Saliva as a Biospecimen: Then and Now in the Era of COVID-19

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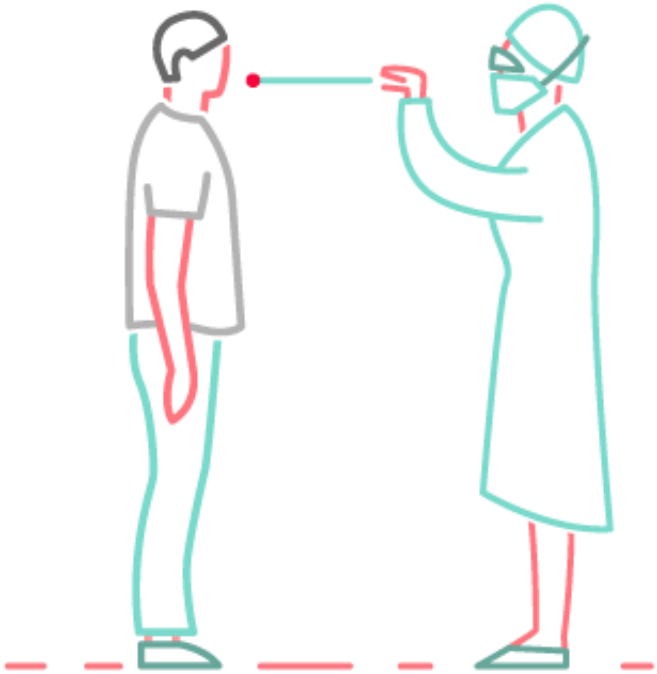

In early May, the U.S. Food and Drug Administration granted emergency use authorization to an at-home coronavirus test. This test relies on little more than spitting into a cup and sending it to a lab at Rutgers University, and results are received within 24 hours. This breakthrough is one of a growing list of saliva-based tests that have emerged since the COVID-19 pandemic unleashed a furious race for tests, treatments, and a vaccine.

Behind the recent developments, however, lies a decades-long arc in which salivary bioscience has become increasingly useful in diverse areas, including behavioral science fields like behavioral economics and cognitive science. The pandemic has accelerated this integration and will likely lead to a new set of practices and protocols for how saliva is classified, collected, and handled.

A Conceptual Pivot

Saliva's role in behavioral science has its roots in the 1990s, when psychological science experienced a noteworthy turning point, becoming more integrated, transdisciplinary, and biopsychosocial. This change can be attributed, at least in part, to the efforts of investigators like Norman B. Anderson (Anderson, 1997), the first director of the NIH Office of Behavioral and Social Sciences Research (OBSSR), which established funding initiatives aimed at encouraging cooperation between behavioral

and biological scientists. Meanwhile, new interdisciplinary programs and departments such as health psychology and biobehavioral health were emerging on university campuses; more biology-oriented faculty were hired in psychology departments; funding increased for psychology graduate students to cross-train in biological science; and researchers increasingly focused on translating observations from basic science into models of human health and development. These themes continue to define modern psychological science today.

Progress in the behavioral sciences following this conceptual pivot has been largely facilitated by technical advances enabling the measurement of biological parameters in saliva and oral fluids (Granger & Taylor, 2020). In the time since, and increasingly so in the last decade, the integration of salivary bioscience tactics into behavioral science has contributed to the generation of thousands of empirical articles.

Several particular advantages of saliva as a research biospecimen, characterized and discussed elsewhere (Granger et al., 2012), make this possible, including the ease of sample collection and portability. For instance, samples can be collected in the context of people's everyday social worlds (i.e., while at play, work, or home); repeated samplings can be obtained from the same individual with low participant burden; and samples can be self-collected in the field and returned by post.

As salivary bioscience matured as a field, the behavioral sciences began to integrate individual and intra-individual differences in biological processes into conceptual models of human health, behavior, and development. Eventually, working theories were revised to account for the accumulation of novel observations (e.g., Boyce & Ellis, 2005; Del Giudice et al., 2011; McEwen, 2000).

What psychological scientists may not yet appreciate, however, is that while this work was underway, salivary bioscience was progressing at an even faster pace. Public and private resources were channeled to explore the potential of saliva and oral fluid as the "diagnostic fluid of the future" (e.g., Malamud & Tabak, 1993). The focus was on characterizing the diversity of biomarkers present in oral fluids, discovering clinical applications and utilities, and advancing technologies to enable multiple biomarker determinations from single samples and quick turn-around results at the point of care. Consequentially, salivary bioscience can now be applied to studying a wide range of biological markers, including those for mediators of inflammation, antibodies to infectious disease, cardiometabolic and endocrine concerns, therapeutic drugs, drugs of abuse, enzymes, and environmental chemicals, as well as human (and microbial) genetic polymorphisms and epigenetic markers (Granger & Taylor, 2020).

The broad array of biological systems that can be incorporated into conceptual models using saliva creates new potential for advancing our understanding of how biobehavioral, psychological, and social factors interact to influence human development, behavior, and underlying diseases.

Prior to COVID-19, the most apparent contributions of salivary bioscience to psychological science research were twofold: It afforded the opportunity to study biobehavioral processes related to the psychobiology of the stress response, and it helped to determine the effects of individual differences in biological reactivity and in regulating responses to adversity or challenges on risk and resilience trajectories (e.g., Blair et al., 2011; Stroud et al., 2009). The results of this research fill the pages of top journals and underscore the importance of social context as a moderator of the expression of biology-behavior relationships (e.g., Booth, Carver, & Granger, 2004).

Salivary Bioscience Post-COVID-19

Enter the disruptor—the COVID-19 pandemic. Prior to 2020, another advantage of saliva as a biospecimen was safety. The US Centers for Disease Control (CDC) did not consider saliva as a class II biohazard unless it was visibly contaminated with blood. This meant it could be tested and collected without the use of universal precautions such as lab coats, gloves, and eye protection in the field (US Department of Health and Human Services, 2000). At the time of writing, however, it is understood that transmission of COVID-19 occurs through human contact with nasal secretions, and respiratory droplets (aerosols) from breath and saliva.

For now, the majority of academic research not related to COVID-19 has been indefinitely suspended. But when the world begins to resume normal activities again, the COVID-19 pandemic will remain a major disruption to the research enterprise. Certainly, there will be a new "normal" for salivary bioscience in particular, requiring a new set of best practices for the collection, handling, transport, and assay of saliva samples. The CDC has already specified some of this.

Here are some of the new practices and protocols we might expect.

One of the first changes likely to impact saliva research is its reclassification as a category "B" biospecimen, reflecting the fact that saliva is a viable source of peer-to-peer and community transmission of COVID-19. To mitigate the risk of infection, protections may need to include exclusion criteria using a combination of self-reported symptoms, body temperature, COVID-19 exposure history, recent travel history, and, perhaps in the future, COVID-19 vaccination history. Guidelines for collecting specimens while maintaining appropriate degrees of social distancing will also be needed. Creating standardized training for field researchers will be a critical step.

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Once samples are collected, protocols for labelling and shipping samples from collection sites to field stations or analytical laboratories will need to reflect the designation of saliva samples as a potential source of COVID-19 transmission. It seems reasonable to assume that policies may restrict the transport of samples between countries. This is especially likely when samples originate from COVID-19 "hot spots."

When saliva samples arrive at analytical research laboratories, they will need to be handled under more restrictive operating procedures. In addition to universal precautions and disinfecting work surfaces, all laboratory operations with saliva will need to take place within biosafety cabinets where the chance of aerosol-based transmission is mitigated. Further, it is possible that coronaviruses can withstand multiple freeze thaw cycles (e.g., Casanova et al., 2010). Accordingly, saliva samples collected after the fall of 2019 that are housed in biorepositories or sample archives should be identified as potential sources of COVID-19. A worthwhile next step will be to encourage laboratories that specialize in research

involving salivary testing to harmonize their standard operating procedures.

The risk of peer-to-peer and community transmission of COVID-19 through contact with saliva compromises several advantages of saliva as a biospecimen. Principal investigators responsible for overseeing research programs that involve saliva specimens will need to implement new training programs and standard operating procedures. These protocols should be developed in close consultation with local institutions' environmental/occupational health and safety officers to ensure that field researchers (project coordinators, data collectors, students) and laboratory technicians collect, handle, and assay samples safely.

Even after the COVID-19 pandemic subsides, it is likely that these changes will be the new normal. As a field, we will need to adapt with the goal of maximizing safety and minimizing risk while continuing efforts to advance our knowledge of influential interactions among biological, behavioral, psychological, and social factors.

Despite these added risks, salivary bioscience has never been so valuable to the psychological research enterprise. Exposure to persistent uncertainty associated with the pandemic will, for some more than others, influence the expression of biology-behavior relationships; and salivary bioscience methods will enable the programmatic investigation of the pandemic's consequences for human development and underlying health disparities. The post-COVID-19 era will renew interest in saliva sampling as a means of determining the presence of pathogen-specific antibodies, providing information on the type and temporality of infection, and supporting epidemiological surveillance (e.g., Randad et al., 2020).

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