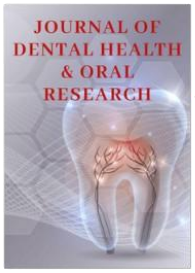

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Review Article

Artificial Intelligence and Biomarker Integration in Oral Pathology: Transforming Early Detection and Risk Prediction of Oral Potentially Malignant Disorders

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Abstract

Oral Potentially Malignant Disorders (OPMDs), including oral leukoplakia, erythroplakia, oral lichen planus and oral submucous fibrosis, carry a documented risk of progression to Oral Squamous Cell Carcinoma (OSCC). Conventional diagnosis relies on histopathological assessment, which is limited by interobserver variability and inadequate risk stratification. This narrative review examines the current evidence on Artificial Intelligence (AI) and molecular biomarkers in oral pathology, with emphasis on early detection and malignant transformation prediction. Reviewed studies indicate that multimarker panels, incorporating p53, Ki-67, EGFR and salivary microRNAs, improve risk classification compared with standard histopathology. AI-based tools, including deep learning models and surface-enhanced Raman spectroscopy combined with machine learning, demonstrate promising sensitivity for OPMD detection. Despite these advances, significant challenges remain regarding standardization, external validation, algorithmic bias and equitable access. Integrating AI and biomarker strategies into clinical workflows holds substantial potential for personalized, early-stage oral cancer prevention.

Keywords: Artificial Intelligence; Oral Potentially Malignant Disorders; Biomarkers; Early Detection; Risk Stratification; Oral Squamous Cell Carcinoma

Introduction

Oral Potentially Malignant Disorders (OPMDs) represent a heterogeneous group of mucosal lesions that occupy an intermediate stage in the multistep process of oral carcinogenesis. As a category, they are defined by their documented potential to undergo malignant transformation and they share the common endpoint of Oral Squamous Cell Carcinoma (OSCC) if left unrecognized or inadequately managed [1]. The entities currently recognized as OPMDs with significant transformation risk include oral leukoplakia, erythroplakia, Oral Lichen Planus (OLP), Oral Submucous Fibrosis (OSF), oral lichenoid lesions, actinic cheilitis and several less common conditions. Early identification remains therapeutically critical, since timely clinical intervention can interrupt progression toward invasive carcinoma and substantially improve patient outcomes [2,3].

From a global health perspective, OPMDs represent a considerable public health burden. Oral leukoplakia is the most prevalent OPMD and is widely regarded as the most important precancerous lesion for OSCC [4]. OLP affects between 0.5% and 2% of the world population and is more prevalent among middle-aged women; the World Health Organization (WHO) classifies OLP as an OPMD on the basis of its documented malignant transformation rates, which range from 0.2% to 3.5% [2,3]. OSF is a chronic fibrotic condition characterized by aberrant collagen deposition in the oral submucosa; it is particularly prevalent among South and Southeast Asian populations where betel nut chewing is common and it is estimated to affect approximately five million individuals globally [5].

The malignant transformation potential of OPMDs varies considerably by lesion type and by individual risk profile. Erythroplakia carries the highest transformation risk among all OPMDs; however, leukoplakia contributes the greatest absolute number of OSCC cases in clinical practice due to its higher prevalence, despite wide variation in transformation risk across individual lesions [1,5]. Transformation rates for OLP range from 0.2% to 3.5%, while OSF has reported rates between 1.2% and 23%, influenced by geographic region, disease duration and ongoing exposure to etiologic factors [2,4]. The progression of OSF to oral cancer has been documented to occur over a predictable interval of three to sixteen years following diagnosis, underscoring the need for long-term surveillance and systematic risk assessment (Fig. 1) [4,6].

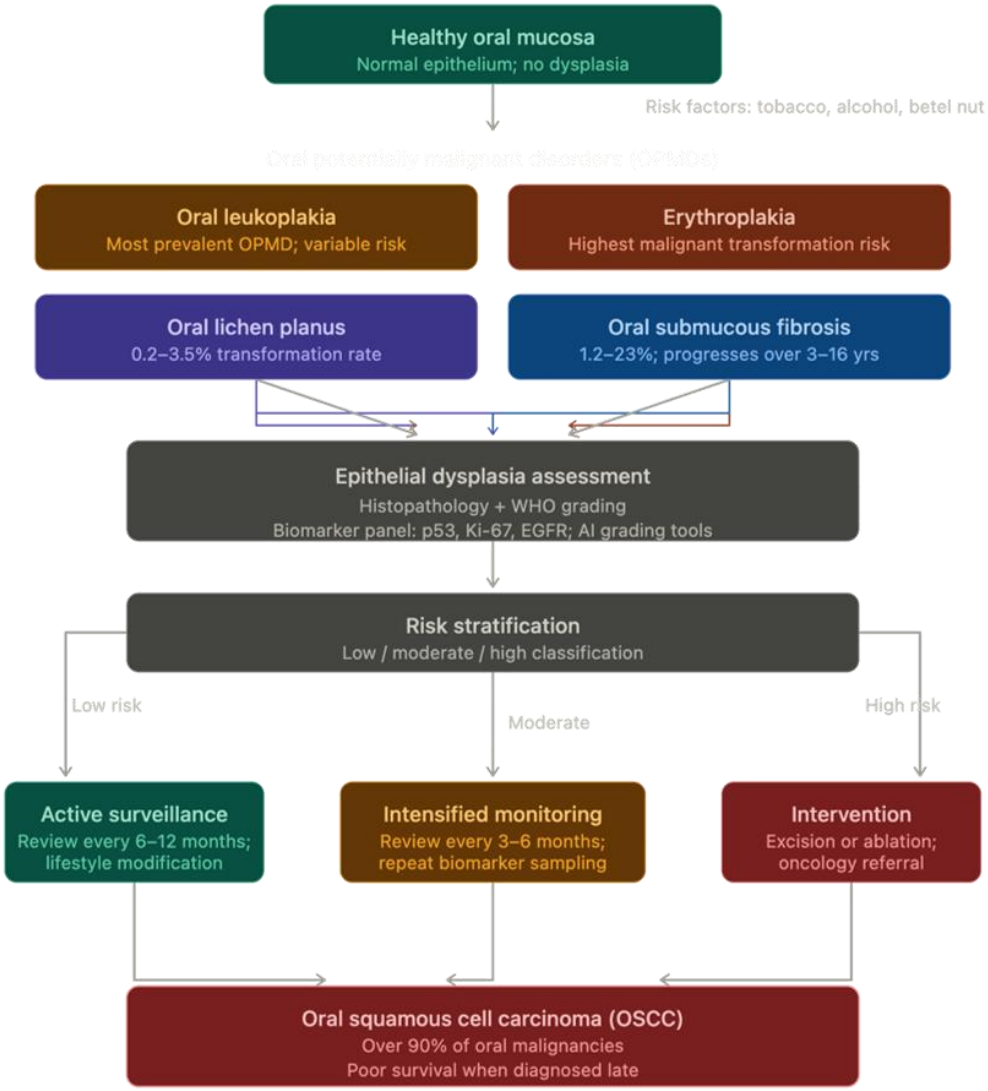

Figure 1: Stepwise malignant transformation pathway from healthy oral mucosa through Oral Potentially Malignant Disorders (OPMDs) to Oral Squamous Cell Carcinoma (OSCC). Biomarker checkpoints (p53, Ki-67, EGFR) and AI-assisted grading tools are integrated at the dysplasia assessment stage. Risk stratification directs patients toward active surveillance, intensified monitoring or intervention, with ongoing re-evaluation at each visit. OLP: Oral Lichen Planus; OSF: Oral Submucous Fibrosis; EGFR: Epidermal Growth Factor Receptor; OSCC: Oral Squamous Cell Carcinoma [1-9,11,13,15-17,22].

Despite advances in oral health care, late diagnosis remains the central obstacle to effective oral cancer prevention. OSCC accounts for more than 90% of all oral malignancies and survival rates remain poor, largely because most patients present at advanced disease stages [3,7]. Early-stage lesions are frequently asymptomatic or exhibit subtle clinical signs that may be overlooked during routine examination; consequently, late diagnosis is associated with increased morbidity, poorer prognosis and substantially higher treatment costs [5].

Conventional oral examination remains an indispensable component of clinical screening; however, it carries well-recognized limitations. Visual inspection and palpation can identify suspicious lesions, but they cannot reliably predict malignant transformation or detect the underlying molecular alterations associated with early carcinogenesis [7,8]. Furthermore, many OPMDs share overlapping clinical features, which increases the likelihood of diagnostic misclassification and introduces meaningful inter-clinician variability. Although oral biopsy with histopathological assessment remains the diagnostic gold standard, grading dysplasia accurately and stratifying risk remain genuinely difficult tasks in everyday practice. These limitations collectively highlight the need for more objective, reproducible and molecularly informed diagnostic tools, including enhanced histopathological examination, validated molecular biomarkers and AI-based technologies, which are explored in the sections that follow [9,10].

Histopathological Challenges and Diagnostic Limitations

Despite the recognized clinical importance of OPMDs as precursor lesions to OSCC, conventional histopathology, while remaining the diagnostic gold standard, presents significant limitations that affect both diagnostic accuracy and prognostic reliability in day-to-day patient management [6]. These deficiencies underscore the urgent need for complementary approaches, including molecular biomarkers and AI-based systems [11].

Inter- and intra-observer variability represents one of the primary obstacles in the grading of Oral Epithelial Dysplasia (OED). An international survey of 132 pathologists revealed a low level of agreement regarding the recognition of features such as irregular epithelial stratification and teardrop-shaped rete ridges, whereas loss of cellular cohesion was identified more consistently [7,12]. When four grading systems were compared across 137 cases, inter-observer agreement proved to be only moderate to low, with kappa values ranging from 0.17 to 0.42; agreement was particularly low when applying the two-tier model. [8] This variability is further compounded in oral lichen planus and lichenoid lesions, where disagreement reached 43.1% for atypical mitotic figures, 38.5% for loss of cellular cohesion and 38.5% for teardrop-shaped rete ridges [13]. Although calibration among pathologists can improve results (kappa 0.75 to 0.78), agreement typically decreases markedly under routine clinical conditions (kappa 0.491) [9].

Limitations in sampling and tissue representation further compound these inconsistencies. Small incisional biopsies are frequently insufficient, particularly in verrucous lesions, where intense inflammation can obscure cytological and architectural detail [14]. In an analysis of 23 cases, 69% of initial biopsies were classified as atypical squamoproliferative lesions; however, 81% proved to be conventional squamous cell carcinoma upon complete resection [10,15]. Lesional heterogeneity, superficial sampling and technical artifacts all contribute to diagnostic underestimation.

The difficulty of grading dysplasia and interpreting its prognostic significance represents another substantial challenge. The traditional WHO three-tier system tends to oversimplify a complex and biologically continuous process, leading to prognostic inconsistencies [6,16]. Moderate dysplasia, for instance, is frequently not associated with a meaningful increase in transformation risk, unlike severe dysplasia, which carries a reported hazard ratio of 13.7 [17]. Although the updated 2022 WHO criteria incorporate additional morphological features, further refinement remains necessary; proposed new thresholds requiring four or more architectural and six or more cytological alterations appear to improve discriminatory performance [11]. Feature-specific models, such as six-point and two-point scoring systems, also demonstrate predictive performance superior to that of the conventional grading approach [18].

These limitations carry direct clinical consequences for risk prediction and therapeutic decision-making. Diagnostic subjectivity and false-negative results can lead to both undertreatment of high-risk lesions and unnecessarily aggressive interventions, generating uncertainty and delays in follow-up [7,9]. Although clinicopathological correlation is fundamental, it is frequently insufficient when used in isolation.

Taken together, conventional histopathology faces significant challenges with respect to reproducibility, sampling quality and prognostic accuracy when evaluating OPMDs. Overcoming these barriers will require a multidisciplinary approach that integrates molecular biomarkers and artificial intelligence tools, enabling earlier detection and more individualized patient management [19].

Biomarkers in Oral Potentially Malignant Disorders

Predicting the malignant potential of OPMDs remains one of the most difficult challenges in oral pathology. Although histopathological evaluation is widely regarded as the diagnostic gold standard, it does not consistently provide an accurate indication of which lesions will eventually progress to OSCC [13,20]. This limitation has driven growing interest in molecular biomarkers capable of providing complementary information about lesion behavior and supporting more objective risk stratification [14].

Biomarkers are measurable biological indicators that reflect molecular and cellular changes occurring during disease progression. Among the most extensively studied markers in OPMDs are p53, Ki-67, Cyclin D1 and EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR), all of which are directly involved in the regulation of cell cycle progression and proliferative activity [21]. Aberrant p53 expression combined with elevated Ki-67 levels has been associated with higher grades of epithelial dysplasia and an increased likelihood of progression to OSCC [13,15,16]. Overexpression of Cyclin D1 and EGFR has similarly been linked to enhanced proliferative activity and more aggressive biological behavior, supporting their potential role in the malignant transformation of OPMDs [17,18,22].

Salivary microRNAs have emerged as a particularly compelling biomarker category for the non-invasive detection of early molecular alterations associated with oral carcinogenesis. Among these, miR-21, miR-34a and miR-320a have demonstrated promise in identifying lesions with an elevated likelihood of malignant transformation [19,23,24]. Furthermore, higher salivary concentrations of pro-inflammatory cytokines, including Interleukin-6 (IL-6), IL-8 and Tumor Necrosis Factor-Alpha (TNF-alpha), have been identified in patients with OPMDs and oral cancer, supporting their potential utility as markers for monitoring disease progression [20,21].

Despite the promising sensitivity and predictive capacity reported for many individual biomarkers, their specificity remains variable across studies. Current evidence does not support the use of any single biomarker as a sufficiently accurate, standalone predictor of malignant transformation [21,22]. From a clinical perspective, biomarkers are most valuable when integrated alongside conventional histopathological assessment; salivary biomarkers are particularly attractive in this context, given their simple, non-invasive collection method and suitability for serial monitoring [23]. Combining multiple biomarkers in panel-based approaches appears to improve both diagnostic performance and predictive accuracy compared with individual markers alone and such multimarker strategies could facilitate more precise risk stratification and support personalized OPMD management [24,25].

In summary, biomarkers have emerged as meaningful adjuncts to histopathological diagnosis in OPMDs. Although broader clinical validation is still needed, their capacity to support early detection and risk stratification positions them as important components of future precision diagnostic models, including those incorporating artificial intelligence (Table 1) [26].

Biomarker	Type	Function	Sensitivity	Specificity
p53	Protein	Tumor suppressor	Moderate-High	Moderate
Ki-67	Protein	Proliferation index	High	Moderate
Cyclin D1	Protein	Cell cycle regulator	Moderate	Moderate
EGFR	Receptor	Growth signaling	Moderate	Moderate
miR-21, miR-34a, miR-320a	miRNA	Post-transcriptional regulation	Moderate-High	Variable

IL-6, IL-8, TNF-a	Cytokine	Inflammatory mediators	Moderate	Variable
Salivary proteome	Multi-analyte	Disease monitoring	Emerging	Variable

Table 1: Summary of key biomarkers investigated in oral potentially malignant disorders [13,15-23]. miRNA: microRNA; IL: Interleukin; TNF-a: Tumor Necrosis Factor-Alpha; EGFR: Epidermal Growth Factor Receptor.

Artificial Intelligence and Deep Learning in Oral Pathology

The application of Artificial Intelligence (AI) to oral pathology encompasses a broad family of computational techniques that share the capacity to learn from data, identify complex patterns and generate diagnostic or prognostic outputs without explicit rule-based programming. Understanding the structure of these methods is essential for contextualizing their role in OPMD detection and risk prediction [25,26].

Machine Learning and Its Subcategories

Machine Learning (ML) is the foundational discipline within AI that enables computer systems to improve predictive performance from experience, without being directly programmed for each specific task. In oral pathology, ML has been applied to the analysis of clinical images, radiographic datasets and histopathological features, consistently improving the efficiency and reproducibility of diagnostic workflows [27]. ML approaches are broadly organized into three paradigms: supervised learning, in which models are trained on labeled data to generate predictions for new inputs; unsupervised learning, in which algorithms identify hidden structure within unlabeled data; and reinforcement learning, in which a model refines its behavior through iterative reward-based feedback [26,28].

Deep Learning and Convolutional Neural Networks

Deep learning is a specialized branch of ML that employs artificial neural networks with multiple processing layers to extract hierarchical representations directly from raw data. This capacity to learn complex, abstract features without manual feature engineering makes deep learning particularly well-suited to image-intensive medical tasks [27,28]. Convolutional Neural Networks (CNNs) represent the most widely applied deep learning architecture in oral pathology; they are specifically designed for image analysis and can automatically detect lesion-specific patterns in both histopathological slides and clinical photographs. CNNs have demonstrated high accuracy across a range of tasks, including lesion detection, disease classification and malignancy diagnosis [29,30].

AI-Assisted Histopathology and Whole Slide Imaging

AI-assisted histopathology involves the application of advanced computational algorithms to digitized tissue sections, enabling automated detection and classification of oral diseases, OPMDs and OSCC [31]. A critical enabling technology in this domain is Whole Slide Imaging (WSI), which converts conventional histological slides into high-resolution digital formats suitable for computational analysis. Pathologists can navigate and annotate these digital specimens at any magnification and the integration of AI algorithms with WSI has substantially expanded the analytical capacity of the field, supporting tasks that would be impractical by manual review alone [32,33].

Clinical Image Analysis and Computer-Aided Screening

Clinical image analysis employs AI to evaluate oral cavity photographs, identifying visual features associated with potentially malignant and malignant lesions. Through advanced image processing and deep learning techniques, these tools assist clinicians in detecting abnormalities, improving screening efficiency and supporting timely referral and diagnosis [34,35]. Smartphone-based AI screening tools have demonstrated particular promise for community-level OPMD detection in low-resource settings, where access to specialist care is limited [36].

Computer-aided screening and automated diagnostic systems represent complementary but distinct roles of AI: the former focuses on early identification of suspicious lesions from photographic images, while the latter aims to support definitive diagnostic classification using more complex multi-modal input. Deep learning-based computer-aided systems have shown strong performance in detecting and classifying oral lesions across several systematic evaluations [36,37]. Telepathology extends these capabilities further by enabling remote evaluation of tissue samples, connecting underserved regions with specialist pathology services through shared digital imaging networks [35].

Collectively, these AI-based technologies represent a substantial expansion of diagnostic capacity in oral pathology. Their integration into clinical practice will require careful attention to model validation, interpretability and equitable access [38].

Integration of AI and Biomarkers: Toward Precision Oral Medicine

Precision medicine, as applied to the dental setting, refers to a systems-based approach that integrates multi-level biological and clinical data to identify reliable markers of disease activity, guide therapeutic targeting and improve management of chronic conditions [39]. Saliva, in particular, has emerged as a rich and accessible source of molecular data, offering measurable indicators of physiological health, pathological processes and responses to therapeutic intervention in conditions ranging from periodontitis to oral cancer [38].

AI contributes to this precision-medicine framework by analyzing large volumes of clinical, imaging and molecular data simultaneously, identifying patterns that may precede visible signs of disease. In oral oncology, AI-assisted analysis has demonstrated the ability to improve early detection by integrating genetic profiles, imaging features and biomarker data into unified risk models, supporting clinicians in making more accurate and personalized decisions [39,40].

Surface-Enhanced Raman Spectroscopy and AI Integration

Surface-Enhanced Raman Spectroscopy (SERS) is a highly sensitive analytical technique that amplifies spectral signals through the use of plasmonic nanostructures, typically composed of silver or gold. This amplification allows the detection of biomolecules, including DNA, RNA, proteins, lipids and metabolites, at single-cell sensitivity levels [39,41]. SERS is label-free and can be applied to multiple biofluids, including blood, urine, saliva and cerebrospinal fluid, making it particularly suitable for non-invasive cancer diagnostics [42].

The challenge of early-stage cancer detection through manual spectral analysis lies in the subtlety of biochemical differences between malignant and benign conditions. AI resolves this challenge by automatically extracting relevant spectral features from raw SERS data, enabling cancer diagnosis, biomarker quantification and disease progression monitoring without subjective interpretation [43]. Machine learning techniques such as support vector machines, random forests and logistic regression have been successfully applied to SERS-based cancer classification tasks. More recently, deep learning architectures, including CNNs and recurrent neural networks, have outperformed manually engineered feature sets by learning directly from complex spectral datasets [39]. The convergence of SERS and AI thus represents a powerful analytical platform for oral cancer diagnostics. Applied to saliva-based biomarker panels, this combined approach may enable sensitive, non-invasive, real-time detection of OPMD-related molecular signatures, with implications for both population screening and individualized monitoring [40,44].

Multimodal Integration and Clinical Potential

The greatest clinical benefit from AI and biomarker technologies is likely to arise not from their individual application but from their integration within multimodal diagnostic frameworks. Combining salivary biomarker panels, AI-analyzed clinical images, digital pathology outputs and patient-level risk data may provide a substantially richer characterization of OPMD behavior than any single modality can achieve independently [38,40]. Such integrated approaches have the potential to identify high-risk patients earlier, guide surveillance intensity and ultimately reduce the proportion of OSCC cases diagnosed at late stages (Fig. 2) [45].

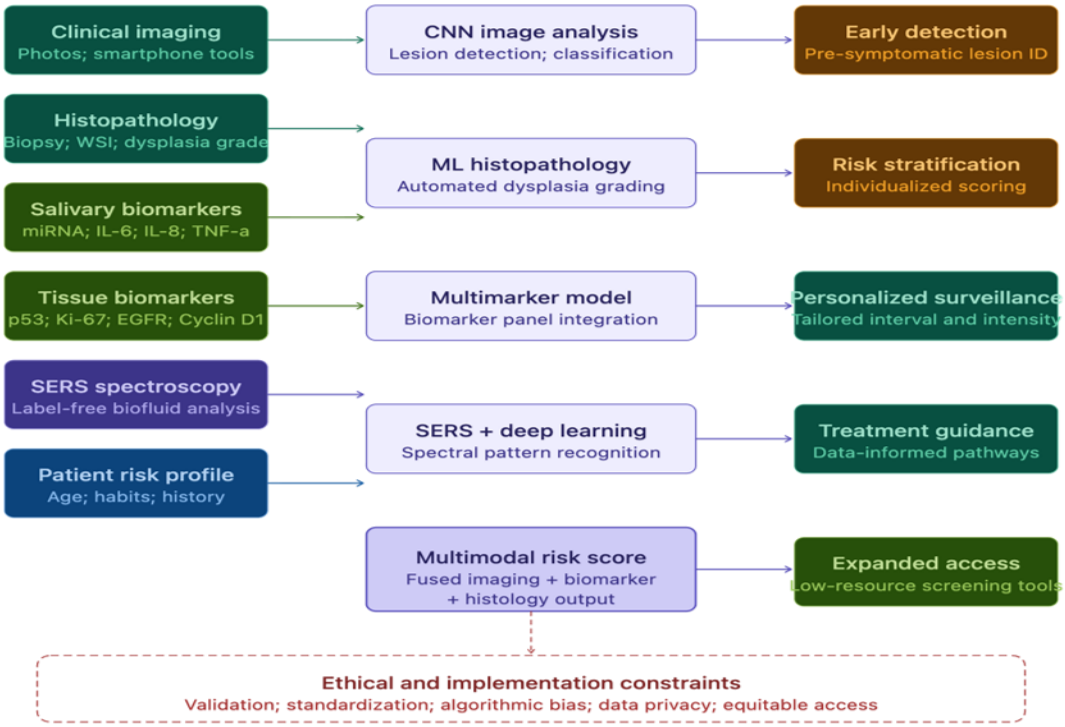

Figure 2: Integrated precision diagnostic framework for OPMDs. Six diagnostic input streams (clinical imaging, histopathology, salivary and tissue biomarkers, SERS and patient risk profile) feed into an AI core comprising CNN image analysis, machine learning histopathology, multimarker modeling and SERS-deep learning integration, generating a multimodal risk score. Clinical outputs include early detection, risk stratification, personalized surveillance and treatment guidance. Ethical constraints are shown at the base. CNN: Convolutional Neural Network; SERS: Surface-Enhanced Raman Spectroscopy; AI: Artificial Intelligence; OPMD: Oral Potentially Malignant Disorder. [25-30,31-35-40,49,50].

Limitations, Ethical Considerations and Future Perspectives

The progressive intersection of AI-based methodologies and molecular biomarker discovery is fundamentally redefining the protocols for OPMD identification, clinical evaluation and long-term surveillance. Contemporary empirical evidence suggests that computational frameworks, incorporating machine learning architectures, deep learning models, whole slide imaging platforms and advanced clinical image analytics, effectively augment specialist capacity for abnormality detection and diagnostic precision [43,44]. Concurrently, maturation in the field of molecular pathology has elucidated the complex biochemical pathways driving malignant transformation, offering novel pathways for individualized risk prediction and clinical management [47,48].

Crucially, the clinical utility of AI and molecular signatures is optimized when they are integrated within comprehensive diagnostic models rather than employed as isolated modalities. The synthesis of clinical examination findings, multimodal imaging datasets, digital histopathology and genomic or proteomic biomarkers facilitates a significantly more robust characterization of biological behavior and disease kinetics than individual assessments [37,47]. Such integrative diagnostic paradigms possess the potential to refine risk classification, enable early-stage therapeutic intervention and support highly personalized monitoring schedules for individuals affected by OPMDs [49].

Current Limitations

Despite these advances, important limitations constrain the current evidence base. Much of the available literature originates from studies with relatively small sample sizes, retrospective designs, heterogeneous methodologies and limited external validation [42,50]. These factors affect the reproducibility of reported findings and restrict their generalizability across diverse populations and healthcare environments. Variations in imaging protocols, biomarker assessment methods and algorithm development further impede direct comparisons between studies, underscoring the need for greater methodological standardization [51].

Ethical Considerations

Responsible implementation of AI in clinical healthcare settings requires careful attention to several intersecting ethical concerns. The increasing use of large clinical and molecular datasets necessarily raises questions related to patient privacy, data confidentiality, security governance and informed consent [49,50]. Algorithmic bias represents an equally important concern: AI models trained on datasets that insufficiently reflect population diversity may underperform in underrepresented groups, potentially widening existing health disparities [37,50]. Model transparency and interpretability, often referred to as "explainability," are also essential, since clinicians must be able to understand and critically evaluate AI-generated outputs before integrating them into patient care decisions [52].

Future Perspectives

Future research should move beyond proof-of-concept studies and prioritize large multicenter collaborations designed to validate AI models and biomarker-based strategies in real-world clinical settings [42,43]. Integrating clinical information, digital pathology, multimodal imaging and molecular biomarker panels may substantially improve diagnostic accuracy and predictive performance [37]. Expanding access to AI-assisted screening tools has the potential to reduce disparities in oral healthcare delivery, particularly in regions where access to trained oral pathology specialists remains limited (Fig. 3) [34,45].

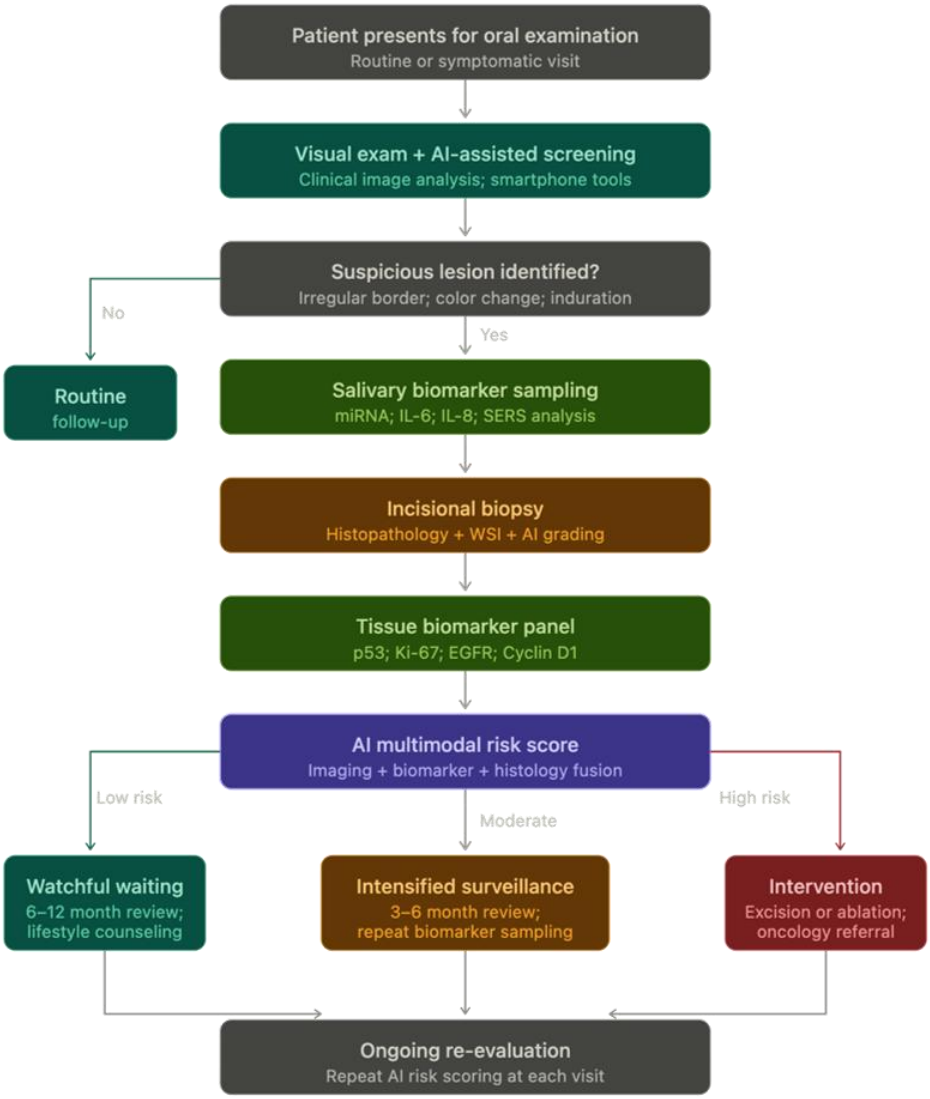

Figure 3: AI-assisted clinical decision pathway for OPMD management. Following visual screening, suspicious lesions proceed through salivary biomarker sampling, incisional biopsy with AI-assisted histopathology and tissue biomarker panel analysis. An AI multimodal risk score stratifies patients into watchful waiting (low risk), intensified surveillance (moderate risk) or active intervention (high risk), with repeat AI scoring at each follow-up visit. WSI: Whole Slide Imaging; EGFR: Epidermal Growth Factor Receptor; AI: Artificial Intelligence.

Continued collaboration among clinicians, researchers, data scientists, bioethicists and policymakers will be essential to ensure that these innovations are implemented responsibly and that they translate into meaningful, measurable improvements in patient outcomes across diverse populations [53].

Conclusion

The present review demonstrates that AI and molecular biomarker technologies represent complementary and synergistic advances in the early detection and risk stratification of OPMDs. Multimarker approaches, AI-assisted image analysis, deep learning histopathology and SERS-based diagnostics all show meaningful promise in improving upon the limitations of conventional histopathological assessment. Nevertheless, successful translation into routine clinical practice will depend on addressing persistent challenges related to validation, methodological standardization, data privacy, algorithmic bias and equitable access to care. When these conditions are met, the integration of AI and biomarker strategies has the potential to fundamentally shift the management of OPMDs toward earlier, more precise and more personalized intervention.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The project did not meet the definition of human subject research under the preview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was obtained from all participants included in the study.

Authors' Contributions

All authors contributed equally to this paper.

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