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Commentary

A breath of fresh air – the potential for COVID-19 breath diagnostics

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As the world continues to grapple with the ongoing SARS-CoV-2 pandemic, it remains clear that frequent and widespread virus testing is a valuable tool to understand disease spread and to guide public health actions by communities and governments. To date, most traditional diagnostic tests continue to rely on established polymerase chain reaction (PCR) technologies, which have proven to be quite robust as a tool for mass screening and remain the gold standard within modern medicine. When employed using standardized protocols, PCR typically has a high accuracy and high specificity (eg, low false positives and low false negatives). Early in the pandemic, there were challenges to quickly establish and distribute the best testing methods. Once resolved, the test was widely and successfully rolled out in protocols across the world. However, other challenges have emerged when using this as a tool to combat COVID-19 spread.

For one, there are known sampling issues with nasopharyngeal PCR tests. While PCR itself is incredibly robust, it relies on collecting samples of actively amplifying viral genetic material. Though uncommon, it is possible to "miss" swabbing an area with active viral loads, which leads to a false-negative test result. There have been many more issues with the operational logistics and product supply chains that have strained testing systems during this public health crisis. The liquid reagents needed for the PCR test and the nasal swabs are in high demand, thus limiting availability in some locations causing alterations to planned testing protocols. Finally, although PCR is very reliable, there can be a significant time delay between sampling and when the results are available – hours-to-days, depending on processing capabilities of the test site.

Recently, a new approach to viral diagnostics has been considered by examining exhaled breath for signatures of the host-response to infection [1]. For several decades, it has been known that endogenously produced volatile organic compounds (VOCs) are present in exhaled breath, and these are frequent targets of breath diagnostics research and represent metabolic endpoints that can be quickly assessed for health information [2]. There are also reports of scent dogs being trained to detect human diseases, and observations of this phenomenon have also been recently expanded to include COVID-19 diagnosis [3, 4]. While the cellular and molecular mechanisms and fundamental understandings of breath signature VOC generation are still being developed, some prior work in cell culture models pointed to viral-associated breath VOCs for both rhinovirus [5] and seasonal influenza respiratory tract infections [6]. Specific oxidative stress VOCs were also observed post-vaccination in another previous study [7], when a nasally-delivered attenuated live virus vaccine was used. This was also followed by at least one porcine animal study that looked at breath VOC signatures in influenza infected animals [8]. Earlier this year, two other reports have also tentatively linked specific breath VOCs with SARS-CoV-2 infections [9, 10], and clearly this emerging area is likely to continue to yield interesting results.

A study recently published in *EBioMedicine* by Grassin-Delyle et al. [1] measured very specific VOCs in exhaled breath from mechanically ventilated adults with COVID-19 and compared that signature to control ventilated patients with non-COVID acute respiratory distress syndrome. As in the studies published by Ruszkiewicz et al. and Shan et al., this third group has also shown that COVID-19 associated breath signatures can specifically distinguish infection – in this case with 93% accuracy. While ongoing work is still needed to confirm these results in larger cohorts, it represents a potential rapid near-real-time test that could be deployed to augment PCR testing strategies. Even if not used as a final confirmatory measure, the rapid nature of this reagent-free, logistically simple test may be useful for high throughput screening of asymptomatic cases in large or unique populations (eg, prior to boarding an airplane, or entering a sports stadium).

While still a very new approach, there are benefits to considering breath testing for SARS-CoV-2 infections. When coupled with several of the near-real-time VOC detectors that are under development or recently available, it may provide a quick test – potentially yielding results in minutes, before a subject has left the testing area. This could lead to higher quarantine compliance and limit community spread, as there is no latency lag-time for asymptomatic or pre-symptomatic individuals. While the promise of vaccine deployment is tantalizingly close, it is clear that society will need to continue to test for SARS-CoV-2 infections for some time. These rapid breath-based tests could be a

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key part of the international response strategy. Breath analysis research teams need to collectively meet this global need.

Contributors

The authors confirm sole responsibility for the conception and preparation of this invited Commentary.

Declaration of Competing Interest

Dr. Davis reports patents #10,111,606 and #10,067,119 and #9398,881 and PCT/US2017/063,018 licensed to SensIT Ventures, Inc., and a patent #9824,870 issued and Prof. Davis is a co-founder of the start-up company SensIT Ventures, Inc. Dr. Kenyon reports patents #10,111,606 and #10,067,119 and #9398,881 and PCT/US2017/063,018 licensed to SensIT Ventures, Inc. Dr. Schivo reports patent PCT/US2017/063,018 licensed to SensIT Ventures, Inc.

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