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EDITORIAL

Future potential of Rapid Acceleration of Diagnostics (RADx Tech) in molecular diagnostics

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While necessity is the mother of invention, anomalies have formed the basis for most disruptive discoveries that seed innovations in the sciences. They provide the impetus for paradigm change within a field and reflect differences between observed and theoretically expected data. The coronavirus pandemic was such an anomaly that spawned innovation in the molecular diagnostic testing market and initiated a paradigm change in public health policies, regulatory hurdles, and consumer views of point-of-care (POC) testing. Prior close calls with other viruses, including SARS, MERS, and Ebola, should have prepared the world for the coronavirus pandemic. Yet, many nations, including the United States, found themselves largely unprepared.

Countries responded to the unprecedented challenge of the coronavirus pandemic differently, but in each case, innovation was at the core of the response. After the authorization of the CDC test via Emergency Use Authorization (EUA) from the U.S. FDA on 4 February 2020, lab-developed tests from Clinical Laboratory Improvement Amendments (CLIA)-certified labs were authorized soon thereafter. Multiple commercial diagnostic companies rapidly validated and received EUA for SARS-CoV-2 diagnostic assays on existing platforms, which enabled private testing to rapidly outstrip public health department testing. On 24 April 2020, Congress appropriated 1.5 USD billion for SARS-CoV-2 testing to the U.S. National Institutes of Health (NIH). Within 5 days after the legislation was signed into law, the NIH launched RADx Tech to support the development, commercialization, and production scale-up of accurate, rapid assays that directly detect the presence of SARS-CoV-2 with antigen and molecular tests [1]. The goal was to expand capacity so that approximately 2% of the U.S. population (6 million persons) could be tested per day, with more tests ready for rapid deployment in proportion to national demand.

During its first 7 months, the RADx Tech program evaluated over 700 applications. As of December 2020, RADx Tech-supported companies were shipping 1 million tests/day, based on market demand, though their combined capacity for producing tests was substantially higher. By early February 2021, 15 diagnostic tests had received an EUA from the U.S. FDA, including 4 antigen tests and 9 molecular tests (two are neither), and 6 POC tests (3 antigen, 3 molecular). A multidisciplinary and interagency public-private collaborative group catalyzed this achievement. This is particularly noteworthy given that it typically takes 3 to 7 years to bring medical devices including diagnostics to the market [2]. Numerous other unprecedented aspects of the RADx Tech program and lessons learned will increase its applicability for future development of molecular diagnostics.

The RADx Tech program leveraged the Point-of-Care Technology Research Network (POCTRN) of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), which has accelerated the clinical and commercial development of POC diagnostics since 2007 [3,4]. In addition to funding pilot projects, POCTRN Centers also provide experts in clinical and user input, commercialization advice, and access to clinical specimens. The RADx Tech program built on the POCTRN model by adding a deep dive (due diligence) evaluation process plus individualized and integrated assistance in relevant technical, clinical, manufacturing, and regulatory areas and concerns.

The development of a new infectious disease diagnostic does not ensure adoption of the device. Emphasis has moved from strictly technology-driven adoption valuing innovation and potential for wide variety of application to clinical needs driven adoption, particularly for devices meant to be deployed at the point of care [5]. Consideration must be given to the clinical use case and the 'voice of the consumer' to guide

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development. An early understanding of who might use the device and in what context informs early development and can prevent costly changes and delays. In addition, when this input is provided early in development, clinical considerations can be incorporated in the device design before freeze. Consequently, one key component to accelerating diagnostic development in RADx Tech was early clinical input on the potential use case for new devices. RADx Tech convened a multidisciplinary committee of pediatricians, internists, specialists in emergency care, and infectious disease clinicians, as well as pathologists experienced in POC devices, laboratorians, bioengineers, and business leaders all drawn from the POCTRN Centers. These committee members had deep experience in diagnostic development, performance accuracy testing, and clinical studies. In a one-hour consultative meeting provided to RADx Tech-supported projects, common themes identified included: biosafety concerns, cumbersome workflows, inadequate understanding of lab information systems within different healthcare settings, and supply chain bottlenecks. At the time of their application for funding, few of the funded companies had verified the limit of detection (LOD) in the proposed sample matrix and performance with real clinical samples.

To that end, RADx Tech leveraged the engineering, scientific, and clinical expertise of one of the POCTRN Centers to function as the RADx Tech Test Verification Core. The Core was stood up within weeks of the launch of RADx Tech and established a mechanism to efficiently verify the performance (e.g. sensitivity, specificity, LOD, cross-reactivity) of SARS-CoV-2 diagnostic tests via an infrastructure comprising biosafety level 3 and level 2 virology laboratories, clinical biobanks of adult and pediatric COVID-19 patient specimens (including nasopharyngeal, nasal, and saliva samples), and community-based collection sites for prospective testing comparing the novel diagnostic technologies with the gold standard RT-PCR test. This test verification model, which entails objective, third-party testing using multiple methodologies, allows for efficient go/no-go decision-making to force 'fast failure' of underperforming technologies while rapidly accelerating the meritorious ones, as well as standardized comparisons of the various RADx Tech technologies that are assessed with the same protocols, personnel, and often, even the same patient samples. The Test Verification Core's results and recommendations were then incorporated into the NIH's decisions regarding whether to provide more funding to quickly scale-up manufacturing of those technologies. In 'testing the tests,' the Test Verification Core has gained experience with and assessed multiple diagnostic technologies in the RADx Tech pipeline. In addition, the Test Verification Core was designed to nimbly pivot and address arising and urgent needs, such as the ongoing effort to assess the performance of the RADx Tech diagnostics in detecting the SARS-CoV-2 variants that are emerging across the globe.

In general, the SARS-CoV-2 diagnostic technologies most amenable to testing and verification fall into two major categories – nucleic acid tests that detect the RNA of the SARS-CoV-2 virus and antigen tests that detect unique biochemical structures of the virus, such as the spike and nucleocapsid proteins. The underlying molecular biology of the nucleic acid tests in RADx Tech varies from more standard RT-PCR to loop-mediated isothermal amplification (LAMP) or CRISPR-based technologies. The intended use cases vary even more, ranging from over-the-counter and POC settings to moderate-to-high complexity clinical laboratories, and at much higher throughput and capacity than existing PCR-based diagnostics. The antigen tests in RADx Tech are typically designed for POC use and are incorporated into lateral flow assays used in conjunction with the relevant biospecimen such as nasal swab or saliva. More recently, the Test Verification Core has been charged with assessing novel technologies such as breath-based infectivity assays, which if proven clinically effective and safe, may function as SARS-CoV-2 screening tests given their theoretically high sensitivity as well as engineered biomolecular reagents that can theoretically concentrate viral particles within a biospecimen to enable easier diagnosis, effectively lowering the LOD, potentially to the point of visual detection with the naked eye.

The molecular diagnostics field, up until recently, has been dominated by large firms such as market leader, Roche (29.2% market share as of 2019), followed by Cepheid/Danaher, bioMérieux, Qiagen, Hologic, BD, Siemens, and Luminex. While many of these companies are focused on competitive strategies (e.g. sophisticated automation for molecular testing, test menu expansion) to maintain their position, emerging competitors are also entering the market by developing next-generation technologies [6]. The global COVID-19 pandemic has accelerated these and other new approaches for molecular diagnostics to enter the market, through substantially reduced regulatory hurdles, with many novel technologies coming out of research laboratories.

The NIH launched the RADx Tech initiative to accelerate the development and commercialization of innovative molecular diagnostics by direct detection, which at present remain the most effective tools to track and stop the spread of SARS-CoV-2. While the coronavirus pandemic continues to be the major driving force in the growth of the molecular diagnostics market, it has also highlighted the demand for innovative testing methods needed for other major disease categories (e.g. hepatitis C, human papillomavirus (HPV), cancer, and genetic disease diagnosis and screening). In this regard, the molecular diagnostic products market is the largest-growth segment in the global in vitro diagnostics market, which is predicted to grow from 7.3 USD billion in 2019 to more than 12.1 USD billion by 2024 [6]. Part of this growth will be fueled by tests authorized for home use or over-the-counter sales; accordingly, the RADx Tech program considered both use case and access by accelerating central reference lab testing in addition to POC and over-the-counter tests to meet diagnostic testing need more equitably.

Fortunately, the coronavirus pandemic has accelerated consumer and clinical acceptance of molecular POC diagnostics and the success of RADx Tech validates it as a model for the

development of molecular diagnostics and subsequent platform diversification. Therefore, as the demand for COVID-19 diagnostics wanes, POCTRN anticipates supporting a wide range of molecular platforms as they are adapted to meet future molecular diagnostic testing needs, including for public health surveillance and in response to future pandemics, so that next time, the country will be prepared.

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Reviewer Disclosures

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