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Comment

Saliva as a Mirror of Breast Cancer: Promise, Pitfalls, and Proof-of-Concept. Comment on *Bel'skaya LV*, "Metabolic Portrait of Breast Cancer in Mixed Saliva". Frontiers in Bioscience-Landmark. 2026; 31: 47739.

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We read with interest the study by Bel'skaya describing a salivary "metabolic portrait" in breast cancer [1]. The concept of saliva as a non-invasive diagnostic fluid is attractive and clinically appealing. However, non-plasma biofluids require strict standardization and validation before biological conclusions can be drawn [2]. In this context, interpreting salivary metabolic changes as direct reflections of tumor biology appears premature. Several methodological and conceptual issues warrant further consideration. Recent transcriptomic research defines salivary biomarkers in breast cancer as proof-of-concept, requiring validation and biological correlation before clinical implementation [3]. Without these validation steps, the biological interpretation of any findings remains preliminary.

A central concern is the biological plausibility of using saliva to assess breast tumor metabolism. Bel'skaya suggests that systemic metabolic changes induced by breast cancer are detectable in saliva and can differentiate molecular phenotypes. However, the mechanistic pathway linking a distant breast tumor to salivary metabolites remains unclear. Saliva is produced by the salivary glands and reflects contributions from epithelial cells, immune activity, and the oral microbiome. Salivary molecular signatures may capture systemic signals but also reflect local oral biological processes [3]. Without parallel analyses of blood, plasma, or tumor tissue, it remains unclear whether the observed metabolic differences are tumor-derived or reflect local oral biology. This limitation reinforces the proof-of-concept nature of salivary biomarkers and limits biological interpretation of the findings.

Another major limitation is the variability in salivary composition, which is influenced by oral health, microbiome composition, diet, medication, smoking, and circadian factors. This variability is well recognized and requires strict pre-analytical control [2]. Many reported biomarkers, including cytokines and oxidative stress parameters, are strongly influenced by local inflammatory and microbial processes. Even in the absence of overt oral disease, subclinical inflammation or microbiome variation may alter salivary biomarker profiles. Without systematic control of these confounders, it remains unclear whether the observed differences reflect tumor-related biology or local processes. This substantially limits interpretability of the findings.

An additional concern is internal inconsistency within the authors' own work. Previous studies by the same group suggest that salivary alterations primarily reflect local processes, such as antioxidant defense mechanisms of the salivary glands, rather than tumor-derived signals [4]. In that context, oxidative stress markers were interpreted as part of the oral defense system rather than indicators of tumor biology. This contrasts with the current study, where similar findings are attributed to systemic tumor metabolism. This shift in interpretation raises concerns regarding over-attribution. If salivary markers mainly reflect local responses, their use as surrogates of tumor biology remains questionable. This inconsistency also affects the interpretation of subtype-specific findings.

The interpretation of subtype-specific salivary profiles warrants caution. The authors report distinct metabolic patterns across breast cancer subtypes, including HER2-low disease, and suggest biological relevance [1,5]. However, these findings remain exploratory and lack validation against tumor tissue or blood-based biomarkers [5]. Without such correlation, it is unclear whether these differences reflect tumor biology or indirect systemic or local effects. Given the complexity of breast cancer, attributing subtle salivary variations to specific subtypes risks over-interpretation, particularly given the limited separation between breast cancer subtypes.

Findings related to surgery further challenge biological interpretation. Salivary metabolic alterations partially normalize after tumor removal [6]. However, these changes remain incomplete and non-specific. Many parameters exhibit values intermediate between those of the control and preoperative states. Postoperative profiles also do not clearly distinguish between tumor-related subgroups. If

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salivary metabolites directly reflected tumor biology, consistent normalization would be expected. Instead, these findings suggest that salivary profiles are influenced by systemic or local factors. Subtype separation remains inconsistent, further limiting biological interpretation [6].

Linking salivary metabolic changes to cancer pathways warrants caution. The authors associate alterations in amino acids, lipids, and enzymatic activity with processes such as glycolysis and oxidative stress. However, these associations are indirect and lack mechanistic validation. Many metabolites are non-specific and may originate from diet, oral microbiota, or local tissue turnover. Advanced analytical studies indicate that cancer detection in saliva relies on complex molecular fingerprints rather than individual metabolites [7]. Attributing isolated changes to oncogenic pathways therefore risks over-interpretation. Without validation against tumor or plasma metabolomics, such conclusions remain speculative.

In conclusion, saliva-based diagnostics represent a promising, patient-friendly approach. However, current evidence supports their feasibility at the proof-of-concept level but does not establish them as direct indicators of breast tumor biology. The lack of mechanistic validation, susceptibility to confounding, and reliance on indirect interpretation limit their clinical applicability. Rigorous standardization, biological correlation, integration with tumor- and blood-based data, and validation in independent cohorts are required before clinical implementation.

Author Contributions

WT: Writing – review & editing, Writing – original draft, Validation, Methodology, Conceptualization. The author has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflicts of Interest

The author declares no conflicts of interest.

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