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Molecular biomarkers in salivary diagnostic materials: Point-of-Care solutions — PoC-Diagnostics and -Testing

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Highlights:

- **Advances in biosensor technologies:** Reviews state-of-the-art biosensors, such as surface plasmon resonance and electrochemical sensors, for non-invasive salivary biomarker detection.
- **Point-of-Care innovations:** Discusses the development and optimization of PoC molecular diagnostic tools like lab-on-a-chip and microfluidic devices for accessible and timely clinical applications.
- **Applications beyond oro-dental care:** Explores the versatility of salivary diagnostics in monitoring conditions like diabetes, infectious diseases, and drug abuse, extending applications into forensic sciences.
- **AI-driven salivary diagnostics:** Highlights the role of artificial intelligence, machine learning, and deep learning in enhancing the accuracy of salivary proteomic analysis for early disease detection, including oral cancer.
- **Challenges and future directions:** Examines the need for standardization, improved assay sensitivity, and integration of predictive analytics for widespread clinical adoption of salivary diagnostics.

Abstract: Accurate diagnosis is fundamental to effective healthcare, guiding clinical and surgical decisions and ultimately influencing treatment outcomes and prognosis. Recent advancements in nanomaterials and fabrication techniques, coupled with emerging computational approaches such as artificial intelligence (AI), machine learning, and deep learning, have revolutionized high-throughput screening and laboratory automation. AI-driven algorithms now process and analyze salivary proteomic data with remarkable accuracy, identifying patterns and biomarkers associated with diseases such as oral cancer at an early stage. This capability not only enhances diagnostic precision but also accelerates decision-making, enabling timely interventions. Despite their lower analyte content, oral fluids—particularly saliva—offer a non-invasive and accessible alternative for biomarker testing. This has led to the development and optimization of highly sensitive and amplified detection methods, including polymerase chain reaction, isothermal amplification, microfluidic, lab-on-a-chip, and biosensor technologies such as surface plasmon resonance and electrochemical sensing. These innovations have culminated in reliable Point-of-Care (PoC) solutions for molecular diagnostics, facilitating the detection and monitoring of a broad spectrum of conditions, including steroid levels, growth factors, drug and alcohol abuse, infectious diseases (such as HIV antibodies), diabetes (via salivary glucose), periodontitis, peri-implantitis, and oral cancer, with applications extending even into forensics. The precision, simplicity, and accessibility of salivary-based biomarkers and biosensors present a promising frontier in contemporary oro-dental healthcare, offering significant benefits to clinicians and surgeons. While significant progress has been made, challenges remain in standardizing salivary diagnostic techniques and ensuring their widespread clinical adoption. Addressing these challenges requires continued research into improving assay sensitivity, data integration, and cost-effectiveness. Henceforth, ongoing advancements are expected to further integrate predictive analytics into our routine clinical practice, ultimately improving patient outcomes through personalized, cost-effective, and timely care, thereby enhancing overall healthcare quality and efficiency. These are the topics to be discussed in this review.

Keywords: salivary fluid; biomarkers; molecular diagnosis; point-of-care; lab-on-a-chip; biosensing; nanotechnology; high-throughput screening; laboratory automation; healthcare

1. Introduction

Bapu, the Mahatma Gandhi once said “a correct diagnosis is three-fourths the remedy” [1]. Later, Francis Marion Pottenger Jr., a disciple of the Canadian dentist Weston A. Price, emphasized that “… *the one outstanding need of modern medicine is accurate clinical observation and interpretation* ...” [2]. These quotes highlight a fundamental fact in healthcare: a symptom alone is not a diagnosis. The process of diagnosis, which involves symptomatology and diagnostics, is essential in distinguishing between normal and abnormal states of health. This process relies on methods that healthcare providers and specialists employ, whether through physical observation or distinctive laboratory-based investigations and analyses of symptoms, signs, and other manifestations (Figure 1) [3]. Making the correct diagnosis is crucial, as it not only provides an explanation for a patient’s health problem or complaint but also directs subsequent healthcare decisions. However, diagnosis (D_x) is a continuous process; it does not end with identifying the possible cause of a health issue and initiating therapy. It extends to monitoring the efficacy of the prescribed treatment plan and verifying the accuracy of the original diagnosis [4]. In modern clinical and surgical dentistry, technological advancements have significantly enhanced the quality of oral and dental care. Innovations such as advanced digital imaging, 3D printing, novel orthognathic appliances, cutting-edge dental and surgical biomaterials, and superior cosmetic and aesthetic treatments have expanded our clinical armamentarium and capabilities. For D_x, intra-oral cameras, 2D digital radiography, and 3D computed tomography are a few of the commonly used tools [5].

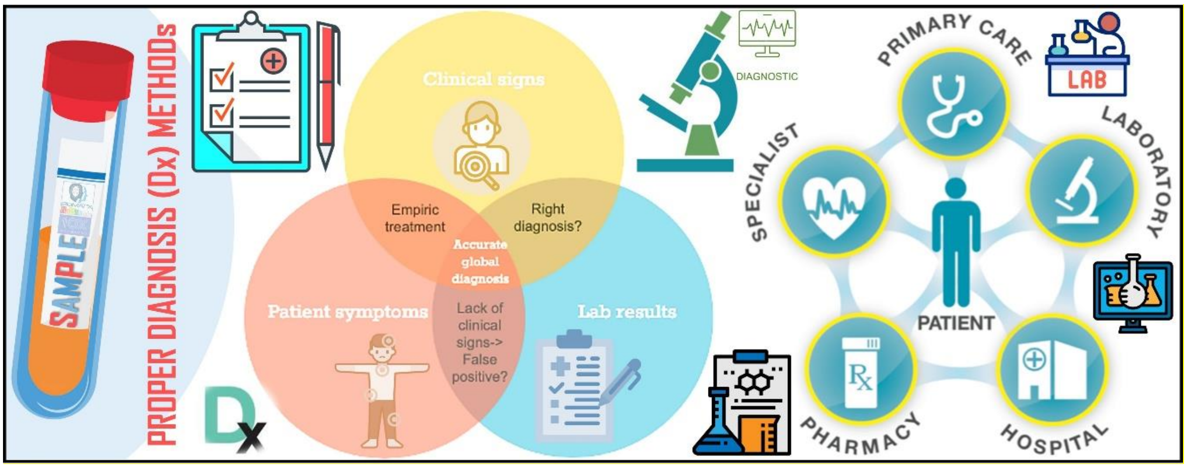

Figure 1. Illustrating the diagnostic (Dx) method flow.

Nonetheless, while these technologies have greatly enhanced our ability to diagnose and treat patients via providing detailed and accurate diagnostic information, they also have limitations. Indeed, traditional imaging methods can be costly, time-consuming, and often require specialized equipment and trained personnel. Additionally, besides accessibility issues, these methods may not always provide immediate results, which can lead to delays diagnosis and treatment with serious consequences, typically in life-threatening situations or during pandemics. This is where Point-of-Care (PoC) solutions offer significant advantages.

2. PoC technological solutions aim to bridge the gap between conventional diagnostic practices and rapid, accessible, real-time and on-site testing for improved patient care

In response to the limitations of traditional diagnostic methods, innovative Point-of-Care (PoC) solutions have emerged as a transformative approach in medical diagnostics. Herein, the emphasis on disease prevention, improving diagnosis and treatment, and implementing stress- and risk-reduction strategies to lower the physical, emotional, and financial burden on patients has led to a surge in the innovative design, development, optimization and translation of PoC solutions [6]. Briefly, PoC refers to a range of diagnostic procedures conducted at or near the site of patient care, rather than sending samples to a distant centralized laboratory, thereby offering significant improvements in speed and accessibility. Indeed, PoC technologies are designed to offer quick and convenient diagnostic and treatment solutions, allowing healthcare providers to obtain results rapidly without the need for extensive laboratory infrastructure or training. This approach facilitates immediate decision-making and treatment, enhancing the efficiency of patient care, without delay and its potential consequences. PoC devices are often compact, portable, and user-friendly, enabling their use in diverse settings such as clinical offices, hospitals, and even remote or underserved areas. By integrating PoC solutions into healthcare practices, clinicians can improve the speed and accessibility of diagnostic services, leading to an overall more effective patient management [6].

Examples—PoC solutions encompasses various types of diagnostic (PoC-D) and testing (PoC-T) methods, each designed to provide rapid and accessible results at or near the site of patient care [6–10]. (a) Immunoassays detect specific proteins or antibodies and are commonly used for tests like pregnancy or infectious disease screenings; (b) Molecular diagnostics, including PCR (Polymerase Chain Reaction

DNA replication and amplification technique) and isothermal amplification, identify genetic material from pathogens or mutations, crucial for diagnosing diseases and genetic conditions; (c) Electrochemical sensors measure electrical signals from biochemical reactions, such as glucose meters for diabetes management; (d) Biosensors integrate biological components with electronic systems to detect analytes, with examples including SPR (surface plasmon resonance) sensors; (e) Microfluidics (devices used for applications such as biochemical assays, cell sorting, and DNA analysis) . utilizes advanced LoC (lab-on-a-chip) technology to handle small fluid volumes (typically in the microliter to nanoliter range) and perform multiple tests simultaneously within microchannels etched into a chip (integrating complex laboratory functions onto a small portable device); (f) Imaging devices**,** such as handheld ultrasounds, provide real-time diagnostics (can be used in emergency settings for quick clinical assessments); and (g) Rapid Diagnostic Tests or RDTs which offer quick, user-friendly results for various conditions. RDTs often utilize immunoassay techniques, where the test detects specific antigens, antibodies, or biomarkers in a sample. They are typically used for screening and diagnosing a variety of conditions and are valued for their ease of use, speed, and minimal need for specialized equipment. Henceforth, each PoC testing type contributes to improved diagnostic efficiency and patient management in wide diverse clinical settings [6].

A recent and widely recognized example of the need, benefits, and utility of PoC technologies is the RDT for COVID-19, which many of us have encountered during travel or public health screenings. This PoC immunoassay was designed to detect specific viral antigens from SARS-CoV-2 using a nasal swab sample. The test provides results swiftly, usually within 15 to 30 minutes, without requiring complex laboratory equipment. By applying the sample to a device containing antibodies specific to the viral antigens, the presence of the virus produces a visible signal, such as a colored line, indicating a positive result. This rapid COVID-19 antigen test exemplifies how PoC immunoassays offer immediate, actionable information at the point of care, making them crucial for prompt diagnosis and timely intervention across various settings, including clinics, airports, and public health initiatives. It underscores the transformative impact of PoC technologies in improving diagnostic efficiency and enhancing patient management, especially in urgent or challenging situations.

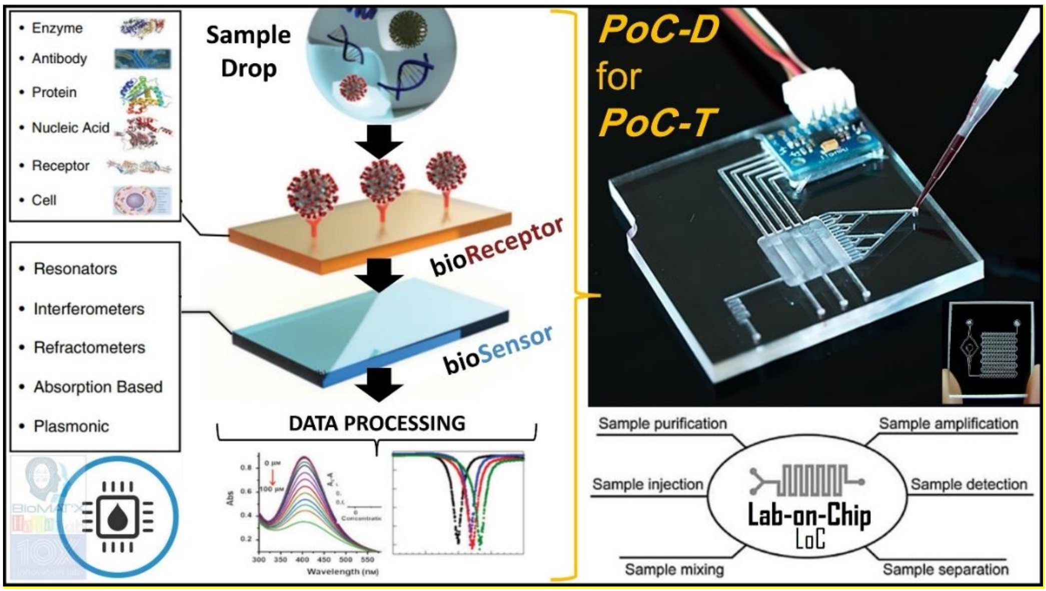

Figure 2. Bio-sensing Lab-on-Chip (LoC) analytical platforms enabling PoC-D for PoC-T.

3. PoC-D

In PoC, Point-of-Care Diagnostics (*PoC-D*) and Point-of-Care Testing (*PoC-T*) are related yet distinct concepts, where PoC-D encompasses a broader scope, focusing on diagnostic technologies and systems that provide comprehensive disease detection, monitoring, and management directly at or near the site of patient care. Therefore, PoC-D includes various types of diagnostic tools and methods that facilitate detailed analysis and decision-making in real-time. On the other hand, PoC-T specifically refers to the actual testing procedures performed at or near the location of the patient. It involves the use of devices and assays to conduct tests and obtain results quickly, often without the need for complex laboratory equipment. Henceforth, PoC-T is a subset of PoC-D, focusing on the execution of diagnostic tests rather than the overall diagnostic system or process or technology used to facilitate on-site disease detection and management [7]. In this section, the focus is on PoC-D technologies.

Recent years, particularly in response to the global COVID-19 pandemic in 2020, have seen a surge in interest, awareness, and advancements in PoC-D, as previously highlighted. The pandemic underscored the need for rapid and accurate disease detection to facilitate timely medical decision-making. PoC-D technologies, including Lab-on-a-Chip or LoC assays (Figure 2), droplet-based biosensors, nano-biosensing devices, and microfluidic bio-analytical platforms, exemplify these advancements. Significant progress in nanomaterials and nanofabrication has facilitated the development of high-throughput, compact and miniature diagnostic devices [8]. Beyond speed and efficiency, PoC-D devices are now designed to be user-friendly, requiring lower sample volumes and reducing invasiveness. They are also cost-effective, sustainable, and environmentally friendly due to the reduced bio-waste. These innovations are revolutionizing disease monitoring and therapeutic outcomes, making rapid, reliable diagnostics more accessible and effective at the point of care [7–10]. Coupled with computational methods (a range of statistical techniques and mathematical algorithms used to process, analyze, and interpret complex data through computer systems) such as artificial intelligence (AI), machine learning (ML), and deep learning (DL), these technologies enable sophisticated data sorting, analysis and pattern (and trend) recognition on-site. AI algorithms can enhance diagnostic accuracy by interpreting complex data from various biosensors and imaging devices, while ML and DL (uses deep neural networks) models improve over time with exposure to more data, leading to more complex patterns and relationships in data, and thereby, much more precise and reliable results [10]. These methods, when optimized [6], can also test hypotheses, perform regression analysis, make predictions, and derive insights from data.

To summarize, the advantages of integrating these computational methods include increased diagnostic speed and accuracy, the ability to handle large volumes of data efficiently, and the provision of real-time insights that support immediate clinical decisions [8–10]. Nevertheless, there are limitations worthy to consider. The accuracy of PoC-D devices and instruments can be impacted by factors such as sample quality and device calibration. Computational methods such as AI and ML require extensive and diverse datasets for training, which may not always be available, potentially leading to biases or errors in diagnostic predictions. Besides, while PoC-D technologies offer many benefits, they may also face challenges in terms of integration into the existing healthcare systems and maintaining *key* regulatory compliance [10].

4. PoC-T

As previously highlighted, Point-of-Care Testing (PoC-T) represents a subset of PoC-D, specifically dealing with the implementation of diagnostic tests rather than the overall diagnostic systems or technologies used for on-site disease detection and management. And so, recent advancements in PoC-D have significantly enhanced the capabilities of PoC-T. Innovations in nanomaterials, microfluidics, and biosensing technologies have improved the sensitivity, specificity, and speed of diagnostic devices. The integration of artificial intelligence, machine learning, and deep learning has enabled real-time data analysis, allowing for more accurate and timely test results. These technical advancements have made PoC-T devices more portable, user-friendly, and cost-effective, improving accessibility and efficiency in various healthcare settings. Thus, PoC-T directly benefits from the progress in PoC-D by offering rapid, reliable, and accessible diagnostic solutions. For PoC-T (Figure 3), the medical diagnostic testing at or near the point of care, involves performing a diagnostic test *outside* of a laboratory, with the purpose of producing a rapid and reliable result which can then facilitate and aid in identifying and/or managing acute infections and chronic diseases [11]. Recent advancements in PoC-D, particularly in bio-sensing technologies, are driving the development of more precise and efficient PoC-T solutions [12]. These innovations enhance access to healthcare, facilitate timely diagnosis and disease management, and improve patient outcomes, especially in critical care settings [13]. Additionally, the ability to perform quick and accurate biomarker sensing using oral fluid-based PoC solutions supports the creation of personalized treatment plans tailored to individual patient needs. This precision in diagnostics and treatment can significantly enhance outcomes by saving lives, improving Quality of Life, and strengthening public safety. For instance, monitoring blood sugar levels allows diabetic patients to manage their condition more effectively and adjust their treatment promptly. Similarly, measuring biomarkers like troponin and B-type natriuretic peptide (BNP) facilitates rapid diagnosis of heart attacks or heart failure, enabling timely intervention. PoC technologies also provide swift diagnosis and management of infectious diseases such as HIV, influenza, strep throat, and tuberculosis. Additionally, they enable early detection of cancers, such as prostate or oral cancer, and screen for substances like drugs or alcohol in the body. Allergy testing through small samples of blood or saliva further helps in managing life-threatening allergies more effectively. Offering rapid and non-invasive PoC-Testing can help reduce diagnostic delays and ensure timely, appropriate care, ultimately contributing to better overall health and well-being for individuals and society [14].

To summarize, PoC-T represents a significant advancement in healthcare by offering rapid, reliable diagnostic results at or near the site of patient care. This technology enhances convenience and accessibility, particularly in emergency situations, remote locations, or for patients with limited mobility, by eliminating the need for travel to centralized laboratories. PoC-T devices are designed to be cost-effective, reducing the need for expensive laboratory infrastructure and streamlining resource use. They also facilitate integration with Electronic Health Records (EHRs), ensuring real-time updates and continuity of care [9]. By enabling personalized medicine, PoC-T allows for tailored treatment plans based on immediate results, thereby improving patient engagement and adherence. Additionally, PoC-T supports early detection and prevention of diseases, which is crucial for conditions such as cancer and infectious diseases. Its versatility in testing applications, combined with the ability to respond quickly in public health emergencies, makes PoC-T an invaluable tool for enhancing overall healthcare delivery and improving patient outcomes. That said, PoC-T also faces limitations. These include potential issues with accuracy and sensitivity, which can lead to false results. Many PoC-T devices are designed for specific tests and may not cover all diagnostic needs. The initial cost of advanced devices can be high, and their effectiveness relies on proper training and usability. Additionally, regulatory and quality control measures may not be as rigorous as those for laboratory tests, and integrating PoC-T results with EHRs can be complex. Environmental factors can also affect device performance, highlighting the need for ongoing improvements to address these challenges as they arise, and they tend to do so [9].

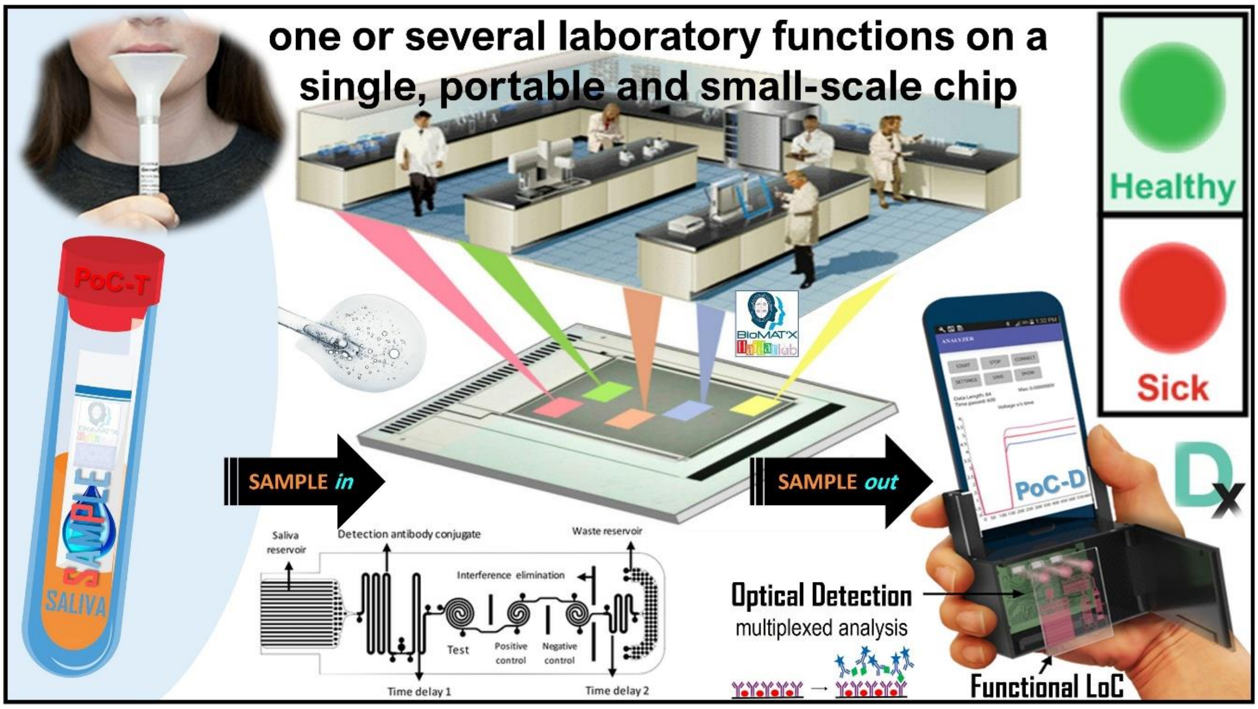

Figure 3. Salivary biofluid sample analysis by functional optical multiplexed analysis.

5. Quantitative detection and analysis of molecular biomarkers, from blood to saliva

Most Point-of-Care Testing (PoC-T) devices have traditionally focused on blood or urine samples for their design, functionality and mode-of-action [15–17]. However, oral fluids, particularly saliva, present a viable non-invasive alternative despite having lower analyte content, as it is an ultra-filtrate but still a versatile biofluid [18]. The accessibility and safety associated with handling oral fluid-based biomarkers (and nucleic acids) have led to innovations in Lab-on-a-Chip (LoC) technologies, microfluidic systems, and biosensor interfaces for molecular diagnostics. To address the challenge of low analyte content, advances in pre-concentration techniques and signal amplification methods have been integrated into these devices, improving their sensitivity and reliability. These advancements facilitate the detection and monitoring of steroids, growth factors, drugs, infectious diseases (including HIV antibodies), diabetes (via salivary glucose), and oral cancers, with applications extending into forensics [19–20]. Devices often use enzymatic amplification methods like PCR (Polymerase Chain Reactions) or ELIZA (Enzyme-Linked Immuno-Assays) [22]. In the clinical field dentistry and stomatology, commercially available PoC-T tools commonly employ activated matrix metalloproteinase-8 (aMMP-8) immunoassays to diagnose and monitor inflammatory conditions such as periodontitis (a serious gum infection that damages the soft tissue and destroys the bone supporting the teeth, leading to gum recession and tooth mobility) and peri-implantitis (an inflammatory condition affecting the tissues around dental implants, characterized by bone loss and potential implant failure, similar to periodontitis but occurring around implants rather than natural teeth) [21]. Additionally, research is focusing on utilizing gingival crevicular fluid (GCF) and peri-implant sulcular fluid in novel, rapid and cost-effective PoC-D/PoC-T devices for enhanced and more precise (*for early detection*) monitoring of oral and dental diseases [22,23]. Alongside MMP-8, biomarkers such as macrophage inflammatory protein-1 alpha, pro-inflammatory cytokines IL-1β and IL-6, and tumor necrosis factor alpha (TNF-α) show promise in diagnostics [24]. It can be stated herein that while current biosensors, primarily optical, predominantly target protein biomarkers and small nucleic acids, ongoing R&D&I (research, development, and innovation) efforts including from our own laboratory, are focused on enhancing biosensing capabilities to accurately and reliably measure complex fluid samples. Future advancements aim to incorporate the detection of biofilm-associated pathogens and address genetic (*polygenic*) risk factors that mediate host immune-inflammatory responses and influence connective tissue and bone metabolism– *genotyping* [25]. For instance, label-free biosensors with high interactive affinity, recognition, and selectivity could revolutionize the real-time measurements by enabling precise detection and differentiation of a wide range of pathogens and biomarkers [26]. This progress promises to advance precision medicine by addressing the diversity of pathogens, underlying conditions, and environmental and genetic factors, thereby improving diagnostic accuracy and patient-specific dental and overall care [26].

6. Omics and proteomic analysis of whole saliva

Relevant to the topic of this article, as it significantly impacts the field of PoC instruments, understanding omics and proteomic analytical methodologies enhances the comprehension of current and future PoC diagnostic and testing capabilities. Briefly, omics refers to the comprehensive study of all the molecules and molecular components in a biological sample, while proteomic analysis focuses specifically on identifying and quantifying all proteins present in that sample (*whole saliva, herein*). In 2017, the U.S. Food and Drug Administration (FDA) approved the use of saliva as a human diagnostic specimen and a DTC or "direct-to-consumer" tool for genetic and disease pre-disposition research (Figure 4) [27]. The reader is highly-encouraged to visit FDA News [27]. Saliva, a complex yet clinically-informative biological fluid produced in volumes of 1–2 liters daily, consists of water, mucus, proteins, electrolytes, and amylase– comprising bicarbonate, phosphate, urea, mucin, and mineral components; playing crucial roles in maintaining oral health by modulating oral pH (surface epithelium) and aiding enamel re-mineralization [28]. Saliva bio-sampling is advantageous for its ease of self-collection, stability, and transportability. DNA and RNA can be extracted from saliva for various applications, such as quantitative polymerase chain reaction (PCR), whole-genome sequencing, and loop-mediated isothermal amplification [29]. However, saliva's lower analyte concentrations—100-to 1000-fold less than blood—pose a challenge, necessitating highly sensitive detection technologies for more accurate diagnostic instruments and clinical D_x, as aforementioned [30]. Indeed, despite the lower analyte content of saliva (and other fluids) where compared to blood or urine, PoC technologies can effectively compete by leveraging advanced detection methods, such as enzymatic amplification and signal enhancement, which substantially improve sensitivity. The ability to multiplex, or detect multiple biomarkers simultaneously, further enhances diagnostic power, while integrating omics and proteomics analysis provides detailed health insights. The non-invasive and convenient nature of saliva collection, combined with the rapid on-site testing capabilities of PoC devices, offers significant advantages, particularly in emergency or resource-limited settings. Additionally, the cost-effectiveness and accessibility of saliva-based PoC tests make them a compelling alternative for widespread screening and monitoring, ultimately balancing the limitations of lower analyte concentrations with practical, cost- and time-effective, clinical and patient benefits.

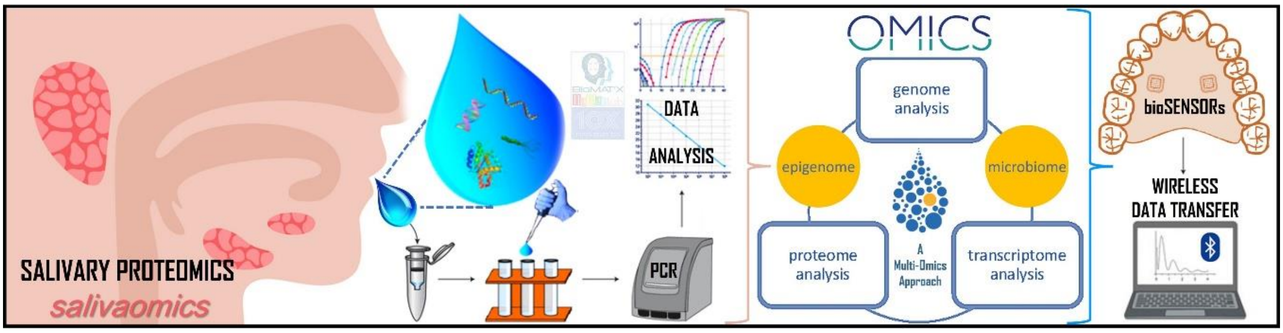

Figure 4. Salivary proteomics (*SalivaOmics*) and future utility of wearable bio-sensing.

Recent advancements in proteomics, which involves simultaneous screening and analysis of proteins and genes, have made it feasible to profile individual patients and gain insights into disease activity. Advances in omics (*i.e.*, *SalivaOmics*) will improve clinical predictions for disease onset and progression by probing different cellular layers at the DNA, RNA, protein, or metabolite levels and correlating the dynamics of the oral microbiome with salivary and gingival crevicular fluid (GCF) proteins [31]. Healthy saliva contains a diverse microbiome of commensal bacteria that contribute to oral, dental and overall health through protective and immuno-stimulatory functions. For example, some bacteria produce *lantibiotics* (additional notes below)—small peptides with antimicrobial properties that combat pathogens responsible for dental caries and periodontal diseases. Other bacteria produce enzymes that break down and remove harmful substances from the oral environment, such as hydrogen peroxide produced by *Streptococcus salivarius*, which can eliminate harmful bacteria such as *Streptococcus pyogenes* that cause strep throat. This protective role of commensal bacteria in saliva helps prevent pathogen colonization and maintains oral and dental health [32]. Henceforth, the integration of non-invasive saliva-omics and proteomics- into novel PoC solutions has a substantial transformative potential for medical diagnostics and patient care. This shift from blood or urine to oral fluids facilitates rapid diagnostics and continuous health monitoring in clinics, homes, and remote areas, improving accessibility to healthcare for all.

7. Conclusion

Ongoing R&D&I approaches, particularly with the integration of artificial intelligence technologies, will significantly enhance LoC platforms [33]. These advancements are expected to accelerate the discovery of new and more *disease-specific* biomarkers, an area that warrants further research [34]. In chair-side dental medicine and surgery, these innovations will improve PoC-D and PoC-T by facilitating the early detection, monitoring, and management (and treatment prognosis) of oral, dental, and a range of systemic conditions [35]. This progress will lead to more reliable, rapid, and sensitive diagnostics, ultimately advancing towards more accurate and comprehensive multiplex assay D_x instruments in our clinical practices.

8. Additional remark

Lantibiotics are a class of small anti-microbial peptides that are produced by some bacteria, including certain members of the oral microbiome. They are characterized by the presence of the unusual amino acids lanthionine and/or methyllanthionine, which are formed by post-translational modifications of specific residues during their biosynthesis. Lantibiotics have a broad spectrum of activity against various Gram-positive and some Gram-negative bacteria, and they are known to have a mode of action that involves disrupting the bacterial cell membrane or wall. Due to potential as therapeutic agents and role in promoting oral health, lantibiotics are an area of active R&D&I.

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Conflicts of interests

Author discloses no potential conflict(s) of interest of any shape or form.

Abbreviations

2D, two-dimensional; 3D, three-dimensional; AI, artificial intelligence; DL, deep learning; DTC, direct-to-consumer; Dx, diagnosis; EHRs, Electronic Health Records; ELIZA, Enzyme-Linked Immuno-Assays; GCF, gingival crevicular fluid; HIV, Human Immunodeficiency Virus; LoC, Lab-on-a-Chip; ML, machine learning; PCR, quantitative polymerase chain reaction; PoC, Point-of-Care; PoC-D, Point-of-Care Diagnostics; PoC-T, Point-of-Care Testing; R&D&I, research, development and innovation; RDT, Rapid Diagnostic Test.

Ethical statement

This work is exempt from any Ethics Committee and/or Institutional Review Board approval as it is deemed neither necessary nor required.

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