Engineering 7 (2021) 3–5

Contents lists available at ScienceDirect

Engineering

journal homepage: www.elsevier.com/locate/eng

News & Highlights

Pandemic Woes: Antigen Tests to the Rescue?

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On 26 August 2020, following unexpectedly strong, post-initial-lockdown resurgences of coronavirus disease 2019 (COVID-19) in the late spring and summer, the medical-manufacturer giant Abbott and the US federal government announced approval, for emergency use in public health efforts to control the pandemic, of a new diagnostic testing device the size of a credit card and costing only 5 USD apiece [1]. Moreover, the federal government would spend 760 million USD to purchase 150 million of the tests and begin shipping them to nursing homes and schools roughly a month later [2].

By late October 2020, three more "antigen tests," making it a total of seven, had also won emergency use authorization (EUA) from the US Food and Drug Administration (US FDA) [3], with many more such tests in development and waiting in the emergency approval pipeline [4]. In addition, while initially hesitant to do so, the World Health Organization followed suit in September and October 2020 with emergency approvals of two antigen tests similar to the ones awarded EUA by the US FDA [5].

These national and international regulatory approvals highlight the importance of testing—and the inadequacy of conventional diagnostic testing—to serve as the linchpin of public health efforts directed against COVID-19. Amid the explosion of invention and adaptation prompted by the pandemic, this technological sector has become a hotspot of biotechnology and engineering innovation.

Coupled to wider measures like mask wearing, social distancing, quarantining, and contact-tracing, faster and cheaper screening tests like the Abbott device provide hope for sorely needed progress against the contagion while treatments and vaccines are intensely developed in parallel efforts. Alarmed by explosive resurgences in many parts of the world that initially appeared to have the pandemic under control, public health leaders have called for fast and frequent testing on a population-wide scale [6]. One recent report from the Rockefeller Foundation suggested that the United States would need to perform—just to meet the testing demand for primary and secondary schools and nursing homes—nearly 200 million rapid screening tests monthly by January 2021 [7]. Although greater accuracy would be preferred, even an antigen test detecting as few as 70% of infected people could provide enough accuracy for ongoing screening, enabling frequent enough retesting to catch infectious carriers missed by previous tests.

According to medical diagnostics expert Mara G. Aspinall, a coauthor of the report and professor of practice in the College of Health Solutions at Arizona State University (ASU) in Tempe, AZ, USA, the number of tests needed to screen the general population in the United States may be more than double that needed just for schools. "Now is the time," Aspinall said, "We have the protocols. We have the tests. I hope we have the community will to reduce transmission and take back control."

Tests using the reverse transcription-polymerase chain reaction (RT-PCR) currently serve as the gold standard for making COVID-19 diagnoses [8]. However, such conventional testing is complicated, costly, and slow, taking hours to run a sample through multiple, temperature-controlled steps. It also relies on skilled technicians, expensive reagents, and specialized processing laboratories to which samples often must be shipped, further delaying results. When COVID-19 infection rates are low and nations have been able to avoid surges of cases, RT-PCR testing appears to work well. But when caseloads climb steeply, as they have continued to do in many countries, RT-PCR laboratories cannot keep up with demand. Under such conditions, delays of days and sometimes a week or more in reporting results greatly reduces the value of the tests for guiding public health efforts to prevent further disease spread. Their expense also makes them ill-suited for the rapid and frequent testing critically needed to identify asymptomatic and presymptomatic carriers of the virus who could unknowingly spread the disease to others [9].

RT-PCR detects viruses with extraordinary accuracy by seeking out and replicating strands of their genetic material by the billions. In contrast, "lateral-flow antigen assays," like the 150 million Abbott "BinaxNOW" COVID-19 tests purchased by the US government, detect the virus—generally with less fidelity than RT-PCR—by capturing proteins, or "antigens," unique to the virus with custom-designed antibodies, a process that importantly enables "while-you-wait" results. Manufacturers have reported official sensitivities and specificities for many antigen tests that rival those of RT-PCR, but this accuracy generally only applies during a brief window of high viral load during the first five days after the onset of symptoms and not to asymptomatic and presymptomatic carriers, in whom the accuracy of many antigen tests has yet to be determined.

With the Abbott BinaxNOW test (Fig. 1), which is not approved for self-administration, a healthcare professional inserts a test swab from a patient into a tiny well of reagent in the test card to produce a sample solution that migrates by capillary motion along a fibrous strip through a patch of loosely deposited antibodies tagged with colloidal gold. If target proteins are in the sample,

https://doi.org/10.1016/j.eng.2020.12.002

the antibodies capture those molecules to form antigen–antibody-tag complexes that continue to flow. Awaiting that flow downstream, a fixed, "test" line of a different kind of antibodies capture the complexes themselves. The trapped gold tags make the line become visible to the naked eye, indicating a positive result. Taking place entirely at room temperature, the 15 min test requires no readout device or other instruments.

Long used to quickly diagnose illnesses such as influenza, legionella, strep throat, and acquired immune deficiency syndrome (AIDS), among others, antigen assays are not new. But the urgency of the COVID-19 pandemic has spurred the unprecedentedly quick development of new antigen-based and other rapid tests. When the COVID-19 pandemic began, manufacturers foresaw a potentially tremendous demand for antigen tests. Their first steps included investigating which proteins might serve best as markers of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus. Complementary molecules—primarily antibodies—able to recognize and bind those markers also had to be designed and created. Developing just the nine antigen-based assays approved so far by regulators for emergency use has involved combining advanced technologies including microfluidics [10]; nanomaterials (which can influence test sensitivity and speed, readout type, and whether a separate analytical instrument is required); various methods for signaling the presence of the virus such as chromatography [11], fluorescence [12], and electrochemical sensing [13]; and manufacturing integration to produce tests that simultaneously assay for multiple, distinct pathogens—like COVID-19, influenza, and respiratory syncytial virus—in a single instrument [14].

As of early November 2020, the COVID-19 Testing Commons, a public database maintained at ASU by Aspinall and others [4], listed about 1000 tests available or in development worldwide for detecting active SARS-CoV-2 infections, plus another 1000 antibody tests, used to identify individuals who have had COVID-19 but not those with active infections. The bulk of the database entries for active infection tests, about 75%, fall into the RT-PCR category, mostly variations on that laboratory standard that speed up, simplify, or lessen the cost of its complex process. While 10%-plus are lateral-flow antigen assays, with more than 100 such tests listed as in development, another nearly 150 listings represent cutting-edge prototypes and concepts based on a broad range of novel technologies. Nine of these, including two granted US FDA EUAs [15,16], make use of clustered regularly interspaced short palindromic repeats (CRISPR) [17], the acclaimed gene-editing technology recognized this year with the Nobel Prize in Chemistry [18]. Several others harness artificial intelligence, such as a test in development at Oxford University in the United Kingdom that combines microscopic imaging, fast fluorescent labeling, and neural-network analysis to ascertain presence of the virus within 5 min [19]. Multiple companies, including collaborators Gauss (Menlo Park, CA, USA) and Cellex (Research Triangle Park, NC, USA), are incorporating another enhancement that addresses concerns about result verification and reporting, devising tests with results readable only by means of smartphone apps that also securely communicate test results to public health or other authorities [20].

But even the RT-PCR category includes much innovation. The "CovidNudge," for example, a highly miniaturized RT-PCR test, takes just 90 min to run a full RT-PCR cycle in a portable, wall-powered, automated lab-in-a-box about the size of a toaster (Fig. 2) [21]. In trials conducted in three UK hospitals from April to May 2020, the overall accuracy of this point-of-care test, performed without laboratory handling or sample pre-processing, was shown to be comparable to standard RT-PCR laboratory testing [21], prompting the UK government to place a 212 million USD order for 5.8 million test kits for use in National Health Service hospitals beginning in September 2020 [22].

How all these new tests will impact the pandemic—and how they will complement the expected vaccines to come—remains to be determined. But while the experts continue to scrutinize and debate their potential utility, especially for identifying asymptomatic and presymptomatic carriers who may be infectious [23–25], governments, philanthropies, and the global healthcare community are nonetheless rushing to acquire and deploy them by the millions [2,22,26–28].

The increasing availability of rapid testing options is "a very positive advancement," but still "a work in progress," said infectious disease epidemiologist Maria van Kerkhove, the World Health Organization's technical lead for COVID-19 and an honorary lecturer at the Imperial College of London School of Public Health. "Countries are using them, so we are trying to provide guidance on where they perform better, to alleviate some of the pressure on PCR."

Fig. 1. A healthcare professional inserts a patient's nasopharyngeal swab into a BinaxNOW card to be tested for infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing the global COVID-19 pandemic. This sort of inexpensive (5 USD), compact device detects protein fragments (antigens) that are unique to the virus in a person's mucous or other bodily fluids in about 15 min. An order last summer by the US government for 150 million of these novel test cards from the manufacturer, Abbott, has helped vault this and other antigen tests to the forefront of US and international efforts to quell the pandemic. Credit: Abbott (public domain).

Fig. 2. The CovidNudge test showcases recent innovation in RT-PCR, the healthcare industry gold standard for detecting viral infections. When the top of the toaster-size "DnaNudge" testing instrument is slid into operating position over its bottom, the automated device conducts the complex genetics-based RT-PCR process on patient samples in the removable blue cartridge. Prior to the pandemic, DnaNudge's engineer-inventors at the Imperial College of London were already miniaturizing such clinical-laboratory-type equipment to speed up and make portable genetic analyses for a consumer-nutrition startup company. Repurposed to diagnose COVID-19 in healthcare settings and non-laboratory sites such as airports, schools, and large workplaces, the device carries out full RT-PCR for SARS-CoV-2 in less than 90 min, roughly a quarter of the time typically required by standard centralized laboratories and without the delays associated with sample transport. Credit: DnaNudge (public domain).

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