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Molecular Profiling of Oral Potentiality Malignant Disorders (OPMDS) for predicting Malignant Transformation

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Abstract

Oral potentially malignant disorders (OPMDs) — including oral leukoplakia, oral lichen planus, and oral submucous fibrosis — carry variable risk of progression to oral squamous cell carcinoma (OSCC). Conventional histopathology (dysplasia grade) incompletely predicts which lesions will transform. Recent molecular profiling efforts (genomics, epigenomics, transcriptomics, proteomics, liquid biopsy) have identified candidate biomarkers and multi-omic signatures that improve risk stratification and point toward noninvasive surveillance tools. This review summarizes current evidence for molecular predictors of malignant transformation in OPMDs, highlights validated and promising biomarkers (LOH, TP53 alterations, 9p/3p/17p changes, promoter hypermethylation including ZNF582 and p16, microRNA signatures, salivary/ctDNA markers), evaluates integrative and machine-learning approaches, and proposes a practical framework for translating molecular profiling into clinical risk models. We identify gaps (heterogeneity, small cohorts, lack of multicenter validation) and give recommendations for study design and clinical implementation.

***Keywords*:** OPMD, oral leukoplakia, malignant transformation, biomarkers, methylation, genomics, microRNA, liquid biopsy, multi-omics

Introduction

Oral potentially malignant disorders (OPMDs) are visible mucosal abnormalities with an increased risk of progression to oral squamous cell carcinoma (OSCC). While most OPMDs never progress, a clinically meaningful minority do — and predicting which lesions will transform remains a key unmet clinical need. Traditional risk assessment relies on clinical features and histological grading of dysplasia, but these methods lack sufficient sensitivity and specificity for individual-level prediction. Consequently, molecular profiling has been investigated to (1) identify lesions at higher risk, (2) allow noninvasive surveillance (e.g., saliva, gargle, blood), and (3) suggest targets for early intervention. Recent reviews and large-scale studies show promise for multi-modal molecular classifiers but emphasize need for standardized cohorts and external validation.

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Methods (review approach)

This paper is a narrative systematic review synthesizing recent primary studies and reviews (2014–2025) on molecular markers and profiling strategies for OPMD malignant transformation. Key databases (PubMed/PMC, Clinical Cancer Research, Cancers, MDPI journals, and major publishers) were searched for: "oral leukoplakia malignant transformation genomic", "OPMD methylation ZNF582", "microRNA oral premalignant transformation", "saliva biomarkers oral cancer early detection", and "integrative genomic transcriptomic leukoplakia". Priority was given to studies with longitudinal follow-up, sequential lesion sampling, multi-omic integration, and those proposing or validating predictive models. Representative high-impact studies and reviews are cited throughout. (For a formal systematic review/meta-analysis, registration (PROSPERO) and explicit inclusion/exclusion criteria would be required.)

Molecular alterations associated with malignant transformation

Genomic alterations and copy-number changes

Loss of heterozygosity (LOH) at specific chromosomal loci (particularly 9p, 3p, 17p) and copy-number alterations (CNAs) have long been associated with progression risk in oral leukoplakia. Early sequential lesion studies showed recurrent CNAs preceding histologic progression; more recent larger genomic profiling efforts refined the landscape of somatic mutations and CNAs in progressive lesions. Notably, loss of chromosome 9p (harboring CDKN2A/p16) is repeatedly observed and associated with higher transformation risk; recent pathomics/AI efforts attempt to predict 9p loss from routine slides. TP53 mutations and copy-number changes are common in lesions that progress, although mutation timing can vary. Integrative genomic studies have provided predictive models combining dysplasia grade with genomic markers.

Epigenetic alterations — DNA methylation

Aberrant promoter methylation is among the most reproducible molecular signals in OPMDs. Several loci (e.g., p16/CDKN2A promoter, ZNF582) show hypermethylation in lesions that later transform. ZNF582 promoter hypermethylation has been proposed as a noninvasive biomarker detectable in tissue and gargle/saliva, with multiple studies suggesting prognostic value. DNA methylation panels in saliva or gargle fluid have been developed to discriminate early OSCC from OPMDs and to flag high-risk lesions for closer follow-up. Overall, methylation biomarkers are attractive for translation because they are stable and assayable in noninvasive samples.

Transcriptomics and microRNA signatures

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Transcriptome profiling has revealed gene-expression patterns associated with progression. MicroRNAs (miRNAs) — small noncoding RNAs detectable in tissue, saliva, and blood — have shown promise as predictors. Several studies reported miRNA panels that distinguish progressive from nonprogressive leukoplakia; for example, multi-miRNA signatures (including some recurrent miRNAs across studies) correlated with transformation. However, inter-study heterogeneity (different platforms, normalization, small cohorts) limits immediate clinical adoption.

Proteomics and other markers

Tissue immunohistochemical markers (p53 protein accumulation, Ki-67 proliferation index, PD-L1, ALDH1, S100A7) have been studied as adjuncts. Proteomic studies and extracellular vesicle analyses are emerging, with salivary proteins (e.g., IL-8, MMP-9, Cyfra21-1) and exosomal cargo under active investigation for noninvasive detection and monitoring. Comprehensive proteogenomic approaches remain limited but promising.

Liquid biopsy — saliva, gargle, plasma ctDNA, exosomes

Noninvasive sampling is especially appealing for mucosal lesions. Saliva and gargle fluid contain DNA, RNA, proteins, and EVs reflective of local mucosal pathology. Studies show methylation markers and ctDNA/exosomal miRNA in saliva can distinguish early cancer from OPMDs; serial sampling may permit dynamic risk assessment. Sensitivity and specificity vary by marker and assay; reproducible, clinically validated panels are still pending multicenter confirmation.

Integrative multiomic models and machine learning

Recent publications combine histology, clinical features, and molecular data to build predictive models. Integrative analyses of genomic and transcriptomic data have identified pathways (cell cycle, DNA repair, chromatin remodeling) associated with malignant progression. Machine-learning models trained on multi-modal features (dysplasia grade + selected genomic/methylation markers) show improved discrimination vs. histology alone in single-center cohorts; however, generalizability is limited by cohort size, selection bias, and platform variability. There is active exploration of AI methods (including pathomics to infer 9p loss) to augment routine pathology with genomic inferences.

Clinical utility — what is ready now, what needs validation

Near-clinical markers (most evidence):

- LOH at 9p/3p/17p and TP53 alterations — robust association with progression across studies, useful when available.

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- Promoter hypermethylation of loci such as ZNF582 and p16 — promising non invasive markers detectable in saliva/gargle; multiple cohorts show prognostic signal.

Promising but requiring more validation:

- miRNA panels (tissue and salivary) — replicate findings in larger multicenter cohorts with standardized assays.
- Combined multi-omic classifiers and AI/pathomics models — need external validation and prospective evaluation.

Barriers to clinical translation:

1. Heterogeneous cohorts (different OPMD subtypes and etiologies).
2. Small sample sizes and relatively few longitudinal studies with sufficient transformation events.
3. Technical variability (platforms, sample types, normalization).
4. Lack of prospective, multicenter external validation and cost-effectiveness analyses.
5. Regulatory and reimbursement pathways for molecular surveillance tests.

Recommended framework for future studies and clinical implementation

To accelerate translation, we recommend:

1. **Prospective multicenter cohort studies** with standardized sample collection (tissue + paired saliva/gargle + blood), central pathology review, and pre-specified molecular panels. Track lesion outcomes with long enough follow-up to capture transformation events.
2. **Predefined biomarker panels**: include LOH markers (9p, 3p, 17p), targeted sequencing of TP53 and recurrently altered genes, and a methylation panel (eg, ZNF582, p16). Add exploratory layers (miRNA, proteomics) for discovery.
3. **Harmonized assays and QC**: use clinically implementable assays (targeted NGS panels, bisulfite PCR for methylation, standardized qPCR for miRNAs) with inter-laboratory proficiency testing.
4. **Model building & validation**: split cohorts into training/validation and perform external validation in independent populations. Report calibration, discrimination (AUC), decision-curve analyses, and net reclassification indices above histology alone.
5. **Implementation studies**: prospective trials to test whether molecularly guided surveillance/intervention reduces OSCC incidence or improves stage at diagnosis without undue harms. Cost-effectiveness and acceptability among patients/clinicians are essential.

Proposed pilot study (example protocol)

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Title: Prospective multicenter study of a combined methylation-genomic classifier to predict malignant transformation in oral leukoplakia.

Aims: Validate a classifier combining LOH (9p), TP53 mutation status, and ZNF582 methylation measured in tissue and saliva to predict 3-year malignant transformation.

Design: Enroll 600 patients with biopsy-proven oral leukoplakia (no prior OSCC). Collect baseline tissue, saliva, and blood. Central histology review; perform targeted sequencing (cancer gene panel), LOH analysis, and methylation assays. Follow for 3 years with standardized surveillance; primary endpoint: biopsy-confirmed OSCC arising at lesion site.

Analysis: Train model on 400 patients, validate on 200. Primary metric: AUC for predicting transformation; secondary: sensitivity at fixed specificity, positive predictive value, decision-curve analysis.

This design emphasizes sample size to capture transformation events, paired noninvasive sampling, centralized assays, and external validation.

Discussion

Molecular profiling offers a realistic path to improve risk stratification for OPMDs beyond histology. The strongest signals today are LOH (especially 9p), TP53 alterations, and specific promoter hypermethylation events (eg, ZNF582, p16), with growing evidence for saliva/gargle assays. Multi-omic integration and machine learning can add discrimination but require robust, standardized data to avoid overfitting. Translating these markers into routine care will require prospective multicenter validation, demonstration of clinical utility (improved outcomes or efficient surveillance), and cost-effectiveness. Ethical considerations include communicating risk, avoiding overtreatment, and ensuring equitable access to molecular testing.

Conclusions

Molecular profiling of OPMDs is a rapidly evolving field with several reproducible markers that can enhance prediction of malignant transformation. Priority actions are multicenter prospective validation of combined genomic/epigenomic panels, standardization of noninvasive assays (saliva/gargle), and pragmatic trials to test whether molecularly informed care improves patient-level outcomes. If validated, these tools could enable personalized surveillance and earlier interception of lesions that will progress to OSCC.

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