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LETTER TO THE EDITOR

Fragmented Thresholds, Unified Vision: Advancing Salivary Diagnostics for OSCC and OPMD

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ABSTRACT

Salivary diagnostics for oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMD) have advanced significantly, yet clinical translation remains limited. A key barrier is the lack of harmonized thresholds for candidate biomarkers, ranging from cytokines to genetic and epigenetic markers, across studies. This variability undermines biosensor calibration, impedes algorithmic integration, and restricts the scalability of AI and eHealth tools. Paradoxically, saliva is well-established in systemic disease diagnostics but remains undervalued in oral oncology. Recent initiatives, such as COST Action CA21140—INTERCEPTOR, are working to intercept oral carcinogenesis through collaborative innovation in molecular diagnostics and surveillance technologies. This letter calls for standardized protocols, multicenter validation, and digital integration to unlock saliva's full potential as a frontline diagnostic fluid. By addressing biomarker variability and embracing cross-sector collaboration, the field can move toward clinically actionable, digitally enabled solutions for early detection and monitoring of OSCC and OPMD.

Dear Editor,

The pursuit of early, non-invasive diagnostics for oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMD) has yielded a rich landscape of candidate biomarkers, ranging from cytokines such as IL-6 and IL-8 to genetic and epigenetic targets (e.g., ORAOV1, S100A7, LINC00657), transcriptomic signatures, and salivary microRNAs. Recent systematic reviews and meta-analyses confirm the diagnostic promise of some salivary biomarkers for oral cancer detection while highlighting the diversity and heterogeneity of other molecular targets currently under investigation [1–3]. Yet despite these advances, clinical translation remains elusive. A key barrier lies in the lack of harmonized biomarker thresholds across studies, which impedes the development of robust biosensors and digital diagnostic platforms.

This issue is not confined to inflammatory markers but extends across the biomarker spectrum, including methylated DNA markers, transcriptomic signatures, metabolomic profiles, and proteomic panels [1, 2, 4]. Across the literature, studies frequently define biomarker cutoff criteria based on local cohorts, analytical platforms, and experimental protocols. Consequently, even promising biomarkers may demonstrate inconsistent diagnostic thresholds across studies, resulting in a fragmented evidence base that complicates cross-population validation and large-scale clinical implementation [1–3].

Such variability poses a significant challenge for emerging computational approaches such as artificial intelligence (AI), machine learning (ML), and digital health platforms. These systems depend on consistent and high-quality input data to generate reliable predictions and clinically actionable outputs. When biomarker concentrations and diagnostic thresholds vary substantially between studies, algorithmic models may become prone to overfitting or misclassification. Similar challenges arise for biosensor calibration. Biosensors, too, suffer from this inconsistency: a device optimized to detect IL-8 elevation at a specific concentration threshold may perform inconsistently when applied to populations with different baseline biomarker distributions. Without harmonized reference

ranges and standardized reporting frameworks, the integration of salivary biomarkers into digital diagnostic ecosystems remains difficult [5].

At the same time, saliva has already demonstrated diagnostic potential across a range of systemic conditions, including metabolic, infectious, and neurological diseases, underscoring its value as a clinically relevant biofluid [6]. Paradoxically, despite being in direct contact with the oral microenvironment, making it uniquely suited for OSCC and OPMD detection, saliva remains underutilized in oral oncology diagnostics. The majority of oral biosensor development has focused on mechanical sensing or food-related applications, leaving a gap in disease-specific platforms [7]. This gap is not due to a lack of biomarker candidates. Instead, it reflects broader challenges related to analytical variability, lack of standardized validation pipelines, and limited integration between molecular diagnostics, biosensor engineering, and clinical workflows.

Recent advances in salivary proteomics, omics-driven biomarker discovery, and biosensor technologies have nevertheless demonstrated promising avenues for OSCC and OPMD detection [3, 7, 8]. However, multiple reviews emphasize that the transition from biomarker discovery to clinically deployable diagnostics requires larger multicenter validation studies, standardized sampling protocols, and harmonized analytical pipelines [3, 6, 8]. These steps are essential to transform promising biomarker signals into reproducible diagnostic tools.

Encouragingly, collaborative initiatives are emerging to address these translational barriers. One example is the COST Action CA21140—INTERCEPTOR (Interception of Oral Cancer Development), which brings together multidisciplinary research groups to investigate early molecular events in oral carcinogenesis and to promote the development of predictive diagnostic frameworks and risk stratification. Similar efforts are advancing globally through international networks such as the International Head and Neck Cancer Epidemiology (INHANCE) consortium, the Global Oral Cancer Screening Network coordinated by the International Agency for Research on Cancer (IARC), and multicenter translational platforms such as HEADSpAcE, alongside broader precision oncology and epidemiological initiatives. Such collaborative networks provide an important foundation for harmonizing research practices and advancing clinically relevant salivary diagnostics to reach digital readiness.

To move the field forward, several priorities should be emphasized:

1. Standardized protocols for saliva collection, processing, and biomarker quantification should be adopted across research centers.
2. Multicenter validation studies are needed to establish population-adjusted reference ranges and clinically meaningful diagnostic thresholds.
3. Biomarker panels should increasingly be integrated into AI and ML frameworks capable of modeling biological variability and generating probabilistic risk assessments rather than relying solely on binary outputs.
4. Biosensor platforms should evolve toward multiplexed detection systems capable of integrating multiple biomarkers within digitally connected diagnostic workflows.
5. The transition to digital health must be embraced through interoperable eHealth tools, cloud-based data sharing, and collaborative governance involving clinicians, researchers, technologists, and patients.

The digitalization of oral diagnostics is not a distant aspiration but an emerging necessity. As molecular discovery continues to expand the catalogue of candidate salivary biomarkers, the next critical step lies in harmonizing evidence, validating thresholds, and translating these findings into scalable diagnostic technologies. By addressing biomarker variability and strengthening collaborative frameworks for digital integration, saliva may ultimately realize its full potential as a frontline diagnostic fluid for early detection and monitoring of oral diseases.

Author Contributions

H.M. and **F.G.:** conceptualization, investigation, writing – original draft, writing – review and editing, project administration, data curation, supervision.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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