Point-of-care Platforms for Salivary Diagnostics

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Saliva reflects the physiologic state of the body, including emotional, endocrinal, nutritional and metabolic variations, and so can be used to monitor both oral and systemic health. In the past decade, salivary diagnostic approaches have been developed to monitor oral and systemic diseases. Along with these exciting scientific advancements, there is an emerging need to move salivary diagnostics out of the lab and into clinical practice. Point-of-care (POC) technologies specifically developed for salivary diagnostics can provide rapid, simple, low-cost and accurate measurements directly from saliva. To further transform salivary diagnostics into clinical reality, an integrated platform-based POC application is necessary, which includes sample processing, detection, a user-friendly interface and medical information technology. This review presents the requirements for POC platforms in salivary diagnostics and describes current applications of POC platforms for monitoring medical conditions using saliva. By advancing POC platforms for salivary diagnostics, dentists are anticipated to engage in chairside screening of medical conditions.

Key words: *salivary diagnostics, point-of-care devices*

Introduction

Salivary diagnostics for oral and systemic disease detection

Saliva is a complex fluid containing a variety of enzymes, hormones, antibodies, antimicrobial constituents, and cytokines[1,2]. Its composition mirrors that of body fluids such as blood, therefore it reflects virtually the entire spectrum of normal and disease states. The use of saliva as a diagnostic fluid meets the demands for a simple-to-collect, inexpensive, non-invasive and accessible diagnostic tool. Over the past few years, saliva has been used to detect a growing number of diseases and biomarkers, including caries risk assessment, periodontal diseases, oral cancer, breast cancer, salivary gland diseases and systemic disorders such as hepatitis, HIV and HCV[3-10].

There are compelling reasons for using saliva as a point-of-care diagnostic fluid. First, saliva collection is non-invasive and inexpensive. For patients, the non-invasive nature of saliva collection dramatically reduces their anxiety and discomfort, and it simplifies the procurement of repeated samples for longitudinal monitoring. For professionals, saliva collection is safer than blood collection, which exposes healthcare providers to risks such as virus contraction. Second, saliva is easier than blood to handle for diagnostic procedures as it does not clot. This makes saliva a promising medium for monitoring the medical condition of the human body. Saliva-based diagnostics may therefore prove to be more accessible and accurate than current methodologies, as well as being less expensive and lower risk for the patient.

Salivary biomarkers

Biomarker detection is rapidly emerging as an important clinical tool for monitoring the physical condition of the body. Usually, the physical condition-related medical

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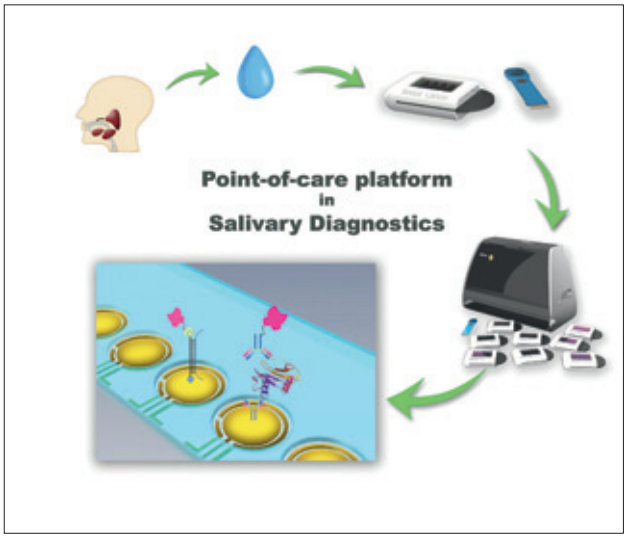

Fig 1 Illustration of the point-of-care platform for salivary diagnostics. The process requires that the saliva sample is put directly on the sensor cartridge; the on-site multiplexing detection of different types of biomarker is then carried out on the same chip.

status is a complex system, with time-dependent dynamics; presymptomatic indicators are useful for early detection, accurate diagnosis and developing therapeutic strategies[11-13]. Such biomarkers provide a 'signature' of the health state; they are found in biological fluids, such as blood and urine and, more recently, saliva. Saliva diagnostics utilises transcriptomic[5], proteomic[14,15], metabolomic[16,17], microRNA[18,19] and microbiome[20,21] technologies to decipher the most discriminatory biomarker panel. The Human Salivary Proteome Project has discovered all salivary secretory proteome components, post-translational modifications and protein complexes and has compiled information on their structures and functions. The database is fully accessible and available to the public (http://www.hspp.ucla.edu). Recently, the salivary transcriptome, including messenger RNA (mRNA), genomic DNA (gDNA)[5], micro RNA (miRNA)[19], microbiome[20,21] and metabolites[16,17], has been shown to contain promising candidates for salivary diagnostics[4,18,19,22,23]. Other biomarkers in saliva, such as hormones, suggest additional applications for saliva as a valuable diagnostic fluid and offer the potential to identify disease in a non-invasive and specific manner[14,24-28]. Consequently, saliva provides a biomarker source for the monitoring of both oral and systemic health.

Point-of-care technologies for saliva

Point-of-care testing can be defined as testing performed close to the patient at the time that care is required. This patient-centred approach responds to the need to improve the quality and accessibility of care, while also reducing cost. Included in this challenge is the need to reduce health disparities and provide care for an aging population. The results of point-of-care testing should enable a clinician to make a decision that leads to clinical action, such as a positive result from cancer screening leading to counselling and a definitive cancer diagnosis, e.g. a biopsy. For point-of-care testing to be effective, the combination of the test result, the decision and the action should lead to an improved health outcome, e.g. early cancer detection.

The barriers to widespread implementation of saliva diagnostics derive from technological problems. These relate to sensitivity, miniaturisation, high throughput, automation, portability, low cost, high functionality and speed, which are required to enable detection and measurement of multiple disease markers in saliva. However, these problems have now largely been overcome. Recently, the combination of emerging biotechnologies and salivary diagnostics has extended the range of saliva-based diagnostics from the lab-based assay to the real clinical system (Fig 1), as chairside tools for the dentist[29-35]. There are a multitude of reasons for using point-of-care technologies in chairside screening for medical conditions in the dental office. As saliva collection is non-invasive, there is little discomfort for the patient, and saliva-based detection can be carried out more frequently, even in resource-limited areas. Therefore, frequent and early measurements are possible, which are very important in early-stage screening and risk assessments. Additionally, point-of-care technologies make it possible to monitor dynamic development of disease or medical conditions. Therefore, the application of these technologies will permit dentists to engage in chairside screening of medical conditions[36].

Requirements for saliva point-of-care platforms

Saliva is a uniquely useful body fluid for monitoring the body's health. Not only does it reflect virtually the entire spectrum of normal and disease states, its use as a diagnostic fluid also meets the demands for a simple-to-collect, inexpensive, non-invasive and accessible diagnostic tool. However, because of the high mucin content[37], saliva is very viscous compared with other body fluids. This high viscosity causes low efficiency in sample processing. In addition, in saliva the biomarkers

are usually very dilute when compared with blood and urine[38]. Currently, although point-of-care technology has been widely applied to other body fluids, there are several specific requirements for saliva-based point-of-care technology due to particular physical, chemical and biological properties of saliva that hinder its use in clinical applications.

Accuracy

The low levels of biomarkers in saliva require that the point-of-care tests detect a small amount of a target molecule in the saliva matrix. Detection of low levels of a target requires high sensitivity, together with high specificity owing to the complexity of any mixture. However, current detection in saliva requires a compromise between specificity and sensitivity. Several techniques have been developed to amplify the signal, which helps increase the sensitivity. In most detection methods, the signal intensity relates to the number of target molecules within the detection region, which is usually very small compared with the overall sample volume. Hence, either amplifying the amount of target in the sample volume or concentrating the target into a small detection region enables high signal intensity. The first method increases the total number of target, probe and/or signal molecules, bringing out a high intensity measurement output. For example, polymerised chain reaction (PCR), primed *in situ* labelling (PRINS) and nucleic acid sequence-based amplification (NASBA) are techniques used to increase the total number of target nucleic acid molecules[39]. Ligase chain reaction (LCR) and rolling circle amplification (RCA) are used to amplify the probes[39]. Branched DNA (bDNA) and tyramide signal amplification (TSA) provide signal amplification[40].

Unlike direct amplification of the target/probe/signal, the second method focuses on increasing the local concentration of the target, instead of creating more copies. For example, nanotechnology can concentrate the few target molecules within the sample into a detection region by applying nanoparticle-based techniques.

Increasing both the overall amount and the local concentration of a target results in high sensitivity. However, this would also produce a higher background noise level and more false-positive results as both the specific and non-specific signals would be amplified.

To counter this, highly specific probes have been designed to decrease the background noise level, such as the molecular beacon and other structurally constrained probes[41-44]. Typically, these methods are based on a high affinity for proteins and on distance-sensitive signal-transducing processes in nucleic acid detection, such as fluorescence resonance energy transfer (FRET), intercalating dye[45] and electrochemistry. However, by improving the specificity, the limit of detection of these probes is not satisfactory because a large amount of target is required to achieve a measureable signal; hence, they result in more false-negative results.

A point-of-care method with both high-sensitivity and high-specificity detection is highly desired in salivary diagnostics. To verify the accuracy of the point-of-care test using saliva, comparison with the respective gold standards in traditional laboratory-based assays is required, such as enzyme-linked immunosorbent assay (ELISA) for proteins and PCR for nucleic acids. To determine the specificity of the point-of-care test, the effect of variations in saliva content must be tested in a single patient under controlled conditions (e.g. after overnight fasting) and under variable conditions (e.g. time of day).

Multiplexibility

Because of the complexity of biological systems, especially for human diseases, a single biomarker is not sufficient for an accurate diagnosis. Medical decisions based on a single biomarker have a high probability of relying on false-positive or false-negative findings. Accurate diagnosis often requires multiplex detection of endogenous biomarkers. The typical accuracy for salivary biomarkers ranges from 0.65 to 0.85; however, this accuracy is still far below that needed in the real clinical situation. Recently, the use of a combination of biomarkers rather than a single biomarker has been shown to improve accuracy[4,46,47], indicating the importance of multiplexing assays for biomarkers. In addition, the combination of multiple biomarkers does not necessarily need to be limited to biomarkers of a single type, i.e. proteomic or genomic. The biomarkers in the combination could also include nucleic acids, proteins and small molecules. Multiplex detection of different types of biomarker may prove to be essential for accurate clinical diagnosis. However, because of difficulties in measuring the low levels of proteins/RNA/small molecules under the same conditions at the same time, no technology has yet addressed this type of multiplexing mode.

Robustness

The robustness of the point-of-care platform is determined by its repeatability, intermediate precision and reproducibility. For repeatability and intermediate precision, the performance of the assay must be evaluated under the specified range of environmental operating

conditions (temperature, humidity) by different operators, using positive and negative controls. The cumulative variances are expected to be less than 20% for clinical application.

To ensure that the point-of-care platform consistently meets the applicable requirements and specifications, analytical quality controls are necessary. Parameters for the quality control of point-of-care platforms are divided into two areas of application in the assay optimisation process: *(1)* device performance quality control, to ensure the point-of-care instrument's stability, selectivity and responsiveness before, during and after the analysis of a batch of saliva samples; and *(2)* sample batch quality control, to monitor assay performance, accuracy and precision, and to estimate of any errors associated with each sample batch. The goal of the quality control system is to ensure that the point-of-care assay results for salivary applications are consistent, comparable, accurate and within specified limits of precision. In addition, the point-of-care platform must include at least one internal control to further control the quality in each individual test.

Convenience and cost

To move the point-of-care platform into clinical salivary diagnostics, the convenience or user friendliness of the device is a key factor, especially for untrained operators and resource-limited areas. The measurements are expected to be simple and rapid, the saliva collection and processing procedure simple and robust, and the software to perform the measurement user friendly. The total amount of human saliva available is no more than a few millilitres, therefore collecting a large amount of saliva would take a long time and be uncomfortable to the subject. Large saliva samples would also increase the size and processing time of the point-of-care device. The desired detection conditions are room temperature and humidity, to avoid the need for additional temperature and humidity controls. Usually, the point-of-care device for saliva must be operated within a humidity range of 10% to 90% and within a temperature range of 4 to 30 °C.

Most of the point-of-care devices contain a disposable part for each individual test. The cost of the disposable part will determine the price of each test. Where those parts require specific reagent storage and processing, the cost of the test will be relatively high. Lateral force-based chromatography (test strip) has great potential owing to its simple structure, easy storage and low cost. In addition, the biosafety of the disposable part of the point-of-care device must be considered. Biohazard waste will cause further problems for treatment of the waste.

Integrated system for point-of-care testing

Significant improvements in healthcare accessibility, quality and cost are possible if scientific expertise in the miniaturisation, imaging and informatics sciences can be merged with knowledge of specific clinical needs in decentralised healthcare settings. A critical aspect of salivary diagnostics is the development of low-cost point-of-care platforms that can be integrated into healthcare delivery systems through information and communication technologies. To achieve the performance requirements for salivary diagnostics, point-of-care platforms for salivary diagnostics integrate several important parts. The system includes saliva collection, detection, a user interface and data presentation. With the integrated system, the operator simply collects saliva via the collector, introduces the saliva sample into the point-of-care platform, operates the software to control the device then waits for the results to be displayed on the instrument's screen. The incorporation of these components into fully integrated systems that can handle all aspects of analysis remains a challenge, as does providing the necessary connectivity of the analytical devices to clinical information systems and matching these devices to clinical need in order to facilitate their integration into the healthcare system.

Saliva collection

In primary care or under limited resource conditions, the greatest challenges are sample processing without specialised equipment, the use of simple stabilising reagents and sample transportation at ambient temperature[13,48]. Current standard operating procedures for oral sample processing and storage require mandatory centrifugation and a -80 °C freezer or dry ice for shipping. These stringent requirements severely limit the utilisation of salivary samples in situations with limited resources. The saliva point-of-care platform must provide a collector to collect and process saliva samples in an easy, repeatable fashion. Technology that also serves to stabilise the processed saliva at ambient temperature for suitable transportation between collection and clinical analytical sites will be highly desirable.

Detection

The detection module includes the point-of-care platform for the assay and the signal reader instrument. For

the assay, current biological sensing techniques rely largely on detection that is inherently complex, which requires specialised instrumentation and multiple preparative steps for sample processing and must be performed by specially trained personnel. To achieve this goal, the method must satisfy the following: *(1)* supplies real-time information, *(2)* can be operated by a user without special training, and *(3)* can be miniaturised using inexpensive materials and fabrication methods.

Sample processing in the point-of-care device requires effective, simple and reliable fluid control. The reagent cartridge plays an important role, especially when in the multiplexing mode as this requires the handling of different reagents in parallel. The development of microfluidics 'lab-on-a-chip' platforms offers the opportunity for automatic reagent processing without motor controls[10,29,35,49-52]. Meanwhile, lateral force and chromatography-based platforms also play an important role in point-of-care saliva testing because of their simple sample processing[53,54].

User interface and data presentation

For the point-of-care application, a user-friendly interface is important to allow untrained personnel to carry out measurements. The interface should include both the measurement and the data presentation parts.

The detection and stratification of complex disease with high sensitivity and a low rate of false-positive results requires the use of multiple biomarker measurements. Data interpretation and integration therefore faces the challenge of multi-parameter data.

A remote communication module would be very helpful to interface the clinical salivary diagnostics database with the device readout, and the medical information of the consenting, enrolled subject. In this case, data security should be included in the system.

Point-of-care platforms in salivary diagnostics

Different avenues are available for achieving the goal of simple, low-cost point-of-care detection platforms. A growing number of proof-of-principle examples have been established for using saliva to monitor local and systemic diseases and conditions. Techniques are emerging from a combination of miniaturisation technologies, and discoveries in many different fields of biology, chemistry, physics and engineering are leading to high throughput, automated, portable, low-cost, efficient and rapid biochemical analyses. Miniaturised diagnostic technologies, using minute amounts of body fluids, will be able to yield critical patient information, reflecting their health and disease status. These 'lab-on-a-chip' platforms will be able to perform multiple operations in parallel in non-laboratory settings, such as in the field, factory, hospital clinic or home. It is envisioned that such technologies will allow the simultaneous assessment of multiple conditions of health and disease, and will provide clinicians with preventive and therapeutic strategies to meet their patients' needs.

Single biomarker-based point-of-care platforms for saliva

Several point-of-care platforms have been developed for salivary diagnostics, both for local oral and systemic diseases. Different point-of-care platforms are available for oral diseases, for quantification of dental infections and for inflammatory markers in saliva.

A micro-total analysis system (μTAS) based on microelectromechanical technology has been successfully applied to the saliva test. A prototype μTAS developed by the Sandia National Lab (USA) can detect matrix metalloproteinase-8 (MMP-8) in saliva. This test is based on an optical system with a fluorescence-labelled anti-MMP-8 (aMMP-8) antibody, followed by electrophoresis. The detection is completed within 10 minutes using a 20 μl saliva sample. The results have been compared with ELISA using a paired test, giving $R^2 = 0.979$.

Dentognostics (Germany) has developed the Oral Risk Indicator® (ORI) platform for rapid aMMP-8 testing. Increased aMMP-8 values suggest active inflammatory processes in the periodontium, such as gingivitis or periodontitis. The ORI test uses saliva to provide evidence of concealed oral inflammation and collagenolytic overreactions of the immune response. It identifies pathogenic concentrations of the collagenase aMMP-8 in a mouth rinse specimen. The result is delivered in less than 10 minutes and can be conducted by the medical secretary or nurse during the patient's appointment.

For systemic diseases, the development of saliva-based prototypes is ongoing. OraSure Technologies Inc. (USA) has developed several lateral force-based chromatography test strips for rapid screening of infectious diseases using saliva. The assays include HIV, HCV and influenza. HIV-1/2, HCV antibody and influenza A/B testing can be performed in 20 minutes, providing accurate and easy-to-administer testing methods to help healthcare practitioners easily identify those infected.

Other applications of point-of-care platforms for cortisol-related salivary testing have also been reported. Nipro (Japan) has developed a hand-held device to monitor the salivary a-amylase level to evaluate human

stress levels. This device requires 30 µl of saliva, and the measurement can be done in 1 minute with a coefficient of $R^2 = 0.97$.

Integrated point-of-care multiplexing platforms for oral cancer detection in saliva

In addition to the above saliva-based point-of-care platforms, our research group has developed a unique platform capable of measuring both protein and mRNA at the same time.

Oral cancer affects around 43,000 Americans each year, and is the sixth most common cancer in the USA. This life-threatening disease has a 5-year survival rate of less than 50%, and kills as many Americans as skin cancer and cervical cancer. A fully functional point-of-care platform has been developed in salivary diagnostics (SDx) at UCLA by Dr David Wong's laboratory.

The UCLA SDx point-of-care device is an electrochemical platform, integrating sample collection and processing, and is capable of performing a sensitive and specific multiplexing assay for proteomic, transcriptomic and genomic biomarkers in saliva. Advances in specific molecular probe design, highly controllable surface modification of novel nanomaterials, and facilitated and individually optimised biorecognition have enabled the development of highly sensitive, highly specific sensors. The SDx point-of-care platform technology can detect both salivary proteins and nucleic acids, and can measure up to eight different biomarkers in a single test in less than 15 minutes. The SDx test is robust and direct. All the tests are consistently performed under ambient conditions, without the need for controlled temperature and humidity; in addition, no sample extraction or amplification is needed. There is minimal manual operation; the operator only needs to insert the sensor and cartridge and push the menu button. Readable diagnostic results are displayed once the testing is complete.

The SDx point-of-care platform has been tested in an Indian cohort of oral cancer saliva samples, and the results correlated well with results obtained using traditional ELISA and quantitative PCR assays for protein and RNA biomarkers, respectively. The clinical study assessed two salivary biomarkers for oral cancer; IL-8 mRNA and IL-8 protein. In multiplexing mode, the limit of detection of salivary IL-8 mRNA reached 3.9 fM in saliva. For IL-8 protein, the limit of detection was 7.4 pg/ml in saliva. A multiplex assay of these two biomarkers directly from 28 cancer and 28 matched control saliva samples showed significant clinical discrimination. From the receiver operating characteristic curve analysis, the electrochemical sensor yielded 90% sensitivity and 90% specificity for both IL-8 mRNA and IL-8 protein[31]. With the SDx point-of-care platform, the salivary test will screen for and assess the risk of oral cancer, with only test-positive patients being directed to biopsy. This will significantly reduce the number of unnecessary biopsies. The test is expected to detect oral cancer at an earlier stage, when treatment is more effective and less costly.

The future of point-of-care technologies in salivary diagnostics

The current healthcare system is inadequate owing to the increasingly unhealthy population and growing number of individuals with multiple chronic conditions. A desirable goal is higher quality healthcare at reduced cost, with a shift in focus from utilising specialised care for the treatment of late-stage disease to an emphasis on patient-centred approaches and coordinated care teams that promote wellness and effective disease management. Salivary diagnostics has a potential role in the healthcare delivery system in which more significant roles for primary care physicians and nurses are envisioned, with substantial involvement of the patient in decision-making and self-care. These expanded scopes of practice require the development of inexpensive and easy-to-use medical devices, as well as appropriate means for information sharing, to provide timely health status information at the point of care. Point-of-care devices can provide these needed capabilities, including diagnostic tools for the evaluation of patient samples, such as blood, saliva and urine, in non-laboratory settings.

Accuracy

Both natural substances and a large variety of molecules introduced for therapeutic, dependency or recreational purposes can be monitored in saliva, as can markers for emotional, hormonal, immunological, neurological, nutritional and metabolic status. A major concern in the use of saliva as a diagnostic fluid has been that informative analytes are generally present in lower amounts in saliva than in serum[38]. However, new biosensor techniques are demonstrating better sensitivity than conventional methods in simple solutions, so it may be possible to detect the lower level of analytes in saliva.

Advances in three areas are likely to make the concept of sophisticated point-of-care diagnostic devices practical in the near term. The first is the development in the past decade of microfluidic devices and meth-

odologies[10,29,31,33,49-52,55]. This adaptation of microfabrication to plumbing has allowed miniaturisation of instruments and the automation of complex fluid processes, leading to the elimination of both large robots and human fluid transfer errors. Some of the microfluidic technologies have also lent themselves to preconditioning complex fluid samples, which is essential to allow point-of-care testing of saliva. Microfluidics allows miniaturisation of the fluid components of existing technologies, such as ELISA and related bioassay formats. If the microfluidic components can be manufactured inexpensively (using injection-moulded plastics, for example), there is great potential for making very inexpensive, optically compatible, disposable, single-use assays. Concomitant miniaturisation of optical systems is also possible today, thanks to huge advances in microelectronics and optical transducers over the past few decades.

The second advance is the advent of many new transduction mechanisms over the past few decades, which have been demonstrated to have great promise. These methods are particularly well suited to point-of-care detection when combined with microfluidics. In particular, direct electronic transduction has now been further miniaturised, using nanometre-sized transducers. Such transduction allows the detection of only a few molecules. The big advantage of direct electrical detection is the elimination of all optical components, allowing the design of very small and mechanically robust devices. If the cost of the transducers can be kept low enough to make them fully disposable, they could be more competitive than optically based systems.

The third advance is due to improvements in nanoscience. Nanoparticles have already been combined with selective biomolecules to allow novel types of detection schemes based on optical and electric properties of single and aggregated particles. Nanomaterials have shown emerging potential in salivary diagnostics; their use may overcome some of the signal-to-noise ratio issues because of their enhanced electrical properties compared with traditional materials. These nanomaterials also offer improved biocompatibility and additional binding sites[55-60]. For sensors that detect immobilised biomarkers, the interface between the surface and the fluid medium plays an important role in determining the signal and noise levels in the detection process. When biomolecules are directly immobilised on the metal electrode, their denaturation by surface-protein interaction results in low activity and low signal levels. New nanomaterials, such as the conducting polymer-based nanomaterial interface, can prevent the conformation change of the biomolecule and alleviate this problem[61-65].

All these new technologies will benefit point-of-care platform development in saliva diagnostics, enabling them to be sensitive, specific, rapid and robust. Saliva is particularly full of high molecular weight (sticky) mucins, which compete with the analytes for the chemically selective surfaces of any transducers. Therefore, a saliva-based diagnostic system must incorporate appropriate sample preconditioning fluidics – micro or macro. These latter requirements, the need for speed and selectivity in the presence of real raw samples, will be the essence of the future direction of point-of-care platforms in salivary diagnostics.

Multiplexibility

To improve the accuracy of medical decision-making for many diseases and physical conditions, combinations of multiple biomarkers need to be assayed. These complex combinations are required because a single type of marker is not sufficient. Usually, different types of marker are required, including proteomic, transcriptomic, small-molecule and cellular markers. Looking towards future point-of-care platforms, the development of devices that utilise multiple types of molecules, real-time technologies (to achieve higher throughput in shorter test times, e.g. sequencing metazoan genomes in minutes) and longer read lengths and, most importantly for point-of-care, which require very small amounts of starting material for the multiplexing measurements are strongly encouraged.

Sample processing in point-of-care platforms

For the integrated point-of-care platform for salivary diagnostics, standardised saliva processing is necessary to achieve repeatable and stable measurements[13]. Several different types of collector have been developed for specific applications, such as the OraQuick® (OraSure, USA) for salivary proteins, Oracollect® (DNAgenotek, USA) and SalivaGene® (Stratec, Germany) for DNA/RNA. An integrated system for universal saliva processing applications is needed. Recently, a collector has been developed at UCLA in David Wong's group for both protein and DNA/RNA. Integrated devices process saliva samples and stabilise the processed saliva at ambient temperature for suitable transportation between collection and clinical analytical sites. The future application of the integrated saliva collection system embedded in the point-of-care platform will further improve the performance of the current point-of-care salivary diagnostics platforms.

Data sharing and bioinformatics

Applying point-of-care platforms to salivary diagnostics will have a tremendous impact on the current healthcare system. As huge amounts of medical information will be generated by this type of point-of-care system, bioinformatics need to be introduced into the point-of-care system-generated salivary database. In response, the future point-of-care device will encapsulate data-sharing functions, and will improve standard data formats via remote communication. In addition, the related data-safety function must also be included.

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