# SALIVAOMICS– A NOVEL IMPLEMENT FOR ORAL CANCER DETECTION

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*Abstract*
Salivaomics is the use of salivary biomarkers for the detection of systemic and oral diseases. Oral cancer is the sixth most prevalent cancer in the world. In India due to the various lifestyle practices it is much more frequently encountered. The need of the hour is a reliable, dependable, non- invasive and easy to use diagnostic modality to help in the early detection of this dreaded disease. Salivary diagnostics, commonly known today as a liquid biopsy can play a major role in screening and investigation for the disease. Today world –wide several researches are being done to validate the use of saliva as a diagnostic implement. Salivary proteomics, salivary metabolomics, trancriptome and microbiome are widely being studied for tapping its potential for early detection for various malignancies. This article discusses about the novel role that saliva plays for cancer detection.

## Introduction

Oral cancer along with the oropharyngeal cancer is the sixth most commonly occurring malignancy in the world. (1)Oral cancer is a major threat to the Indian society. India ranks high among the countries with a greater prevalence of oral cancer. The incidence of oral cancer is on a steady rise since the last two decades.More than 100,000 cases of malignancies occurring in the oral cavity and lip region are reported annually.(2)There has been a lot of advancements for oral cancer detection and its management but still the mortality rates have not changed. (3)The rise of oral cancer in India can be attributed to several lifestyle factors like increased tobacco usage, betel quid chewing, alcohol consumption and a lack of diet consumption that is rich in fruits and vegetables.(4)  Today there is a lack in awareness about oral cancer, its causes, signs and symptoms. Hence, the need of the hour is a screening and diagnostic tool which is non-invasive, with high accessibility and ease of use.

Saliva is popularly known as a liquid biopsy tool as it is a non-invasive diagnostic implement to diagnose several systemic conditions.(5)Saliva is a bio-fluid that is secreted by the salivary glands into the oral cavity and is highly useful for diagnostic applications.(6)The success of the treatment and prognosis of oral cancer largely depends on early diagnosis. Biomarkers are now widely used for diagnosis of various systemic conditions. Biomarkers are chemical substances that are widely detected in serum for the evaluation of pathological conditions. Serum collection is an invasive procedure, hence today salivary collection and its detection is largely accepted and is easy to use. Today about 100 potential biomarkers are said to be present in saliva of oral cancer patients. (7)Saliva contains components of proteins, metabolites, DNA, RNA, and microbiota. (5) The success of the ongoing researches in the field of salivary biomarker has proven that salivaomics is a promising future for the early detection of oral cancer.

## Salivaomics (8)

The concept of "salivaomics" was proposed in 2008 to represent the rapid development of salivary biomarkers in the field of proteomics, transcriptomics, metabolomics and microbiomes. (8) The metabolome can be defined as the presence of small molecular metabolites in a biological sample which are also the components of metabolic

intermediates in biochemical pathways, hormones and other signalling molecules. (8) The (NIDCR) National Institute of Dental and Craniofacial Research has discovered that the salivary proteome consists of a massive, 1166 proteins and the salivary transcriptomics consists of about 3000 mRNA molecules. Studies have also shown that the salivary microbiome could be used in the detection of cancer.(6)
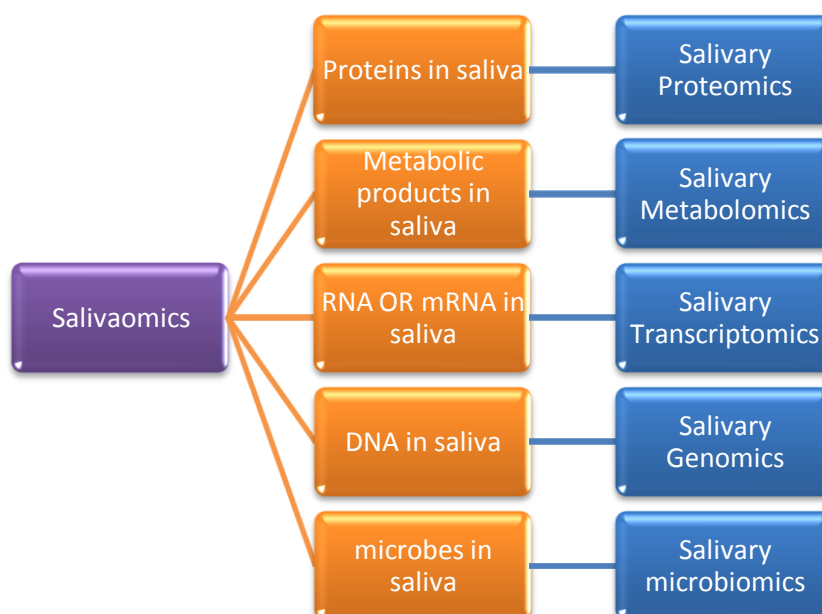


*Figure 1- showing the branches of Salivaomics*

## Salivary biomarkers

Saliva as a bio-fluid has been extensively studied biochemically and physiologically. Salivary biomarkers play an important role in non-invasive detection of various diseases. Biomarkers are cellular, biochemical, molecular, or genetic alterations by which a normal, abnormal, or simply biologic process can be recognized or monitored. Salivary biomarkers can also be used to detect premalignant disorders and oral cancer.(9)

Adequate storage, collection and processing of salivary specimen is needed to assess the salivary biomarkers. The whole saliva contains the oral epithelial cells, protein, DNA, and RNA species that allow for detection of the various cellular changes related to cancer. (10) Saliva contains proteins and nuclear material derived from living cancer cells and inflammatory cells as it is in direct contact with the oral tissues.The saliva should be adequately preserved with protease inhibitors in case of long time preservation to prevent protein denaturation of saliva. Inorganic compounds likeNa, Ca, F, and Mg have also been reported to be increased in oral cancer. (7)A study by Cheng et al shows that the presence of salivary apoptotic cells was shown to be increased when compared to control patients. (11)

## Salivary Proteomics

Salivary proteomics is a branch of salivary diagnostics and salivaomics where the proteins in saliva are detected. This calls for high accuracy testing to detect even the minute increase in salivary protein changes. The source of salivary peptides and proteins is primarily from the major and minor salivary glands, gingival sulcular fluid, and transudate from plasma.(12)In a study on proteomics done by Hu *et al*, they have concluded that proteins that are abundant in saliva includes M2BP, profilm, CD59, MRP14, catalase, Histone H1, S100A12, S100P and hematopoietic lineage cell-specific protein. (13)Other common biomarkers to detect oral cancer are cancer antigen-125 (CA-125), cytokeratin and tissue polypeptide antigen have been reported present in saliva of oral cancer

subjects.(14) Chemokines like epidermal growth factor, vascular endothelial growth factor, interleukins-6 and -8, -4and-10, endothelin and tumour necrosis factor are also extensively studied for their presence in saliva.

## Salivary Metabolomics

"Metabolomics is a systemic study of metabolites, which are small molecules generated by the process of metabolism." (14)The metabolites in saliva includes the metabolic hormones and receptors present in the serum. According to Zolotukhin, the salivary metabolomics also include the hormonal modulators of energy intake and output.(12)In a research done by Wei *et al*, on salivary metabolomics, they analysed that the salivary levels of phenylalanine,GABA and valine were significantly lower, while lactic acid n-eicosanoic acid and were considerably increased, in oral cancer patients.(15)

## Salivary Transcriptomics

Initially, the normal salivary transcriptome was estimated to be around 3,000 mRNAs. (16) The salivary transcriptome has immense diagnostic potential with a high sensitivity and specificity. According to D T Wong, four genes - IL-8, ornithine decarboxylase, spermidine acetyltransferase and IL-1βare present in oral cancer patients and can be successfully used for screening and diagnosing in malignancy states. (16)
Non-coding RNAs are emerging as new mediators of various biological functions, hence its role in oncogenesis is very important. It was discovered that salivary miR-125a and miR-200a were expressed differentially in oral cancer. (17)

## Salivary Genomics

In oral malignancy states, the genetic material like DNA can be obtained from the living cancer cells as sali(18)va is in constant contact with the oral cancer lesion. It was assessed that TP53 is a gene which shows loss of heterozygosity and mutations in oral cancer patients. (19)

## Salivary Microbiomics

The human body fosters a great number of microbial colonies, organized into biofilms.The oral cavity harbours various microbiota which is in harmony with heath and its disturbances may cause disease. A research shows that oral microbiome is charachteristic of different population group and communities.(20) It is known that microbes are the etiological factor for about 20% of all malignancies occurring in human beings. In oral cancer saliva, the phylum Firmicutes showed most abundance populations followed by Actinobacteria, Proteobacteria, Fusobacteria and Spirochaetes. (21)

## Discussion

Development of diagnostic aids will lead to increasingly sensitive and specific detection of pre-malignancy and malignancy states. Potential salivary biomarkers are necessary to observe and detect oral cancer. This is required for effective prevention and therapeutic strategies. In the recent years, many non-invasive diagnostic techniques have gained popularity for the early detection of oral cancer. Saliva has recently gained immense popularity as a diagnostic fluid, as several biomarkers are considerably elevated in saliva.(22)

Salivaomics will eventually result in alleviation of the public health burden imposed by oral cancer. There are several advancements being made for the early detection of oral malignant and premalignant lesions. Salivaomics is being developed extensively to accurately diagnose various cancerous conditions. Biomarkers are measurable and quantifiable biologic parameters that may serve as indicators for health and physiology-related assessments, such as pathogenic processes, environmental exposure, disease diagnosis and prognosis or pharmacologic responses to a therapeutic intervention.(23)

## Conclusion

Individual salivaomic profiles have a great potential to accurately detect oral cancer. This article has reviewed only a drop of water in the large oceanic knowledge of salivaomics. This technology has an immense ability to non-invasively and accurately diagnose oral cancer. Hence, we can safely conclude that salivaomics can be labelled as " liquid biopsy of the future."

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