Detecting viruses by using salivary diagnostics

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ABSTRACT

Background. Diagnostics that involve the use of oral fluids have become increasingly available commercially in recent years and are of particular interest because of their relative ease of use, low cost and noninvasive collection of oral fluid for testing.

Types of Studies Reviewed. The authors discuss the use of salivary diagnostics for virus detection with an emphasis on rapid detection of infection by using point-of-care devices. In particular, they review salivary diagnostics for human immunodeficiency virus, hepatitis C virus and human papillomavirus. Oral mucosal transudate contains secretory immunoglobulin (Ig) A, as well as IgM and IgG, which makes it a good source for immunodiagnostic-based devices.

Clinical Implications. Because patients often visit a dentist more regularly than they do a physician, there is increased discussion in the dental community regarding the need for practitioners to be aware of salivary diagnostics and to be willing and able to administer these tests to their patients.

Key Words. Human immunodeficiency virus; human papillomavirus; hepatitis C virus; saliva; diagnostic; point of care; oral fluid.
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Although research projects on the development of saliva-based diagnostic testing are progressing rapidly and several commercial tests are available, use of these tests by dentists is modest. Point-of-care (POC) salivary tests can be used in the field, in emergency departments, in medical and dental clinics and, eventually, at home. In this review, we highlight the existing screening tests for viral infectious diseases with the hope that dental professionals will play a greater role in this field because the oral cavity and its fluids are in the domain of dentistry.

One key advantage in developing diagnostic tests for viruses and bacteria rather than for systemic diseases is that a single target (that is, analyte) is sufficient to identify the pathogen. In the case of systemic diseases (for example, diabetes, cancer, Alzheimer disease and cardiovascular diseases), multiple biomarkers—or a "signature" profile—typically are required and these can provide a clue, but rarely a definitive diagnosis.

A major clinical issue with respect to infectious diseases is distin-

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guishing a bacterial infection from a viral infection. In the case of upper-respiratory diseases and meningitis or pneumonia, the identification of a bacterial etiology allows appropriate and immediate antibiotic treatment. Misdiagnosis as a viral disease, particularly in the case of meningitis, can lead to death when the infection actually is of bacterial origin. Likewise, the inappropriate use of broad-range antibiotics in cases in which a viral infection is mistaken for a bacterial infection, besides being ineffective, may lead to allergic reactions, toxicity and a deterioration of the patient's condition. Furthermore, the excessive use of broad-range antibiotics is regarded as a major cause of multidrug-resistant bacteria. Although investigators have devoted much attention to novel techniques that allow differentiation between acute viral and bacterial infections[1] (or to addressing biomarker-based disease by means of microarray technology[2]), no simple test currently is available to distinguish between a bacterial and a viral infection.

Another key issue is to ascertain the need for a POC test to obtain an immediate result compared with a laboratory test, which may require days or weeks to obtain results. Diagnosis of microbial infections currently involves blood analysis (sedimentation and white blood cell count), quantification of common biomarkers (for example, C-reactive protein) and, to a lesser extent, the more time-consuming microbial cultivation. When suspecting a viral infection, clinicians may use nucleic acid–based amplification technologies.

The use of widely available rapid antibody detection tests is of value to screen for infections such as human immunodeficiency virus (HIV) in which the presence of antibodies against the pathogen is suggestive of an active infection. For infections with human papillomavirus (HPV) or herpes simplex virus (HSV), antibody detection is not informative because the presence of antibodies may indicate a previous or latent infection. However, some currently available HPV nucleic acid–based tests detect the virus and are specific for types of oral HPV.

In some cases, clinicians can use the ratio of immunoglobulin (Ig) M to IgG to distinguish acute disease from chronic disease. In saliva, a similar approach appears feasible, because salivary IgM is present in cases of acute hepatitis but not in cases of chronic disease.[3-5] Treating any infectious disease at the point of diagnosis will speed up recovery and decrease the opportunity for spread of the disease. In addition, if the patient does not return to the clinician's office for follow-up or obtain test results that are available only after days or weeks, access to therapy will be compromised.

When developing a new diagnostic test, investigators must consider the test sample's source. Most commonly, disease diagnosis involving a physical examination includes obtaining a blood sample, which, for a wide variety of analytes, has become routine. Currently, many infections can be detected with a full-scale blood analysis that includes blood cell counts, antibodies to common conditions and a variety of metabolic markers. Blood tests may be supplemented with, or replaced by, a urine sample in some cases.[6] Salivary tests, although rapidly increasing in use, still constitute a minority of all diagnostic tests performed.

One issue in using a saliva-based test is the nature of the target analyte. If testing for an antibody to a specific virus (for example, HIV, HPV or influenza) in which the antibodies are known to be detectable in blood, they also will be found in saliva, albeit at a somewhat lower concentration. On the other hand, if one is looking for an antigen or nucleic acid associated with a specific pathogen, those targets may or may not be detectable in saliva. Many investigators have conducted studies involving pathogen-derived nucleic acids and antigens, as well as antibodies to viral pathogens found in saliva.[4,5,7-33] Saliva remains an attractive biological matrix for POC diagnosis, especially when focusing on applications in remote settings or home-care situations and, as we propose, in the dental setting. Although diagnostic tests that involve the use of finger-stick blood are well accepted, the advantage of using saliva is that the collection is completely noninvasive and when patients are given a choice, they prefer saliva testing to tests requiring blood.[34,35]

VIRUSES DETECTED BY USING ORAL-BASED CLINICAL SAMPLES

Oral samples. Clinicians can use a number of oral samples to diagnose viruses, including whole saliva, gingival crevicular fluid, oral swabs of mucosal tissue, dental plaque, oral biopsy specimens and volatiles in breath. Studies reported in the literature typically involved the use of whole saliva or another oral

ABBREVIATION KEY. CDC: Centers for Disease Control and Prevention. **FDA:** Food and Drug Administration. **HBV:** Hepatitis B virus. **HCV:** Hepatitis C virus. **HIV:** Human immunodeficiency virus. **HPV:** Human papillomavirus. **HSV:** Herpes simplex virus. **Ig:** Immunoglobulin. **OMT:** Oral mucosal transudate. **OSCC:** Oropharyngeal squamous cell carcinoma. **PCR:** Polymerase chain reaction. **POC:** Point of care. **sIgA:** Secretory immunoglobulin A.

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