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Supplement to PennWell Publications

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A Peer-Reviewed Publication
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Historically, there have been a number of factors that have led to a slower than expected uptake in salivary diagnostics, and several barriers to widespread implementation of salivary diagnostics still exist. These include a lack in standardization of methods used to harvest saliva samples; a requirement for normalization of methods used to interrogate salivary biomarkers; a current lack of understanding of changes in salivary composition due to age; the impact of diurnal and circadian variation in molecules in saliva; and salivary constituent composition based on diet and fluid intake, among many others.32 In the past, funding for specific projects targeting salivary biomarkers has also been difficult to find, providing less incentive for diagnostic and biotechnology companies to pursue options looking at saliva.

Discussion
One of the hallmarks of health care is the critical importance of early disease detection. For example, blood tests are commonly used to detect and monitor a wide variety of diseases and conditions. Diagnostic tests typically utilize various biological fluids including whole blood, serum, plasma, cerebrospinal fluid, peritoneal fluid, drainage fluid, and urine, among others.25 Biomarkers indicative of many diseases are present in the serum in relatively strong concentrations compared to levels in oral fluid specimens. Until recently, identification of the minute concentrations of biomarkers in oral fluid was beyond the detection capabilities of available laboratory technologies. This is not surprising, as disease biomarkers in serum are commonly present in the microgram range (i.e., one millionth of a gram).

In oral fluids, on the other hand, analytes may be present in concentrations of one billionth to one trillionth of a gram (i.e., nanograms and picograms). Recently the advent of new, more sensitive technologies such as next generation sequencing, mass spectrometry, and homogeneous immunoassays, and even quantitative lateral flow technologies for point of care applications, allows adequate detection and quantification of these lower level biomarkers.39

Saliva mirrors bodily health and well-being since most of the biomolecules that are present in blood or urine are also present in saliva.25 Yet utilizing saliva as a diagnostic medium provides a number of advantages over serum, such as non-invasive collection, a virtually unlimited supply, cost effectiveness, and patient comfort. In addition, salivary collection does not require highly-trained professionals such as phlebotomists. Rapid screening of large populations is also readily facilitated using salivary diagnostic methods. When required, sample transportation is also far more cost effective, and saliva also eliminates certain cultural “taboos” associated with blood collection prevalent in some cultures.26

Saliva is comprised of multiple secretions from the parotid, submandibular, sublingual, and other minor glands. It contains a variety of biomolecules, including DNA, RNA, proteins, metabolites, and microbes. Biomarker assays can be developed that target changes in the salivary concentration of these biomolecules, which can then be used to identify early stages of oral and systemic diseases, monitor disease prognosis, stratify risk, and evaluate response to treatment.1,2,3

In order for biomarkers of systemic diseases to appear in the saliva, an action or some type of impact is needed that affects the salivary glands. More specifically, this would be a disease or condition somewhere in the body other than the oral cavity that would exert an effect on the salivary glands in order for the biomarkers to make their way into the saliva. The exact mechanism whereby a distal disease produces biomarkers that appear in the saliva has not yet been determined, although a number of mechanisms for transfer to the oral cavity are known, including passive diffusion36 and through the gingival crevices as an “ultra-filtrate” of blood.39 Some early mouse model cancer studies also suggest that the production of growth factors in tumor tissues alters mRNA expression in salivary glands, causing biomarkers to appear in saliva.1,4

Potential salivary biomarkers are present or have already been identified for a wide variety of diseases. Sjogren’s syndrome (SS), for instance, is an autoimmune disorder that typically presents with a reduction in salivary and lacrimal gland secretions, and associated endocrine disturbances. Salivary protein analysis in SS patients is under investigation as an early diagnostic tool. The present methods to diagnose SS are invasive, expensive, and non-conclusive in many cases.34 Biomarkers for cystic fibrosis (CF), another autoimmune condition, are also being investigated, and appear to be related to oxidative and inflammatory processes ongoing in these individuals.7
Cardiovascular diseases are the leading cause of death in the United States, and levels of several salivary biomarkers have been identified for cardiovascular disease diagnosis, including C-reactive protein (CRP), NT-pro BNP, and cardiac troponin. In the future, salivary tests will ultimately replace blood tests for the detection of cardiovascular diseases. Studies have demonstrated that salivary levels of CRP correlate with plasma CRP levels obtained from individuals at risk for cardiovascular complications. Similarly, reports confirm that levels of NT-pro BNP correlate well between saliva and serum.

Diagnosis of breast cancer, which is the second leading cause of death and the most common form of cancer in women, currently depends on physical examination and imaging technology. Breast cancer is one of the most widely studied diseases, and early detection is universally regarded as a critical factor for favorable long-term outcomes. The sensitivity and specificity of physical examination and mammography is far from ideal, and this highlights the need for methodologies with greater accuracy. The aim of developing a non-invasive, salivary test for early detection of breast cancer is to provide clinicians with a way to identify individuals needing closer monitoring and additional imaging. A secondary but highly important aim is reduction in the number of unnecessary biopsies. The American Cancer Society estimates that a staggering 80% of breast biopsies are unnecessary. Recent studies have confirmed that a number of salivary biomarkers for breast cancer have been discovered with the ability to detect breast cancer with high specificity and sensitivity.

Another area of interest is diabetes mellitus, where specific biomarkers have the potential to provide early detection and improved glycemic control in patients. Earlier work has shown the availability of protein biomarkers for type 2 diabetes in serum samples. More recent research has concluded that these serum markers can also be measured in saliva, and that biomarkers emerge over time as diabetes disease develops. The clinical significance of diabetes biomarker identification is as a disease risk evaluation tool. Salivary biomarkers have the ability to increase the predictive nature of diabetes risk scores and provide an economical strategy for type 2 diabetes screening. Risk factors are predictive over time, so periodic assessment is critically important.

The most common cause of cancer-related death in men and women is lung cancer. Symptoms are frequently absent until the disease has metastasized, leading to a poor prognosis. Early detection offers the potential to reduce morbidity and mortality, yet conventional diagnostic methods are not suitable for large population screening due to the expense involved and a lack of accuracy. One important study identified a panel of five salivary biomarkers, which can differentiate lung cancer patients from cancer-free individuals with 93.75% sensitivity and 82.81% specificity.

A group headed by Dr. David Wong at UCLA has developed an exciting test called EFIRM™ that is based upon a "liquid biopsy" assay that uses saliva as the sample matrix. The EFIRM test detects circulating tumor DNA (ctDNA) in the saliva (or blood) of lung cancer patients through the implementation of an electric field-induced release and measurement (EFIRM) technique. It is currently directed towards patients with non-small cell lung carcinoma (NSCLC) and tyrosine-kinase-inhibitor-sensitizing mutations (exon 19 deletion and exon 21 L858R substitution). The EFIRM test has attracted attention in the popular media and may eventually revolutionize cancer testing, as the same principles may be applied to other cancers as well.

Salivary diagnostic technology is also widely used in forensics, where samples are obtained from glasses, cigarettes, envelopes, and food products, among many other sources. Dry DNA samples from saliva are relatively stable, enabling the use of the items noted above for analysis. Crime suspect identification and legal actions to determine paternity both utilize salivary evaluation of blood group antigens, and a significant number of molecular tests now utilize saliva as a viable option for collection and testing purposes. The applications to home collections and consumer-based testing are on the rise.

Technologies based on salivary diagnostics have been available to the dental profession for years. Salivary testing for oral bacteria, HPV, and genetic susceptibility to periodontal disease are just a few of many examples of specific tests that have been available from a variety of companies for some time.

Oral squamous cell carcinoma (OSCC) is the most common type of cancer in the oral cavity. Approximately 40,000 new cases are diagnosed with 8,000 deaths annually. This disease is the sixth most common cancer worldwide, with an average survival rate of 60%. This is largely the result of late stage diagnosis (stages III and IV), frequent relapses, reoccurrence, and secondary tumors. Early detection of OSCC utilizing protein biomarkers in saliva could facilitate identification during the initiation and progression of OSCC, with improved outcomes and survival rates. To date, many protein and mRNA salivary biomarkers have been discovered that can identify OSCC with a high degree of sensitivity and specificity. The most accurate protocol would offer detection of multiple biomarkers, since OSCC is multifactorial and has a heterogenic pathogenesis. In the case of OSCC, it is likely that multiple biomarkers may be necessary to reach the high sensitivity and accuracy required, and that a single biomarker may not be sufficiently adequate for use as a diagnostic tool. Cancerous lesions in the oral cavity are in continuous contact with saliva and this direct contact is one of the major reasons that salivary diagnostics for OSCC are very promising.

Infection with human papilloma virus-16 (HPV-16) is a major risk factor for oropharyngeal squamous cell carcinoma (OPSCC). The prevalence of HPV-positive OPSCC is rising in the western world, with more than 90% of cases being attributed to HPV-16 infection. The current protocol for detecting HPV-16 tumors involves tissue biopsy; however, when tumors
are anatomically hidden, detection can be difficult. Sites that can be difficult to access include the tonsillar crypts and base of the tongue. A non-invasive alternative to biopsy for HPV-16 detection would have a number of advantages. Detection of HPV-16 in oral rinse specimens is presently commercially available using the OraRisk HPV 16/18/HR Assay (OralDNA Labs, Eden Prairie, Minnesota). The applications for HPV-16 detection are not restricted to OPSCC. Applications include HPV status in patients with head and neck squamous cell carcinoma as well as a potential diagnostic aid for HPV infection.

There are presently a number of commercially available salivary diagnostic tests for periodontal bacteria. These tests utilize a salivary sample obtained in the dental office, which is then sent to an offsite testing laboratory. The availability of an accurate salivary marker for periodontitis should be applicable to entire populations regardless of systemic diseases, smoking habits, or number of teeth of the individuals in a given population.

A 2015 study investigated a panel of four periodontal pathogens as biomarkers indicative of periodontitis. Previous studies relied on harvesting bacterial samples from subgingival sites, but collection of more readily available saliva specimens offers a number of benefits. These include the ability of non-dental healthcare professionals or patients themselves to collect the sample, ease of transportation, elimination of pain, and user friendliness, among others. This specific study evaluated the salivary concentrations of Porphyromonas gingivalis, Tannerella forsythia, Prevotella intermedia and Aggregatibacter actinomycetemcomitans to determine if these bacteria could serve as adequate biomarkers for the diagnosis of periodontitis. The study also looked at the diagnostic effectiveness of the combination of bacteria and each individual species at the same time. The aim of the study was to find salivary biomarkers that could provide an accurate assessment of periodontal risk. The authors concluded that the combination of P. gingivalis and T. forsythia had the strongest association with periodontitis when compared to the four bacteria analyzed individually or in combination. Applications for this type of risk assessment test might include home testing, collection at remote sites, and geriatric collection and testing, among others. Chairside bacterial identification tests are also currently under development. In addition, researchers are investigating genetic, microbial, and protein biomarkers with the objective of enabling patient screening, monitoring, and treatment planning. The capability to provide risk determination at the clinical level can potentially reduce or eliminate disease occurrence and provide earlier intervention with improved treatment outcomes.

A different approach utilizing salivary diagnostics for periodontal disease involves identification of biomarkers associated with bone remodeling as an alternative to bacterial identification. Researchers have identified and examined levels of biomolecules associated with biological events occurring during bone remodeling in patients with chronic periodontitis. In their study, the protein biomarker was identified, which was 18-times higher in periodontitis patients than in normal, healthy subjects, with the ability to discriminate between periodontal disease and normal health status. The study authors concluded that their findings, along with those from other studies, suggest that the combined presence of elevated levels of a panel of salivary biomarkers representing the three biological phases (inflammatory, connective tissue destruction and bone remodeling) of periodontal disease may offer the sensitivity and specificity for screening for periodontal disease in non-dental settings as well as potentially providing an understanding of the dynamics of the periodontitis lesion, and to the use of biofluid panels as adjuncts in the diagnostic assessment of periodontal disease in the near future.

A further study from 2014 examined the association between three salivary biomarkers and clinically evident periodontal parameters. The concentrations of these biomarkers, MMP-8, interleukin (IL)-1β, and P. gingivalis, were used to calculate a novel risk score called the cumulative risk score (CRS), for each of the 493 enrolled study subjects. The authors concluded that together, the salivary concentrations of the three biomarkers were associated with clinical and radiographic measures of periodontitis more strongly than any of the markers alone, regardless of the coronary artery disease status of the study subjects.

The consensus among various studies appears to indicate the importance of using a variety of biomarkers rather than relying on a single biomarker. Given the progressive nature of many diseases, including periodontal disease, the use of multiple biomarkers (i.e., multiplexing), should provide a greater level of sensitivity and specificity and lead to an enhancement in the accuracy of the results.

Conclusions

Fortunately, over the last five years there has been a dramatic increase in the interest in salivary diagnostics as a result of a few significant factors, including the availability of new technologies, both for saliva collection and testing, standardization of collection protocols, more effective technologies to find relatively small quantities of specific analytes in saliva, as well as more effective downstream technologies to quantify low level analytes in oral specimens. Other contributing factors include greater knowledge of saliva sample preparation, including stabilization of samples, isolation of sub-components of saliva, and more effective means of purifying complex saliva matrices.

The availability of an at-home oral fluid test for HIV allowing members of the general public to test themselves for HIV in the privacy of their own homes has paved the way for multiple other tests using saliva, and the impact over the next 5 to 10 years is expected to be exponential. In the areas of drug abuse testing, law enforcement professionals in the near future will be able to detect levels of various drugs in saliva at the roadside in 5 minutes or less and apprehend drivers suspected of driving...
under the influence of a number of illicit drugs. Saliva is already in widespread use for the detection of nucleic acids (DNA and RNA) and many hundreds of thousands of people every year have their genome tested by companies such as 23andMe and Ancestry.com in an attempt to identify specific genetic traits or determine where they came from. Neurodegenerative diseases such as Parkinson’s and Alzheimer’s diseases are being investigated in saliva and work is ongoing to determine tendencies to commit suicide or the incidence of traumatic brain disorder. One other area that will be of direct relevance to the dental community is the investigation of various biomarkers in saliva associated with sleep disorders.

Many of the disease targets under development at this time could end up as chairside or at-home tests as the overall in vitro diagnostic market becomes more “patient-centric”. The future of salivary diagnostics is indeed very bright and is forecast to move into many areas of disease detection diagnosis and patient monitoring. This is all very good news for the patient!

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1. Which of the following statements is correct?
   a. Biomarkers of disease in serum are commonly found in picogram quantities.
   b. In oral fluid, analytes are commonly present in microgram quantities.
   c. In oral fluid, analytes can be in nanogram quantities.
   d. None of the above

2. Diagnostic tests utilizing biological fluids obtain samples from:
   a. Blood
   b. Cerebrospinal fluid
   c. Peritoneal fluid
   d. All of the above

3. Which of the following are advantages of using salivary testing compared to serum?
   a. Invasive nature of salivary testing.
   b. Virtually unlimited supply of saliva.
   c. Blood testing is more cost effective than salivary testing.
   d. Salivary testing is less comfortable for patients than blood testing.

4. Saliva is comprised of secretions from the:
   a. Parotid
   b. Submandibular
   c. Minor salivary glands
   d. All of the above

5. Which of the following statements is true regarding salivary biomarkers?
   a. The exact mechanism whereby a distal disease produces biomarkers that appear in the saliva has not yet been determined.
   b. The exact mechanism whereby a distal disease produces biomarkers that appear in the saliva has been determined.
   c. Some type of impact on the salivary glands is unnecessary for biomarkers of systemic diseases to appear in the saliva.
   d. Biomarkers automatically appear in the saliva.

6. Salivary biomarkers are under development for which of the following conditions?
   a. Sjogren’s syndrome
   b. Cystic fibrosis
   c. Diabetes mellitus
   d. All of the above

7. Current methods to diagnose Sjogren’s syndrome are:
   a. Invasive
   b. Inexpensive
   c. Highly accurate
   d. Non-invasive

8. Biomolecules normally contained in saliva include all of the following except:
   a. DNA and RNA
   b. Proteins
   c. Gastric enzymes
   d. Metabolites

9. The consensus among researchers appears to indicate the importance of using:
   a. A single biomarker
   b. A variety of biomarkers
   c. Three or more biomarkers
   d. No consensus exists at this time

10. Salivary diagnostic approaches to the identification of periodontal disease include:
    a. Genetic biomarkers
    b. Protein biomarkers
    c. Bone remodeling biomarkers
    d. All of the above

11. A 2014 study by Salminen et al concluded that:
    a. Concentrations of CRS, (MMP)-8 and (IL)-1β were the best markers to predict the presence of periodontal disease.
    b. Concentrations of P. gingivalis, (IL)-1β, and CRP were the best markers to predict the presence of periodontal disease.
    c. Concentrations of (MMP)-8, interleukin (IL)-1β, and P. gingivalis were the best markers to predict the presence of periodontal disease.
    d. Concentrations of P. gingivalis and (IL)-1β were the best markers to predict the presence of periodontal disease.

12. The ability to provide chairside periodontal bacterial identification could potentially:
    a. Increase periodontal disease occurrence.
    b. Improve periodontal treatment outcomes.
    c. Decrease the longevity of favorable therapeutic results.
    d. Reduce the efficacy of biofilm control devices.

13. Which of the following statements is correct regarding oral squamous cell carcinoma (OSCC)?
    a. OSCC is the most common type of oral cancer.
    b. OSCC incidence is decreasing.
    c. OSCC is unrelated to the presence of human papilloma virus.
    d. Approximately 80,000 new cases of OSCC are diagnosed annually in the US.

14. Which of the following is correct regarding human papilloma virus-16 (HPV-16) and oropharyngeal squamous cell carcinoma (OPSCC)?
    a. The prevalence of HPV-positive OPSCC is rising, with less than 60 % of cases being attributed to HPV-16 infection.
    b. The prevalence of HPV-positive OPSCC is rising, with more than 90 % of cases being attributed to HPV-16 infection.
    c. The prevalence of HPV-positive OPSCC is decreasing, with more than 90 % of cases being attributed to HPV-16 infection.
    d. The prevalence of HPV-positive OPSCC is rising, with less than 80 % of cases being attributed to HPV-16 infection.

15. Which of the following is accurate regarding oral cancer detection?
    a. The current protocol for detecting HPV-16 oral tumors involves biopsy.
    b. When tumors are anatomically hidden, detection can be difficult.
    c. A non-invasive alternative to biopsy for oral cancer detection would not be advantageous.
    d. Both a and b.

16. Which of the following is true regarding oral cancer?
    a. The survival rate of OSCC is 50%.
    b. OSCC is the fifth most common cancer worldwide.
    c. Eight thousand deaths annually are attributable to oral cancer.
    d. None of the above.

17. The most common cause of cancer–related death in men and women is:
    b. Lung cancer in men only.
    c. Lung cancer in women only.
    d. Lung cancer for both men and women.

18. Biomarkers for diabetes mellitus:
    a. Have the potential to improve glycemic control.
    b. Will likely need to be evaluated periodically over time.
    c. Will likely need to be evaluated periodically over time.
    d. Both a and c.

19. Which of the following is true regarding salivary testing for cardiovascular diseases?
    a. Biomarkers of cardiovascular disease have been identified including C-reactive protein (CRP) and cardiac troponin.
    b. Biomarkers of cardiovascular disease have been identified including CRP and MMP-8.
    c. Biomarkers of cardiovascular disease have been identified including CRP and MMP-8.
    d. Biomarkers of cardiovascular disease have been identified including CRS and cardiac troponin.

20. Commercially available salivary tests presently include:
    a. Periodontal pathogens
    b. HPV
    c. Lung cancer
    d. Both a and b

21. Which of the following is accurate regarding utilization of forensic salivary testing?
    a. Dry salivary samples are not sufficiently stable for sampling.
    b. Paternity can only be determined by blood testing.
    c. Saliva samples can be obtained from used envelopes.
    d. Saliva samples cannot be obtained from food products.

22. A 2012 study by Al-Sabbagh et al:
    a. Examined bone remodeling as an indicator of periodontal disease.
    b. Examined bone remodeling as an indicator of periodontal disease.
    c. Saliva samples can be obtained from used envelopes.
    d. Found that the MIP-1α biomarker level was 28 times higher in disease vs. health.
23. A 2015 study of periodontal pathogens by Salminen et al concluded that:
   a. T. forsythia and P. intermedia were the best indicators of periodontitis.
   b. T. forsythia and P. gingivalis were the best indicators of periodontitis.
   c. P. intermedia and P. gingivalis were the best indicators of periodontitis.
   d. P. gingivalis and A. actinomycetemcomitans were the best indicators of periodontitis.

24. Which of the following is true regarding chairside salivary testing for periodontitis?
   a. The objective is to enable patient screening, monitoring and treatment planning.
   b. Researchers are investigating genetic, microbial and protein biomarkers.
   c. Researchers are investigating only genetic and protein biomarkers.
   d. Both a and b.

25. Which of the following is true regarding commercially available salivary diagnostic tests for periodontal bacteria?
   a. Patients with systemic diseases cannot be tested.
   b. Salivary samples are obtained and evaluated in the dental office.
   c. Patients who smoke are not candidates for testing.
   d. None of the above

26. Salivary testing for the presence of diabetes:
   a. Is presently available for type 1 DM.
   b. Is presently available for type 2 DM.
   c. Is presently available for both types 1 and 2 DM.
   d. Is not presently available.

26. The EFIRM™ liquid biopsy technique is an acronym for:
   a. Electric field-induced release and measurement.
   b. Electric field-induced release and monitoring.
   c. Electric field-induced removal and measurement.
   d. Electric field-induced removal and monitoring.

27. Which of the following is accurate regarding salivary diagnostic testing?
   a. Transportation of salivary samples is more expensive than blood samples.
   b. Blood sampling is appropriate for all cultures.
   c. Rapid screening of large populations is enhanced with salivary diagnostics.
   d. Salivary samples are less stable than blood samples.

28. Biomarkers of disease that are present in saliva may be derived from:
   b. Active diffusion.
   c. As an ultra-filtrate of saliva.
   d. As an ultra-filtrate of gingival crevicular fluid.

29. Biomarkers for cystic fibrosis (CF) appear to be related to:
   a. Oxidative processes in individuals with CF.
   b. Inflammatory processes in individuals with CF.
   c. Both a and b.
   d. Neither a or b.

30. Which of the following is accurate regarding breast cancer detection?
   a. The sensitivity and specificity of physical examination and mammography is less than ideal.
   b. A goal of finding salivary tests for breast cancer detection is to reduce the number of biopsies.
   c. Early detection is universally regarded as a critical factor for long term favorable outcomes.
   d. All of the above
The Impact of Salivary Diagnostics

Educational Objectives

1. Discuss the advantages of salivary diagnostics
2. Discuss the potential impact of salivary diagnostics on a variety of systemic diseases and conditions
3. Describe how saliva testing is currently used by the dental profession
4. Implement saliva testing in the dental practice to enhance patient care

Course Evaluation

1. Were the individual course objectives met?
   Objective #1: Yes No Objective #2: Yes No
   Objective #3: Yes No Objective #4: Yes No

   Please evaluate this course by responding to the following statements, using a scale of Excellent = 5 to Poor = 0.

   2. To what extent were the course objectives accomplished overall? 5 4 3 2 1 0
   3. Rate your personal mastery of the course objectives. 5 4 3 2 1 0
   4. How would you rate the objectives and educational methods? 5 4 3 2 1 0
   5. How do you rate the author’s grasp of the topic? 5 4 3 2 1 0
   6. Please rate the instructor’s effectiveness. 5 4 3 2 1 0
   7. Was the overall administration of the course effective? 5 4 3 2 1 0
   8. Please rate the usefulness and clinical applicability of this course. 5 4 3 2 1 0
   9. Please rate the usefulness of the supplemental Weblogiography. 5 4 3 2 1 0
   10. Do you feel that the references were adequate? Yes No
   11. Would you participate in a similar program on a different topic? Yes No
   12. If any of the continuing education questions were unclear or ambiguous, please list them.

   13. Was there any subject matter you found confusing? Please describe.

   14. How long did it take you to complete this course?

   15. What additional continuing dental education topics would you like to see?

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