomarkers for oral cancer detection with untargeted and targeted quantitative proteomics approaches*[S]. Molecular & Cellular Proteomics, 18(9), 1796-1806.
10. Cui, Y., Kim, H. S., Cho, E. S., Han, D., Park, J. A., Park, J. Y., ... & Cha, Y. H. (2021). Longitudinal detection of somatic mutations in saliva and plasma for the surveillance of oral squamous cell carcinomas. PloS one, 16(9), e0256979.
11. D'souza, S., & Addepalli, V. (2018). Preventive measures in oral cancer: An overview. Biomedicine & Pharmacotherapy, 107, 72-80.
12. D'Cruz, A. K., Vaish, R., & Dhar, H. (2018). Oral cancers: current status. Oral oncology, 87, 64-69.
13. Dey, S., Biswas, B., Manoj Appadan, A., Shah, J., Pal, J. K., Basu, S., & Sur, S. (2023). Non-coding RNAs in oral cancer: emerging roles and clinical applications. Cancers, 15(15), 3752.
14. Dixit, S., Kumar, A., & Srinivasan, K. (2023). A current review of machine learning and deep learning models in oral cancer diagnosis: recent technologies, open challenges, and future research directions. Diagnostics, 13(7), 1353.
15. Farah, C. S. (2021). Molecular, genomic and mutational landscape of oral leukoplakia. Oral diseases, 27(4), 803-812.
16. Goldoni, R., Scolaro, A., Boccalari, E., Dolci, C., Scarano, A., Inchingolo, F., ... & Tartaglia, G. (2021). Malignancies and biosensors: A focus on oral cancer detection through salivary biomarkers. Biosensors, 11(10), 396.
17. González-Moles, M. Á., Aguilar-Ruiz, M., & Ramos-García, P. (2022). Challenges in the early diagnosis of oral cancer, evidence gaps and strategies for improvement: a scoping review of systematic reviews. Cancers, 14(19), 4967.
18. H. Alsarraf, A., Kujan, O., & Farah, C. S. (2018). The utility of oral brush cytology in the early detection of oral cancer and oral potentially malignant disorders: a systematic review. Journal of Oral Pathology & Medicine, 47(2), 104-116.
19. Honoré, N., Van Marcke, C., Galot, R., Helaers, R., Ambroise, J., Van Maanen, A., ... & Machiels, J. P. (2023). Tumor-agnostic plasma assay for circulating tumor DNA detects minimal residual disease and predicts outcome in locally advanced squamous cell carcinoma of the head and neck. Annals of Oncology, 34(12), 1175-1186.
20. Hsu, P. C., Huang, J. H., Tsai, C. C., Lin, Y. H., & Kuo, C. Y. (2025). Early molecular diagnosis and comprehensive treatment of oral cancer. Current Issues in Molecular Biology, 47(6), 452.
21. Irimie, A. I., Ciocan, C., Gulei, D., Mehterov, N., Atanasov, A. G., Dudea, D., & Berindan-Neagoe, I. (2018). Current insights into oral cancer epigenetics. International journal of molecular sciences, 19(3), 670.
22. Jia, Z., Jiang, Y., Shang, T., Cao, H., Li, J., Cong, L., ... & Liu, J. (2025). Advanced strategy for cancer detection based on volatile organic compounds in breath. Journal of Nanobiotechnology, 23(1), 468.
23. Karunakaran, K., & Muniyan, R. (2020). Genetic alterations and clinical dimensions of oral cancer: a review. Molecular biology reports, 47(11), 9135-9148.

24. Kaur, J., Jacobs, R., Huang, Y., Salvo, N., & Politis, C. (2018). Salivary biomarkers for oral cancer and pre-cancer screening: a review. Clinical oral investigations, 22(2), 633-640.
25. Kumar, J., Teoh, S. L., Das, S., & Mahakknaukrauh, P. (2017). Oxidative stress in oral diseases: understanding its relation with other systemic diseases. Frontiers in physiology, 8, 693.
26. Kumari, P., Debta, P., & Dixit, A. (2022). Oral potentially malignant disorders: etiology, pathogenesis, and transformation into oral cancer. Frontiers in pharmacology, 13, 825266.
27. Lee, L. T., Wong, Y. K., Hsiao, H. Y., Wang, Y. W., Chan, M. Y., & Chang, K. W. (2018). Evaluation of saliva and plasma cytokine biomarkers in patients with oral squamous cell carcinoma. International Journal of Oral and Maxillofacial Surgery, 47(6), 699-707.
28. Liu, J., Ouyang, Y., Xia, Z., Mai, W., Song, H., Zhou, F., ... & Liao, J. (2024b). FAP is a prognostic marker, but not a viable therapeutic target for clinical translation in HNSCC: J. Liu et al. Cellular Oncology, 47(2), 623-638.
29. Liu, Z., Zhang, Z., Zhang, Y., Zhou, W., Zhang, X., Peng, C., ... & Ren, Z. (2024a). Spatial transcriptomics reveals that metabolic characteristics define the tumor immunosuppression microenvironment via iCAF transformation in oral squamous cell carcinoma. International Journal of Oral Science, 16(1), 9.
30. Mesgari, H., Esmaelian, S., Nasiri, K., Ghasemzadeh, S., Doroudgar, P., & Payandeh, Z. (2023). Epigenetic regulation in oral squamous cell carcinoma microenvironment: a comprehensive review. Cancers, 15(23), 5600.
31. Minami, S., Chikazu, D., Ochiya, T., & Yoshioka, Y. (2023). Extracellular vesicle-based liquid biopsies in cancer: Future biomarkers for oral cancer. Translational oncology, 38, 101786.
32. Nandini, D. B., Rao, R. S., Hosmani, J., Khan, S., Patil, S., & Awan, K. H. (2020). Novel therapies in the management of oral cancer: An update. Disease-a-Month, 66(12), 101036.
33. Natarajan, P. M., & Umapathy, V. R. (2025). Role of transcriptomics in the study of oral cancer. Frontiers in Oral Health, 6, 1524364.
34. Osan, C., Chira, S., Nutu, A. M., Braicu, C., Baciut, M., Korban, S. S., & Berindan-Neagoe, I. (2021). The connection between MicroRNAs and oral cancer pathogenesis: emerging biomarkers in oral cancer management. Genes, 12(12), 1989.
35. Pekarek, L., Garrido-Gil, M. J., Sánchez-Cendra, A., Cassinello, J., Pekarek, T., Fraile-Martinez, O., ... & Ortega, M. A. (2023). Emerging histological and serological biomarkers in oral squamous cell carcinoma: Applications in diagnosis, prognosis evaluation and personalized therapeutics. Oncology reports, 50(6), 213.
36. Pillai, J., Chincholkar, T., Dixit, R., & Pandey, M. (2021). A systematic review of proteomic biomarkers in oral squamous cell cancer. World Journal of Surgical Oncology, 19(1), 315.
37. Prakash, N., & Pradeep, G. L. (2022). Circulating biomarkers in oral cancer: Unravelling the mystery. Journal of Oral and Maxillofacial Pathology: JOMFP, 26(3), 300.
38. Radaic, A., Kamarajan, P., Cho, A., Wang, S., Hung, G. C., Najarzadegan, F., ... & Kapila, Y. L. (2024). Biological biomarkers of oral cancer. Periodontology 2000, 96(1), 250-280.
39. Ren, Z. H., Hu, C. Y., He, H. R., Li, Y. J., & Lyu, J. (2020). Global and regional burdens of oral cancer from 1990 to 2017: Results from the global burden of disease study. Cancer Communications, 40(2-3), 81-92.
40. Romani, P. C., Baronchelli, M. M., Assoni, M. C., Calza, P. S., Piazza, M. C., & Bossi, M. P. (2024). Stability of circulating miRNA in saliva: The influence of sample associated pre-analytical variables. Clinica Chimica Acta, 553, 117702.
41. Sadeghzade, A., Ghanbari, M., Malmir, S., Mohammadikhah, M., Purtaji, B., Namazikhah, M., & Tajeryan, Z. (2025). Artificial intelligence and nanotechnology in oral and maxillofacial cancer: a review of diagnosis and treatment advances. Nanomedicine Research Journal, 10(3), 202-209.
42. Saikishore, R., Velmurugan, P., Ranjithkumar, D., Latha, R., Sathiamoorthi, T., Arun, A., ... & Sivakumar, S. (2020). The circular RNA-miRNA axis: a special RNA signature regulatory transcriptome as a potential biomarker for OSCC. Molecular Therapy Nucleic Acids, 22, 352-361.
43. Sarode, G., Maniyar, N., Sarode, S. C., Jafer, M., Patil, S., & Awan, K. H. (2020). Epidemiologic aspects of oral cancer. Disease-a-Month, 66(12), 100988.
44. Sasahira, T., & Kirita, T. (2018). Hallmarks of cancer-related newly prognostic factors of oral squamous cell carcinoma. International journal of molecular sciences, 19(8), 2413.
45. Saxena, S., Sankhla, B., Sundaragiri, K. S., & Bhargava, A. (2017). A review of salivary biomarker: a tool for early oral cancer diagnosis. Advanced biomedical research, 6, 90.
46. Shan, J., Sun, Z., Yang, J., Xu, J., Shi, W., Wu, Y., ... & Li, H. (2019). Discovery and preclinical validation of proteomic biomarkers in saliva for early detection of oral squamous cell carcinomas. Oral diseases, 25(1), 97-107.
47. Sharma, V., Nandan, A., Sharma, A. K., Singh, H., Bharadwaj, M., Sinha, D. N., & Mehrotra, R. (2017). Signature of genetic associations in oral cancer. Tumor Biology, 39(10), 1010428317725923.
48. Suri, S., Boora, G. S., Kaur, R., Chauhan, A., Ghoshal, S., & Pal, A. (2024). Recent advances in minimally invasive biomarkers of OSCC: from generalized to personalized approach. Frontiers in oral health, 5, 1426507.
49. Tampa, M., Mitran, M. I., Mitran, C. I., Sarbu, M. I., Matei, C., Nicolae, I., ... & Georgescu, S. R. (2018). Mediators of inflammation–a potential source of biomarkers in oral squamous cell carcinoma. Journal of immunology research, 2018(1), 1061780.
50. Tarle, M., & Lukšić, I. (2024). Pathogenesis and therapy of oral carcinogenesis. International journal of molecular sciences, 25(12), 6343.
51. Umapathy, V. R., Natarajan, P. M., & Swamikannu, B. (2024). Molecular and therapeutic roles of non-coding rnas in oral cancer—a review. Molecules, 29(10), 2402.

52. Vitorio, J. G., Duarte-Andrade, F. F., dos Santos Fontes Pereira, T., Fonseca, F. P., Amorim, L. S. D., Martins-Chaves, R. R., ... & Gomez, R. S. (2020). Metabolic landscape of oral squamous cell carcinoma. Metabolomics, 16(10), 105.
53. Wang, L., Wang, X., Li, Y., Hou, Y., Sun, F., Zhou, S., ... & Zhang, B. (2017). Plasma lipid profiling and diagnostic biomarkers for oral squamous cell carcinoma. Oncotarget, 8(54), 92324.
54. Wu, J., Chen, H., Liu, Y., Yang, R., & An, N. (2025). The global, regional, and national burden of oral cancer, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. Journal of Cancer Research and Clinical Oncology, 151(2), 53.
55. Xie, L., & Shang, Z. (2022). Burden of oral cancer in Asia from 1990 to 2019: Estimates from the Global Burden of Disease 2019 study. PLoS One, 17(3), e0265950.
56. Zhang, H., Qian, Y., Zhang, Y., Zhou, X., Shen, S., Li, J., ... & Wang, W. (2024). Multi-omics analysis deciphers intercellular communication regulating oxidative stress to promote oral squamous cell carcinoma progression. NPJ Precision Oncology, 8(1), 272.
57. Zoupanou, S., Volpe, A., Primiceri, E., Gaudiuso, C., Ancona, A., Ferrara, F., & Chiriaco, M. S. (2021). SMILE platform: an innovative microfluidic approach for on-chip sample manipulation and analysis in oral cancer diagnosis. Micromachines, 12(8), 885.