Disruptive innovations in laboratory medicine: saliva as a disruptive specimen

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A disruptive innovation can be defined as "*an innovation that disrupts (or in other words interrupts) an existing market and creates a new one by providing a different set of values, which ultimately, and unexpectedly, overtakes the existing market*" (1). Laboratory medicine is a fertile soil for disruptive innovations because it is heavily reliant on technology and technology developments (2). Over the last 5 decades, laboratory medicine has witnessed a remarkable wave of innovations that transformed the field from a peripheral to a central player in healthcare delivery. These advances enabled the introduction and performance of new tests on a large scale, some in a decentralized setting, in an accurate and a precise manner, thus leading to better diagnosis, more accurate prediction of disease prognosis, tailored guide to therapy and improved patient management. This evolution was the result of both sustaining and disruptive innovation, the latter being "*a new concept, technology, product, or process that is at first inferior to an existing one but with time it improves, becomes superior to it, and eventually replaces it*" (3). Some examples of disruptive innovation in laboratory medicine include continuous flow analysis, dry reagents on dipsticks, pregnancy home testing, polymerase chain reaction (PCR), point-of-care (POCT) testing, and use of MALDI-TOF mass spectrometry for pathogen identification. Therefore, disruptive innovation in laboratory medicine has been traditionally conceived as the development and introduction of innovative analytical technologies. However, disruptive innovations may also regard other steps of the total testing process, including the pre-pre-analytical phase and, in particular, innovative specimen types which may provide easier and non-invasive access for patients to laboratory testing. The prototype of this innovative and disruptive sampling is the so-called "liquid biopsy" which may overcome the challenges and limitations of invasive biopsy (4). The emergence of liquid biopsy expands the types of molecules that can be tested including cell-free DNA, miRNA, long coding RNAs, peptides and circulating tumor cells (5). Saliva is another example of "disruptive" specimen as it represents a simple and non-invasive collection method. Saliva cannot be defined "an innovative specimen", but for a long time it has been used mainly in dentistry and for studies in oral diseases, including studies to assess the risk of caries, and other diseases involving oral cavity and salivary glands (6,7). However, in the middle of 2000, an increasing interest on salivary assays has been documented in a review by Chiappin et al. which provided evidence of several saliva investigations for diagnostic purposes including viral and bacterial infections, cancer, pharmaceutical and abuse drugs, hormones, DNA tests and sialochemistry (8). More recently, the COVID-19 pandemic raised new interest in saliva as a promising alternative to naso/oropharyngeal swabs for SARS-CoV-2 detection, circumventing some limitations of swab collection including patient discomfort, the need for the adoption of expensive personal protection equipment (PPE), healthcare staff exposure and mainly, difficulty or impossibility of self-collection. A body of evidence has been collected to demonstrate that saliva is a good candidate for SARS-CoV-2 detection in earlier disease phase, and that the temporal profile is more consistent as compared with swabs, thus allowing the use for disease monitoring (9). In many meta-analyses and systematic reviews, saliva gave comparable and very good diagnostic performances, providing evidence that it is a clinically acceptable alternative specimen collection method, being the pooled sensitivity 83.2% [95% credible interval (CrI), 74.7%-91.4%] and the pooled specificity 99.2% (95% CrI, 98.2%-99.8%) (10,11). This prompted our group to conduct a surveillance program based on self-collection of saliva every 2 weeks (October 2020-June 2021) involving 8 183 employees of the Padua University, who voluntarily took part in the program. This salivary-based surveillance with contact tracing, effectively allowed to limit SARS-CoV-2 contagion, also in a population with a high incidence (12). Obviously, some analytical evaluations and validation of both molecular testing and antigen-based assays have been previously performed to assure quality, accuracy and reliability to laboratory testing in salivary samples, taking into account all steps of the total testing, namely sample collection and handling (13-15). Today, saliva is receiving more and more interest as a specimen to be used in laboratory medicine: currently, the diagnostic topics of saliva (now called "salivaomics") include the study of salivary proteins (proteomics), salivary RNAs (transcriptomics), salivary metabolytes (metabolomics), salivary microRNAs (microRNA) and salivary microbiota (microbiome) (16,17). We therefore should welcome Livia Barenghi and all coworkers for publishing this interesting, updated and exhaustive review titled "Saliva: challenges, possibilities,

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and limits of its diagnostic use". In this issue of the Journal, the readers may find the first part of the review Part 1 - Anatomical and basic pathophysiological aspects (18), while they should wait for a while (next issue of the Journal) to enjoy part 2 which will deal with its diagnostic use (19). As in a Netflix series, therefore, the editors decided to increase curiosity and expectations of the readership by announcing the entire scope of the review, but splitting it into two episodes. The first part of the review, therefore, presents a very exhaustive and detailed description of the saliva physiology, namely its sources, regulation of secretion and composition, which represent fundamental requirements to understand main sources of variability and, even more interesting, to control all steps in the pre-pre-analytical phase, particularly sample collection. As a matter of fact, the complexity of this body fluid requires the adoption of procedures other than those traditionally adopted for plasma/serum samples. If neglected, these aspects may explain some contradictory results reported in the literature. Evaluation and validation of laboratory methods to be used on saliva specimens, therefore, are mandatory as most diagnostic systems are developed and validated by manufacturers in samples other than saliva. In addition, this is increasingly important as POCT and other near-patient testing devices with self-collected salivary samples can be offered to the users without any evidence of accuracy and reliability. As highlighted in the paper by Fleming et al. "*without systems to ensure diagnostic safety and quality, expanded access (to laboratory testing) is of questionable value, potentially causing harm and wasting resources"* (20). Only the knowledge of saliva composition both in stimulated and non-stimulated samples, of circadian rhythms and biological variability, as well as of collection methods, handling and storage conditions may assure good analytical results. To anticipate the second episode, I would like to highlight that saliva cannot be simply defined "*a promising specimen"* as, for example, in Cushing's disease diagnosis and management the late-night salivary cortisol (LNSC) assay represents the first laboratory test to be performed, followed by the overnight 1 mg dexamethasone suppression test (DST) or low-dose 2-day dexamethasone test (LDDT), and 24-h urinary free cortisol measurement (21). Coming back to the fundamental question "is salivary specimen a disruptive innovation?", we should answer that the review by Barenghi et al (18,19) represents a formidable tool for improving and updating our knowledge on the complex saliva composition, secretory mechanisms and function. As saliva is a non-invasive, easy to handle specimen which allows self-collection, it presents many advantages in several clinical contexts and may contribute to reduce the current diagnostic gap in many different health conditions (20). However laboratory professionals should improve and spread the knowledge on the right procedures to be used in the pre-analytical phase, in assuring accuracy and reliability of analytical results, and finally in identifying appropriate reference intervals and thresholds in the post-analytical phase

REFERENCES

1. Bower JL, Christensen CM. Disruptive technologies: catching the wave. Harv Bus Rev 1995;73:43-53.
2. Khatab Z, Yousef GM. Disruptive innovations in the clinical laboratory: catching the wave of precision diagnostics. Crit Rev Clin Lab Sci 2021;58:546-62.
3. Rifai N, Topol E, Chan E, et al. Disruptive innovation in Laboratory Medicine. Clin Chem 2015;61:1129-32.
4. Markou A, Tzanikou E, Lianidou E. The potential of liquid biopsy in the management of cancer patients. Semin Cancer Biol 2022;84:69-79.
5. Di Meo A, Batruch I, Brown MD, et al. Identification of prognostic biomarkers in the urinary peptidome of the small renal mass. Am J Pathol 2019;189:2366-76.
6. Van Nieuw Amerongen A, Bolscher JG, Veerman EC. Salivary proteins: protective and diagnostic value in cariology? Caries Res 2004;38:247-53.
7. Pedersen AM, Bardow A, Nauntofte B. Salivary changes and dental caries as potential oral markers of autoimmune salivary gland dysfunction in primary Sjogren's syndrome. BMC Clin Pathol 2005;5:4.
8. Chiappin S, Antonelli G, Gatti R, et al. Saliva specimen: a new laboratory tool for diagnostic and basic investigation. Clin Chim Acta 2007;383:30-40.
9. Sapkota D, Søland TM, Galtung HK, et al. COVID-19 salivary signature: diagnostic and research opportunities. J Clin Pathol 2020 doi: 10.1136/jclinpath-2020-206834.
10. Tsang NNY, So HC, Ng KY, et al. Diagnostic performance of different sampling approaches for SARS-CoV-2 RT-PCR testing: a systematic review and meta-analysis. Lancet Infect Dis. 2021;21:1233-45.
11. Butler-Laporte G, Lawandi A, Schiller I, et al. Comparison of saliva and nasopharyngeal swab nucleic acid amplification testing for detection of SARS-CoV-2: A systematic review and meta-analysis. JAMA Intern Med 2021;181:353-60.
12. Basso D, Aita A, Navaglia F, et al. The University of Padua salivary-based SARS-CoV-2 surveillance program minimized viral transmission during the second and third pandemic wave. BMC Med 2022;20:96.
13. Aita A, Basso D, Cattelan AM, et al. SARS-CoV-2 identification and IgA antibodies in saliva: one sample two tests approach for diagnosis. Clin Chim Acta 2020;510:717-22.
14. Basso D, Aita A, Padoan A, et al. Salivary SARS-CoV-2 antigen rapid detection: a prospective cohort study. Clin Chim Acta 2021;517:54-9.
15. Padoan A, Cosma C, Aita A, et al. Hyris bCUBE SARS-CoV-2 rapid molecular saliva testing: a POCT innovation on its way. Clin Chem Lab Med 2022;60:766-70.
16. Aro K, Kaczor-Urbanowicz K, Carreras-Presas CM. Salivaomics in oral cancer. Curr Opin Otolaryngol Head Neck Surg 2019;27:91-7.
17. Aita A, Battisti I, Contran N, et al. Salivary proteomic analysis in asymptomatic and symptomatic SARS-CoV-2 infection: innate immunity, taste perception and FABP5 proteins make the difference. Clin Chim Acta 2022;537:26-37.

18. Barenghi L, Spadari F, Giannì AB, et al. Saliva: challenges,possibilities, and limits of the diagnostic use. Part 1- Anatomical and basic pathophysiological aspects. Biochim Clin 2022;46:292-300
19. Barenghi L, Spadari F, Giannì AB, et al. Saliva: Challenges, possibilities, and limits of the diagnostic use. Part 2 – Pre-analytical and analytical aspects. Biochim Clin 2022 aop. Doi 10.19186/BC_2022.071.
20. Fleming KA, Horton S, Wilson ML, et al. The Lancet Commission on diagnostics: transforming access to diagnostics. Lancet 2021;398:1997-2050. Erratum in: Lancet. 2021;398:1964.
21. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol 2021;9:847-75.