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Principles and Practice of Emergency Research Response

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11 Accelerating Diagnostic Innovation for Pandemic Control

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Learning Objectives

This chapter will help readers understand and describe:

- How government research and development institutes can catalyze diagnostic innovation to meet the needs of an infectious disease emergency caused by a novel pathogen
- Elements of the RADx Tech program that could serve as examples in future response to EID outbreaks
- Barriers to the development and deployment of point-of-care testing (POC) and over-the-counter (OTC) tests during the COVID-19 pandemic
- Steps to take now to improve diagnostic readiness for the next pandemic

1 Introduction

1.1 Background on Testing Technologies for Diagnosing Acute SARS-CoV-2 Infection

Testing is an essential component of the public health response to an emerging infectious disease for

- Mitigating pathogen transmission
- Characterizing the pathogen and pathogenesis
- Enabling contact tracing and quarantine of infected persons
- Informing clinical and public health decision making
- Enabling identification of infection for enrollment in clinical trials
- Ascertaining endpoints in vaccine and/or therapeutic clinical trials
- Providing a pathway to safe return to work, school, and leisure

The COVID-19 pandemic provided a stark illustration of challenges to the development and distribution of tests to detect the novel SARS-CoV-2 virus. In the beginning, viral testing was conducted exclusively in centralized, high-complexity clinical laboratories by order of a healthcare provider, leading to massive shortages of tests and slow return of results. This, coupled with early missteps in expanding capacity and approving new tests, hindered the ability of public health systems to control viral spread. However, the pandemic also generated an unprecedented R&D investment in diagnostic innovation that will likely have lasting benefits for how existing and emerging diseases are detected, treated, and controlled. This chapter will provide an overview of how the U.S. National Institutes of Health (NIH) built a national program to accelerate innovation in COVID-19 diagnostic testing and convey some lessons learned from the experience that may be applicable to future efforts in pandemic control.

This chapter will focus exclusively on testing for acute or active viral infection (viral tests), rather than tests to measure prior infection (antibody or serology tests). While antibody tests are critical for understanding the epidemiology of SARS-CoV-2 and monitoring levels of acquired or vaccine-induced immunity in individuals or populations, they are not suitable for the diagnosis of acute viral infection or for tracking community transmission since human antibodies to the virus may not be detectable for weeks after initial exposure. Among viral tests, there are generally three primary purposes (HHS 2020); a fourth use for testing arose as tests became increasingly available.

1. *Diagnostic testing* to confirm or support a clinical diagnosis of viral infection in symptomatic individuals and inform treatment, enrollment in or endpoint for clinical trials, and implement preventive measures to contain further spread.
2. *Contact tracing testing* to trace, test, and monitor persons who may have been in contact with infected individuals.
3. *Surveillance testing* to enable public health authorities to assess and manage risks associated with the infectious disease, guide implementation of control measures, detect and control outbreaks, and monitor epidemiological trends.

	Molecular	Antigen
Point of Care	Mesa Biotech/ThermoFisher, Visby Medical  	Quidel 
Self-test / At home, work, etc.	Detect 	Quidel, Ellume  

Fig. 1 Examples of SARS-CoV-2 molecular and antigen testing technologies developed with NIH support via the Rapid Acceleration of Diagnostics Technology initiative. (Courtesy ThermoFisher, Quidel, Detect, Acula)

4. *Managing exposure risk*. As diagnostic innovation continued through the pandemic and tests for home use became increasingly available, a fourth primary purpose arose: enabling individuals and families to test for potential infection and reduce the risk they could expose and infect others.

There are three primary environments (discussed further in ▶ Sect. 1.2) in which each of these viral testing strategies can be implemented:

1. In central reference laboratories in the commercial diagnostic, hospital, academic, or public health sectors
2. At the point of care (POC), such as in a physician's office, urgent care facility, or worksite clinic
3. At one's home, workplace, or other non-medical location

The primary purpose of the test as well as its intended use environment will help determine the choice of underlying detection technology, as well as the requirements for test usability, performance (sensitivity, specificity, time to result), cost, and accessibility. Viral tests typically involve the collection of a sample from the nose, nasopharynx, or mouth and can largely be grouped into two categories based on whether they assess for the presence of viral genetic material or antigens. Nucleic acid amplification tests (NAATs), also referred to as molecular tests, specifically amplify and detect viral ribonucleic acid sequences from the SARS-CoV-2 genome, with amplification driven by either the reverse transcription polymerase chain reaction (RT-PCR) or a variety of isothermal amplification methods. Antigen tests, on the other hand, typically detect the presence of a specific viral protein through antibody–antigen interactions that are coupled to some type of measurable signal, often in the form of visible light or fluorescence. Figure 1 provides examples of SARS-CoV-2 diagnostic technologies for molecular and antigen tests that can be used either at POC or at home and that were developed with NIH support.

1.2 Implementation of Testing Technologies

Research and development of new diagnostic technologies require appropriate implementation and rigorous commercialization plans. To facilitate implementation, diagnostic testing tools and playbooks can guide health officials, employers, community organizations, and the public on testing modalities for specific use cases and/or settings. This section describes the implementation of diagnostics in the three primary environments: labs, at the point of care, and at home for self-testing (see

Fig. 3), as well as considerations distinguishing disease diagnosis from screening.

1.2.1 Lab-Based Testing

Lab-based diagnostics can be performed by clinical, hospital, or research laboratories that are certified and accredited to perform moderate to highly complex tests and report individual results (FDA 2021a). These labs can offer testing of individual or pooled samples to detect targeted antigens or nucleic acid sequences with high sensitivity (>95% for molecular assays that involve RT-PCR or next-generation sequencing). Lab-based testing can scale to thousands or hundreds of thousands of tests per day with innovations in the pre-analytical and analytical processes, such as bar coding of samples for quick accessioning and automated equipment interoperating with laboratory information management systems.

While labs can process diagnostic assays relatively quickly (e.g., less than an hour for viral antigen tests, 4–6 h for molecular tests/NAATs), sample shipment and accessioning for offsite laboratories can increase the turnaround time for lab-based tests to 12–24 h or more. A hub and spoke model, with multiple sample collection sites feeding into one or more testing hubs, can minimize turnaround times. The hub and spoke model can also provide testing support over a larger area and can be used to mitigate issues with supplies or capacity at a single lab by sending samples to another hub.

Various approaches to sample collection can be used to support lab-based testing, depending on the requirements for sample stability over time and transport options. Samples can be collected by health providers and then sent to the lab for processing through partnerships between labs and patient care facilities or local health departments. Lab-based assays can also be validated for use with samples collected by the patients themselves using a home collection kit. Assays may require biospecimens to be stored in saline, buffer solutions, or viral transport media, but maintaining biospecimens on dry swabs may also be an option, if validated with the lab-based assay.

Box 1: Clinical Laboratory Improvement Amendments (CLIA)

The U.S. Food and Drug Administration (FDA) , as authorized by CLIA, categorizes diagnostic tests by the complexity of their testing methodology—from the least to the most complex: waived tests, moderate complexity tests, and high complexity tests. CLIA categorization is determined after the FDA has cleared or approved a marketing submission or upon request for legally marketed devices. Under CLIA, laboratories performing only waived tests are subject to minimal regulation. Waived tests may also include any tests approved or cleared for home use by untrained individuals. Laboratories performing moderate- or high-complexity tests are subject to specific laboratory standards governing certification, personnel, proficiency testing, patient test management, quality assurance, quality control, and inspections (FDA 2021a).

1.2.2 Point-of-Care (POC) Testing

Diagnostics implemented in the POC setting include tests performed on-site under a Clinical Laboratory Improvement Amendments (CLIA) (► Box 1) certificate of waiver at public health clinics, urgent care centers, physicians' offices, pharmacies, retail clinics, emergency departments, and hospital labs. POC tests, often based on qualitative detection of an antigen or nucleic acid sequence, generally require less expensive, less complex equipment or instrumentation, and may have similar or somewhat limited detec-

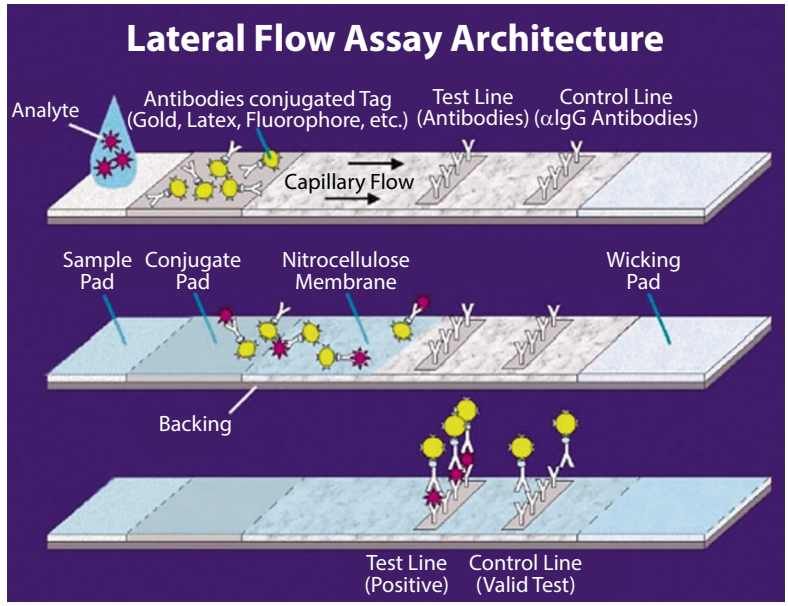

Fig. 2 Diagram describing the architecture of a generic lateral flow immunochromatographic assay. (NASA, public domain [► https://commons.wikimedia.org/wiki/File:Lateral_Flow_Assay.jpg])

tion thresholds compared to lab-based assays. Examples include lateral flow assays (Fig. 2) with a visual or instrument reader, loop-mediated isothermal amplification instruments, and sample in, result out RT-PCR platforms. With results typically available within 30 min, POC tests facilitate timely clinical decision-making for infected patients.

1.2.3 Self-Testing

Self-tests are diagnostic tests that can be used at home and other nonlaboratory settings—offices, schools, sporting events, airports, etc.—where individuals perform the test themselves. Self-tests may detect antigens or nucleic acid sequences but are most commonly noninstrumented, antigen-based rapid lateral flow assays, similar to home pregnancy tests.

Over-the-counter (OTC) tests require end-users to use and interpret the results themselves, thus requiring usability data to support their reliability. Home use tests requiring a prescription may be supervised or verified by a healthcare provider (e.g., through telehealth services). OTC tests can increase testing accessibility since they are available online, at retail stores, or via government distribution, potentially at no cost to the individual.

Packaged with quick-read instructions, self-tests may also have an associated digital app, which can reduce the incidence of errors or invalid results. A digital app can also enable reporting of an OTC result to public health departments. Individuals testing positive with OTC tests are advised to follow up with a clinical provider, to confirm a diagnosis, inform clinical care, and for public health reporting.

1.2.4 Asymptomatic Screening

Diagnostic tests may also be used for asymptomatic screening. When asymptomatic transmission is common for a given pathogen, as it is for SARS-CoV-2, community screening may be an important tool to identify infections and prevent further transmission. Screening programs may also be implemented by businesses, communities, and schools to reduce asymptomatic spread within a subpopulation, or to control access to sports, social, or entertainment venues.

Repeated or serial testing (e.g., 2–3 times per week) with rapid self or POC tests can increase the likelihood of identifying an asymptomatic positive case during an early stage of infection and enabling safety measures such as quarantine to protect others from being infected. Serial testing by schools of those who have been in close contact with a

positive case can avert the need for precautionary quarantine of everyone exposed, reducing the burden of remote learning for quarantined students.

1.3 Overview of the NIH Rapid Acceleration of Diagnostics (RADx) Initiative

Early in the COVID-19 pandemic, only nucleic acid amplification tests (NAATs) were available to diagnose acute infection with SARS-CoV-2. While highly sensitive and accurate, NAATs are generally conducted in centralized, high-complexity laboratories with strict regulatory requirements and skilled technicians. Given the time required for both transport and testing, test results generally were not available until days or even weeks after sample collection, greatly limiting their utility in preventing transmission. Supply chain limitations for common consumables such as pipette tips and nucleic acid extraction reagents led to additional delays. The need for alternative tests that could be used more widely and return results much faster was evident. A coordinated testing strategy had to have the following components:

- Public–private partnerships to accelerate innovation in diagnostic technology
- Increased manufacturing capacity and better supply chain management to enable sustainable domestic production
- Robust, secure data collection and utilization systems
- Methods for ensuring testing access for underserved populations to address health disparities

In response to the demand for greatly increased testing, NIH launched the Rapid Acceleration of Diagnostics (RADx) initiative in April 2020 to support the development, production scale-up, and deployment of accurate, rapid tests across the country (NIH 2022c) (◘ Fig. 3).

The emergence of COVID-19 illuminated some of the challenges a society faces when it relies on a hospital- and office-based healthcare model to address a rapidly spreading infectious disease. In particular, it highlighted the immediate need for a dynamic, distributed, and accessible diagnostic testing ecosystem. NIH's RADx Initiative was established as an integrated, holistic approach to these challenges through four initial programs to speed inno-

◘ **Fig. 3** Comparison of lab-based POC and self/at-home tests across multiple parameters. (Authors)

	Lab-based	Point of Care (POC)	Self / At-home
Test Type	Molecular (primarily)	Molecular, Antigen	Antigen (primarily)
Sensitivity	> 95%	> 90%	> 80%
Specificity	> 95%	> 90%	> 90%
Limit of Detection (copies/mL)	$> 10^2$	$> 10^2$ (molecular); $> 10^3$ (antigen)	$> 10^3$
Time to Result	24-48 hours longer if testing volume exceeds capacity	~ 30 – 60 min	~ 15 – 30 min
Cost per Result	$$$	$$	$
Results Reporting	Integrated with public health reporting infrastructure to automatically provide test result	May be integrated with public health reporting or may require healthcare provider to manually report test result	Typically requires user to voluntarily report test result to a public health agency or the test manufacturer

vation in technologies for COVID-19 testing and build an equitable national testing infrastructure (NIH 2022c) and others that followed.

- RADx Tech aims to identify and accelerate the development, scale-up, and deployment of innovative POC and at-home testing technologies.
- RADx Advanced Technology Platforms (RADx ATP) supports the scale-up of more advanced technologies that can achieve immediate, substantial increases in testing capacity.
- RADx Underserved Populations (RADx UP) establishes community-engaged implementation projects to improve access to testing in underserved and vulnerable populations.
- RADx rad (shorthand for radical) focuses on innovative testing methods that have a slightly longer horizon to technology maturation.
- Two additional RADx programs were established later on:
  - The RADx Independent Test Assessment Program (RADx ITAP) provides federal resources for test validation and regulatory prioritization to qualifying manufacturers in order to increase the availability of high-quality OTC COVID-19 tests to the public.
  - The RADx Mobile Application Reporting through Standards (RADx MARS) program promotes a standards-based approach to reporting COVID-19 self-test results with application to future reporting of remote diagnostics.

1.3.1 RADx Tech

RADx Tech is a fast-track technology development program led by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) that leverages the NIH Point of Care Technology Research Network (POCTRN) and partnerships across relevant federal agencies to speed innovation in the development, commercialization, and implementation of technologies for COVID-19 testing. The program's innovation funnel approach (Fig. 4) was designed to compress the customary diagnostic technology development timeline from years to months. As with many other aspects

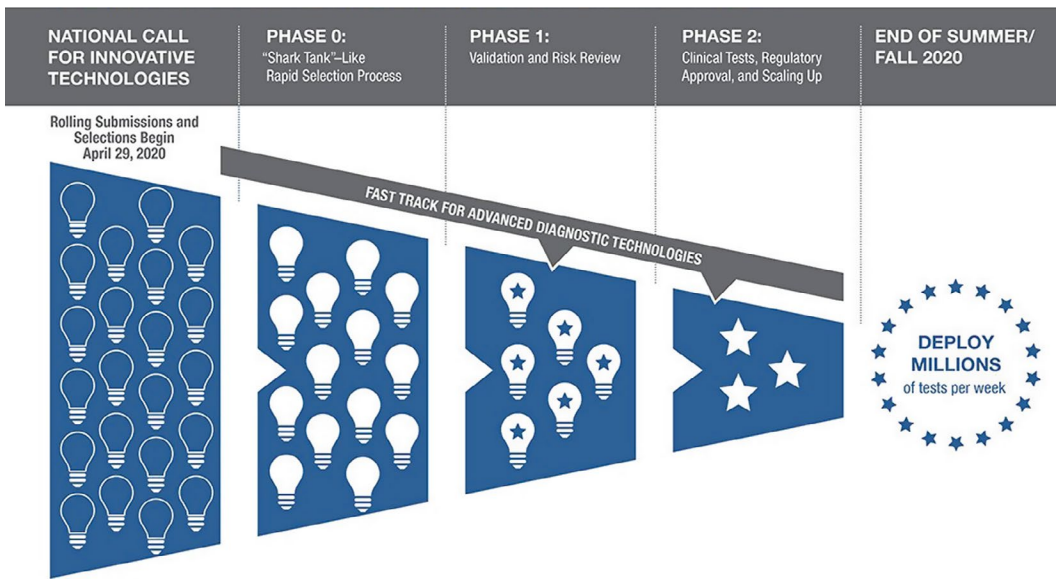

Fig. 4 NIH Rapid Acceleration of Diagnostics (RADx) Initiative for COVID-19 Technology Development Funnel. (@NIHDirector 2020; NIH, public domain)

of expedited research response to public health emergencies, the approach has been employing expert teams in parallel rather than in sequence to address technical, regulatory, clinical, and commercialization requirements and to support the validation, de-risking, scale-up, manufacturing, and deployment of novel tests. The RADx Tech program (along with RADx ATP) represents a new paradigm by which the NIH, and the federal government writ large, can catalyze medical technology development during a public health emergency. A more detailed description of the components and operation of the RADx Tech program is provided in ► Sect. 2.

1.3.2 The RADx Advanced Technology Platforms (RADx ATP)

The RADx Advanced Technology Platforms (RADx ATP) program was established to increase POC testing capacity by identifying existing and late-stage testing platforms for COVID-19 that can potentially achieve rapid scale-up and broader distribution relatively quickly. The program focuses on validating throughput and then improving and/or scaling up applicable technologies, including high-throughput platforms. As with RADx Tech, test and platform developers were evaluated, and then selected projects accelerated using the innovation funnel methodology. Developers that met RADx ATP criteria quickly advanced to Phase 2 of the program following the Phase 0 "deep dive." In contrast to RADx Tech, RADx ATP primarily supported testing technologies that had received or were close to U.S. Food and Drug Administration (FDA) authorization and could be produced in rapidly expanding quantity. Another goal was to establish or expand regional testing hubs and help expand testing to areas with underserved populations. Close collaboration and open communication with the Biomedical Advanced Research and Development Authority (BARDA), Department of Defense (DoD), and FDA were critical to minimize duplication of effort and ensure the tests developed and sold were ready for public use.

1.3.3 RADx UP

COVID-19 has disproportionally affected underserved and vulnerable populations. The RADx Underserved Populations (RADx UP) program was established with the overarching goals of (1) understanding the factors associated with disparities in COVID-19 morbidity and mortality for underserved and vulnerable populations who are disproportionately affected by the COVID-19 pandemic, and (2) laying the foundation for strategies to reduce those disparities. RADx UP funded a diverse cohort of community projects across the United States to assess and expand COVID-19 testing for populations including African Americans, Native Americans, and Alaska Natives; those in nursing homes, jails, and prisons; rural areas and underserved urban areas; pregnant women; and the homeless. Specifically, the program established multiple clinical research sites to evaluate testing methods in varying populations, places, and settings; encouraged collaboration between the program sites and the community to meet their needs; and developed strategies to apply technological advances in real-world settings, such as the "Say Yes! COVID Test" and Return to School testing initiatives.

For example, the Say Yes! COVID Test program (◘ Fig. 5), implemented in collabo-

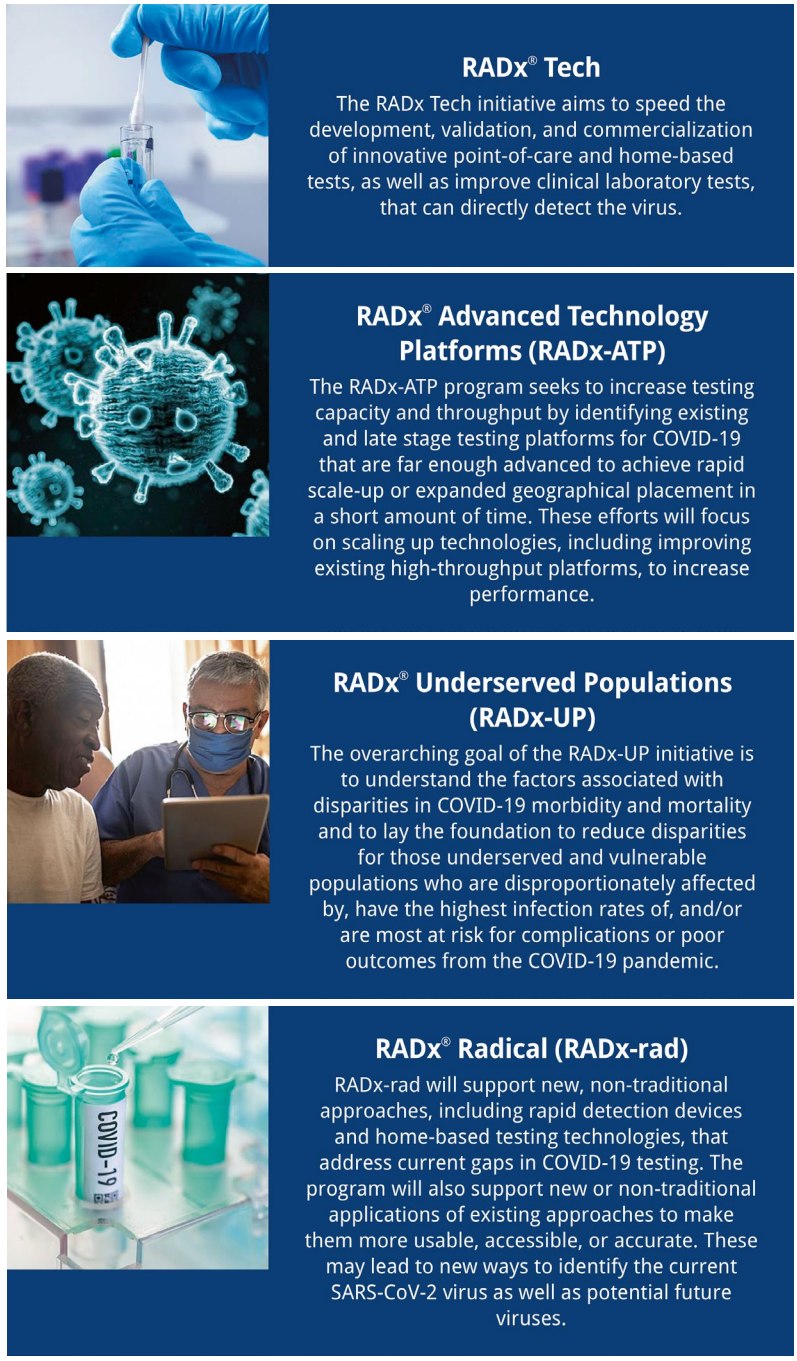

Fig. 5 Overview of the foundational RADx programs established by NIH to speed innovation in the development, commercialization, and implementation of technologies for COVID-19. (NIH, public domain, from ▶ https://www.nih.gov/research-training/medical--research-initiatives/radx/radx-programs)

ration with state health departments and the U.S. Centers for Disease Control and Prevention (CDC), provided select communities and public health departments access to free, rapid antigen tests for at-home use to determine whether frequent self-administered COVID-19 testing helps reduce community transmission. The Safe Return to School Diagnostic Testing Initiative (► Box 2) funded projects in multiple states to determine the best strategies combining frequent testing protocols and proven safety measures to enable students and staff in vulnerable and underserved communities to return to school (NIBIB 2021).

Box 2: Safe Return to School Diagnostic Testing Initiative

The RADx-UP program funded projects at ten institutions across eight states to build evidence on safely returning students, teachers, and support staff to in-person school in areas with vulnerable and underserved populations. The projects evaluated both at-home COVID-19 testing and pooled, in-school testing approaches using either antigen or molecular tests to analyze nasal swabs or saliva samples. While ongoing at the time of this publication, the studies have already demonstrated methods to overcome logistical and operational barriers in forming school–academic–public health partnerships during a pandemic and implementing robust diagnostic testing programs at K-12 schools to help reduce educational and health disparities.

1.3.4 RADx-Rad

RADx Radical (RADx-rad) was established to support new, nontraditional approaches, including rapid detection devices and home-based testing technologies, that address current gaps in COVID-19 testing. The program also supported novel applications of existing approaches to make them more usable, accessible, or accurate, which may lead to new ways to identify the SARS-CoV-2 virus as well as potential future viruses. Many of the technologies supported by RADx-rad are unique approaches, including community wastewater analysis, next-generation sequencing analytical platforms, and testing technologies coupled with artificial intelligence systems. Once sufficiently matured and demonstrated to have commercialization promise, select technologies supported by RADx-rad were encouraged to apply for the RADx Tech program to further accelerate their development, validation, and market entry.

1.3.5 RADx ITAP

The RADx Independent Test Assessment Program (RADx ITAP) was established by NIBIB in partnership with the FDA in order to accelerate regulatory review of OTC COVID-19 tests for the public (POCTRN 2022a). NIH provides dedicated RADx ITAP resources for independent laboratory validation, clinical studies, and streamlined data collection in support of FDA emergency use authorization (EUA) applications. For test manufacturers that can scale up quickly and meet the FDA's performance and quality standards, the FDA will use the information from RADx ITAP to accelerate the EUA review process.

1.3.6 RADx MARS

At-home and self-administered SARS-CoV-2 tests, unlike diagnostic tests in laboratories, are not routinely reported or included in health statistics. The RADx Mobile Application Reporting through Standards (RADx MARS) program was established by NIBIB in partnership with the U.S. Department of Health and Human Services (HHS) Office of the National Coordinator for Health Information Technology (ONC) to accommodate the increased use of at-home testing by enabling results reporting. RADx MARS assists diagnostic manufacturers that provide a compan-

Fig. 6 Online caption at Say Yes! COVID Test: Help us learn more about the different ways to test for COVID-19 at home!

ion mobile application or website to implement standardized results reporting based on two principles: (1) encoding of results and associated data in a healthcare industry-standard format, and (2) identifying one (or a few) destination(s) where these results can be sent and subsequently re-transmitted to appropriate state, federal, and related health systems (Fig. 6).

2 The RADx Tech Program

2.1 Overview of Program Design and Operation

Named to recall the World War II-era program at the Massachusetts Institute of Technology Radiation Laboratory (Rad Lab) that developed radar (Collins 2020), the RADx Tech program was launched in April 2020 by NIBIB to swiftly develop and bring to market millions of diagnostic tests for SARS-CoV-2. Central to the design, implementation, and management of RADx Tech is the NIH Point of Care Technology Research Network (POCTRN 2022b), which was well established prior to the pandemic and uses a partnership model to improve clinical care by developing POC test devices, assessing clinical needs, training technology developers, and providing administrative support. Described as "a competitive shark tank" by U.S. Senator Lamar Alexander, who co-sponsored funding legislation (Senate testimony on new tests for COVID-19 2020), RADx Tech leverages POCTRN and harnesses the strengths of the U.S. government, academic, and private sectors to rapidly vet, fund, support, and bring new tests to market. While other programs under the RADx umbrella focused on early-stage technologies, laboratory-based tests, and supporting underserved populations, RADx Tech initially focused on new POC tests with some support for at-home tests (Tromberg et al. 2020). This focus evolved with time due to real-world test usage studies (Dempsey et al. 2021), the needs of public health agencies, and the proliferation of SARS-CoV-2 variants.

Innovators from across the business, academic, nonprofit, and other sectors with promising COVID-19 diagnostic devices or testing platforms were invited to submit a detailed proposal describing their product and development plans. Proposals were reviewed by an external panel of experts for feasibility based on technical, clinical, regula-

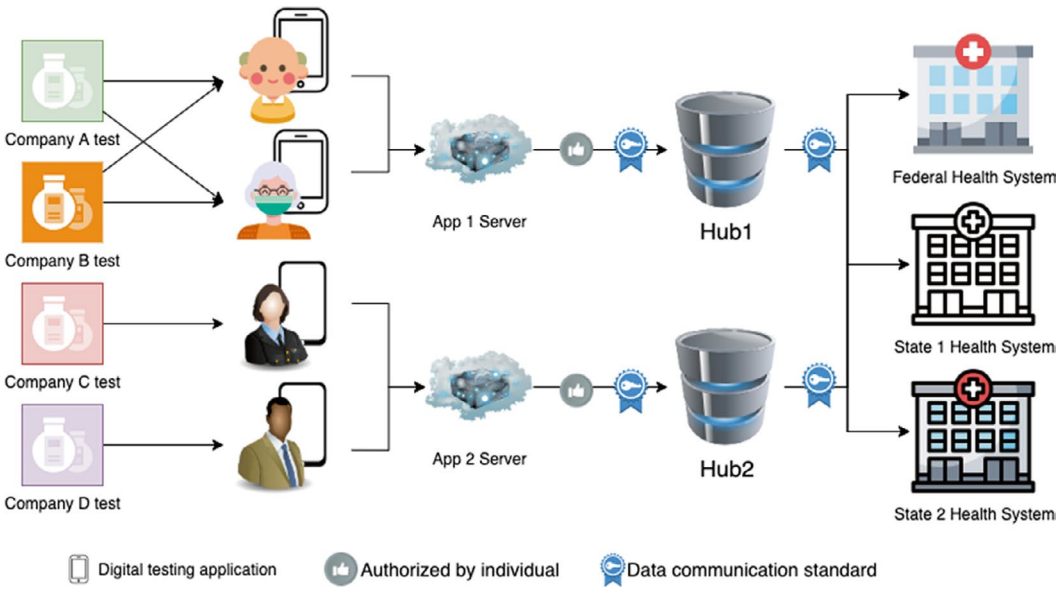

Fig. 7 How results from a self-administered test are sent to public health systems. The workflow supports tests developed by different manufacturers. Results are first captured in a mobile application (app) that accompanies a specific test. The App creates a healthcare data communication standards-based message that it sends to a third-party hub. The hub then relays the message to the appropriate public health system(s). (NIH, public domain, from ▶ https://www.nibib.nih.gov/covid-19/radx-tech-program/mars)

tory, and commercialization criteria (Fig. 7). Qualifying proposals advanced to the "deep dive" stage (Phase 0) for work package (WP) development and were assigned a team of healthcare commercialization and content experts to assess the proposal and identify risk factors that could impede progress. Milestones indicating risk resolution and further progress were assigned. Projects with the greatest potential to increase national testing capacity and fill key gaps in the testing ecosystem were advanced to the next phase (Phase 1) and were provided financial resources via a grant subaward from a POCTRN center; expert advisors; and in-kind technical, clinical, and business support to address high-risk barriers to development success. Sufficiently de-risked projects were issued substantial contract awards by NIBIB in the final phase (Phase 2) to support the full range of activities needed for large-scale distribution to the public, including manufacturing. As of September 2022, the RADx Tech innovation funnel (includes RADx ATP and RADx ITAP) has enabled 35 novel technologies to obtain FDA emergency use authorization, delivering a cumulative five billion additional COVID-19 tests and test products to the market, including the first over-the-counter test for at-home use. The following sections will provide an overview of the program design and operations of RADx Tech; for further information, Schachter and Parrish (2021) published an extensive description of the program's components as a special section in the *IEEE Open Journal of Engineering in Medicine and Biology*.

2.2 The Innovation Funnel

The RADx Tech selection methodology is referred to as the innovation funnel (Fig. 7) because the multistage review process, designed to quickly eliminate unlikely prospects and provide deep, intensive evaluation of likely prospects prior to funding, resulted in a narrowing pipeline ending with the deployment of highly competitive products. The funnel was open for a broad assortment

Category	Criteria
Technical	Can the technology be developed to the highest levels of analytical performance (e.g., sensitivity, specificity, dynamic range, limit of detection, reliability, accuracy, speed, and throughput) as well as operational performance, such as patient- and user-friendly design, alternative sampling strategies (saliva, exhaled breath, etc.), optimization of swab materials and test reagents, mobile-device integration, increased accessibility, and home use? Do these technical and design advances help expand national testing capacity and provide clear advantages over current approaches?
Clinical	Is the proposal a realistic approach to increasing SARS-CoV-2 testing? Can it be rapidly integrated into the healthcare system?
Commercial	Assuming the technology works as anticipated, can it be implemented and produced economically at scale?
Regulatory	Are there feasible plans to perform the studies required for FDA Emergency Use Authorization (EUA) and subsequent FDA clearance?

Fig. 8 RADx Tech project review criteria

of technologies at various stages of maturity from any sponsoring organization. One key principle was that there is strength in diversity, and that RADx Tech would explore the best exemplar of each approach to detecting the SARS-CoV-2 virus.

The 700-plus proposals received by August 11, 2020, when the submissions window initially closed, were reviewed by NIH staff, scientific consultants, and industry experts using a defined set of evaluation criteria (Fig. 8) with the goal of rapidly enabling commercialization (NIH 2022b). As these proposals went through multiple evaluation steps, the numbers narrowed: 140 (20%) from this initial cohort were invited to participate in the "deep dive" process (Phase 0) where reviewers met with the test developer to quickly vet the technology, the team, and the commercialization potential. Fewer than one-third of the 140 projects then advanced to Phase 1: a detailed evaluation of risks, steps required for commercialization, and needed funding. NIBIB funded more than 30 of these work package-1 (WP1) projects in Phase 1, designed to de-risk (i.e., identify risk factors that could impede development and deployment of the proposed technology) the technology and manufacturing process and to obtain regulatory authorization. A handful of proposals were immediately ready for the next stage of support. These, along with successful WP1 projects, were awarded work package-2 (WP2) contracts, for example, to scale up production or broaden their usability, such as taking a POC authorized product and getting over-the-counter authorization. NIBIB reopened the innovation funnel for new applications in July 2021 and, as of November 2021, has awarded more than 45 WP2 contracts in Phase 2, with a cumulative value of almost $700M (NIH 2022a).

Not all projects were successful. While the failure rate of WP1 to WP2 transitions was relatively low, the number of WP2 projects that failed to meet their milestones on time has been relatively high. Due to the ongoing pandemic, NIBIB has made several difficult decisions to discontinue support for projects that met technical milestones but not commercialization goals.

As part of the ongoing evaluation of each funded WP1 and WP2 project, NIH program managers and the RADx network of expert advisors and consultants meet weekly and even daily with the test developer to assess progress. A dedicated team of scientific, technical, and industrial experts provides coaching to get the product from concept to full-scale production and implementation. In addition to deep involvement with the test developer, RADx Tech supported an independent validation process that subjected each product to bench testing, analytical testing, evaluation with clinical samples, and ultimately clinical evaluation against a "gold standard" reverse transcriptase-polymerase chain reaction (RT-PCR) assay. For over-the-counter use, products also underwent human factors evaluation to assess the ability of users to perform the test and read the results accurately. As virus variants evolved and became epidemiologically relevant, tests were also

required to undergo evaluation for their ability to detect these new variant strains. The end goal of this independent validation was to ensure that each product met the FDA's EUA requirements and could provide documentation of device performance. Within a year, the test developers supported by RADx were producing 17 million POC and at-home tests per month.

2.3 Test Validation

Independent verification of the test performance data provided by the developer was a critical component of Phase 1 (WP1) of RADx Tech and enabled NIBIB to make more informed decisions on whether to continue funding the project. It would also prove instrumental in assessing the impact of SARS-CoV-2 variants on the efficacy of rapid antigen tests (Frediani et al. 2021) and in establishing standards for evaluating diagnostic technologies that would go on to become the foundation for RADx ITAP. The Test Verification Core (TVC) was rapidly initiated at the Atlanta Center for Microsystems Engineered Point of Care Technologies, a partnership between Emory University, Georgia Institute of Technology, and Children's Healthcare of Atlanta, to serve as the national test validation hub, providing impartial assessment of the design and performance of diagnostic tests.

The organization, operation, and technical assessments conducted by the TVC are described in detail elsewhere (Nehl et al. 2021). Briefly, a multi-institutional and transdisciplinary team was assembled along the following workstreams: laboratory and clinical device evaluation to understand the sensitivity, specificity, and cross-reactivity of candidate devices in controlled and community settings and compared to RT-PCR tests; regulatory expertise to identify and overcome barriers to device approval and distribution; usability testing by patients and others to identify and overcome device limitations; and engineering assessment to evaluate robustness of design including human factors, manufacturability, shipment and storage requirements, and scalability. This comprehensive test assessment program required extensive laboratory resources, comprising biosafety level 2 and 3 facilities, biobanks of COVID-19 positive and negative patient specimens, community-based collection, and engineering design and human factors assessment labs.

2.4 Clinical Studies

While the Test Verification Core (TVC) provided a detailed assessment of diagnostic tests largely under controlled laboratory conditions, RADx Tech established the Clinical Studies Core (CSC) to evaluate COVID-19 tests in real-world situations and generate clinical data for regulatory authorization. The CSC was created by the Center for Advancing Point of Care Technologies (CAPCaT) in Heart, Lung, Blood, and Sleep Diseases, a POCTRN technology hub at the University of Massachusetts Lowell and the University of Massachusetts Medical School, with contributions from other POCTRN centers at Northwestern, Emory, and Johns Hopkins Universities. The primary objective of the CSC was to design and implement diagnostic device clinical studies to evaluate test performance and usability across diverse use-case populations and settings.

Gibson et al. (2021) describe in detail how the CSC built and maintained clinical studies infrastructure and platform trial designs that could be rapidly adapted for clinical trials of each testing technology entering RADx Tech Phase 2. This included a master protocol, consent form, digital study platform, data management system, single institutional review board (research ethics review committee) with study site reliance agreements, community engagement mechanisms, and multisite partnerships. The infrastructure and core design enabled standardization while accommodating the diverse testing methods and test environments under study. Further accelerating the studies was the Eureka digital research platform through which trials were executed (Eureka 2022). Supported by NIH and developed at the University of California San

Francisco, Eureka engaged study participants through a web-based interface or mobile app to assess their eligibility for the study, obtain their consent to participate, and complete digital surveys on their interpretations of test results and assessments of device usability. Taken together, the CSC's efforts to streamline studies significantly reduced the time and costs of trials and enabled successful products to get to market faster.

2.5 Regulatory Review and Emergency Use Authorization

Before a medical device, including in vitro diagnostics such as COVID-19 tests, can be marketed in the United States, clinical studies are generally needed to demonstrate to the FDA that the device is safe and effective. Following the January 31, 2020, declaration by the Secretary of Health and Human Services of a national public health emergency in response to COVID-19, the FDA exercised its authority to waive some of these requirements and issue emergency use authorization (EUA) for medical devices that had not gone through the entire traditional approval or clearance process. However, test developers were still required to provide sufficient evidence to validate analytical and clinical function of the diagnostic device. The FDA requires rigorous data because unreliable COVID-19 tests could harm individual and public health (FDA 2021b). False positive results can lead to unnecessary quarantine, resources wasted on contact tracing and testing, and delay in accurate diagnosis and appropriate treatment. False negatives could mean patients do not get the treatment they need, even as they potentially spread the disease to others.

To help test developers and manufacturers design their clinical studies, the FDA provides EUA templates that lay out clear protocols and guidelines to follow as one pathway to authorization (FDA 2022). In broad terms, the FDA asks developers to demonstrate that a COVID-19 test meets analytical and clinical criteria in a randomized, blinded clinical study that compares test results with paired reference samples. The analytical study typically includes an assessment of the limit of detection (LOD) (i.e., test sensitivity), cross-reactivity with other pathogens (i.e., test specificity), and flex studies to check that the test will function properly despite minor product or sample variations—the sort of assessment that usually precedes a full clinical study.

The clinical study must demonstrate that an in vitro diagnostic device does what it claims for the population it is intended to serve. Test developers must consider whether the intended population will include children, whether the test distinguishes between levels of infection, whether it is intended only for symptomatic individuals or also for asymptomatic screening, and of course the use environment. For POC and at-home tests, developers must demonstrate that the intended user can successfully run the test "first time out of the box" using only the provided instructions. Usability testing is generally conducted in parallel with the clinical study to accelerate the timeline to regulatory review submission.

With the high opportunity cost of delaying test development during the COVID-19 pandemic, the RADx Tech program sought to accelerate regulatory authorization by conducting some of the analytical, clinical, and usability studies in parallel. While this puts investment at greater risk compared to the traditional sequential approach, it accelerated market entry for tests that met regulatory standards. Coordination between NIH and FDA throughout the RADx initiative was critical to efficient analytical and clinical study design and implementation.

2.6 Deployment: Supply Chain, Manufacturing, and Distribution

In anticipation of FDA emergency use authorization of a RADx Tech-supported test, NIBIB invested considerable effort and funds to enable test developers to produce tests in

high volume immediately upon authorization. It is rare for a medical product to launch with a high production volume; typically, there is a "beta" period after the product has been approved when marketing strategies are developed, supply chains are built, and consistent product quality is assured. Sometimes the production is paired with storage to ensure wide availability after the post-approval steps are complete. These are not options during a pandemic when tests are needed at scale immediately.

Most of the RADx Tech-supported developers had little experience launching new products, while supply chains, manufacturing, and distribution have not normally been within the purview of NIH. Therefore, a team of commercialization, procurement, logistics, and supply chain experts was incorporated into the RADx network as a Deployment Core to provide test developers in Phase 1 and Phase 2 of the program with coordinated infrastructure to enable market entry. Consultative services provided by the Deployment Core included, but were not limited to, procurement and supply chain, manufacturing and development, logistics, distribution, quality management, regulatory, recruiting, reimbursement, market research, and verification/validation (Walsh et al. 2021). Critical to the success of the Deployment Core were close partnerships and collaborations with the HHS Assistant Secretary for Preparedness and Response (ASPR),[1] the Biomedical Advanced Research and Development Authority (BARDA), and multiple components of the Department of Defense, including the U.S. Air Force Acquisition COVID-19 Task Force.

The deployment challenges were compounded by pandemic-related supply chain constraints, labor shortages, and competition for scarce resources. Prior to the formation of the HHS Testing and Diagnostics Working Group, the Deployment Core developed projections of raw material needs, potential suppliers, and market rates. These projections were used to build forecasts for critical components of COVID-19 diagnostic tests, such as nasal swabs, nitrocellulose membranes for lateral flow assays, automated manufacturing equipment, pipette tips for high-throughput assays, sample collection vials, and sterilization and packaging equipment. These forecasts, combined with other Deployment Core outputs, informed RADx Tech programmatic and funding decisions to support additional technologies that used alternative materials or sample collection methods. Strategic, albeit limited implementation of Defense Production Act (DPA) authority to prioritize government contracts with suppliers also helped reduce supply chain limitations. For example, RADx Tech has relied on DPA authorities to support procurement of pressure sensors, fluid flow sensors, microcontrollers, and automation equipment for test developers in its portfolio.

The Deployment Core also developed educational tools to inform the public about available tests and how to use them in a variety of settings. A continually updated online guide (on when to perform testing in various environments, situations, and using different kinds of diagnostic technologies) is a key source for public information (When to test 2022). Built in collaboration with the MIT Institute for Data, Systems, and Society, ▶ WhenToTest.org provides science-based guidance for individuals and organizations on mitigation and testing strategies, and how to combine COVID-19 prevention and containment with the latest testing strategies to minimize the spread of the virus in specific environments (Walsh et al. 2021). Based on individual user input on contacts with others or their organization's mitigation strategies, level of compliance, and community prevalence of COVID-19, the underlying mathematical model provides recommendations and guidance for developing and implementing a specialized testing strategy.

2.7 Digital Health Infrastructure and Tools

Reflecting the potential of digital health technologies to augment COVID-19 testing, a key

1 Now the Administration for Strategic Preparedness and Response.

element of the RADx Tech program was development and evaluation of digital health tools. These fall into four categories, each with the potential to guide individuals through the pandemic in specific but synergistic ways.

2.7.1 Wearables

Wearables for monitoring and detection, including smartwatches, fitness trackers, and other wearable sensors, can continuously monitor physiological signals as individuals go about their lives. Sensor data can be analyzed with statistical or deep learning models to detect anomalies or changes in signals from baseline, a potential indicator of deteriorating health or disease. This approach has been used to detect COVID-19 onset from smartwatch data prior to appearance of symptoms (Mishra et al. 2020). While this strategy has shown promise, it currently suffers from relatively low detection sensitivity and specificity. A practical application of this technology may therefore be to alert individuals of suspected COVID-19 and encourage them to get tested, rather than trying to make a diagnosis from smartwatch data alone.

2.7.2 Digital Contact Tracing and Exposure Notification Systems

Digital Contact Tracing and Exposure Notification Systems, such as the one developed by Apple and Google (2022), were among the widely known mobile health technologies emerging during the COVID-19 pandemic. This smartphone-based technology causes phones that come near each other to exchange anonymous key codes via Bluetooth or other wireless communication protocols; if a phone owner later tests positive, it can trigger a notification to all other phones that were nearby in the preceding days, alerting those notified to get tested. This novel digital approach supplements manual contact tracing, which is resource intensive. However, digital contact tracing has yet to achieve widespread adoption largely due to concerns about privacy, security, and trust (GAO 2021). Future efforts are needed to demonstrate the effectiveness of digital contact tracing tools and better educate the public about their value.

2.7.3 Proof-of-Health Status Technologies

While contact tracing is useful when an individual tests positive, other digital health technologies can offer value to people who test negative. Proof-of-health-status technologies, also known as testing or vaccine passports, can provide a digital record of an individual's test result or vaccination history. Several solutions have emerged during the COVID-19 pandemic that leverage advances in cryptography and blockchain to provide securely identified certification of health status while protecting individual privacy. As with digital contact tracing technologies, public adoption has been limited due to politicization and concerns over security and privacy. Nevertheless, some practical solutions have emerged. For example, through a partnership between the identity verification provider CLEAR and the at-home test manufacturer Lucira Health, the Golden State Warriors NBA team leveraged testing passports to ensure that unvaccinated fans tested negative for SARS-CoV-2 before entering the stadium (NBA 2021).

2.7.4 Smartphone Companion Testing Apps

As self-administered tests became more prevalent during the COVID-19 pandemic, so did the availability of *smartphone companion testing apps*. These apps are generally designed to assist users with test administration, either through on-screen instructions or by connecting users with a live telehealth proctor. Another important feature of these apps enables individuals to share their test results with state and federal health systems. In some cases, the apps can even interpret test results; for example, by analyzing a photograph of the test strip.

2.7.5 Combined Technologies

While each of the above technologies can serve a unique role in guiding individuals through pandemic life, their greatest impact can be achieved by combining them into an integrated system. Consider a person who feels healthy, but whose smartwatch generates an alert about suspected COVID-19 onset. The person self-administers a COVID-19 test

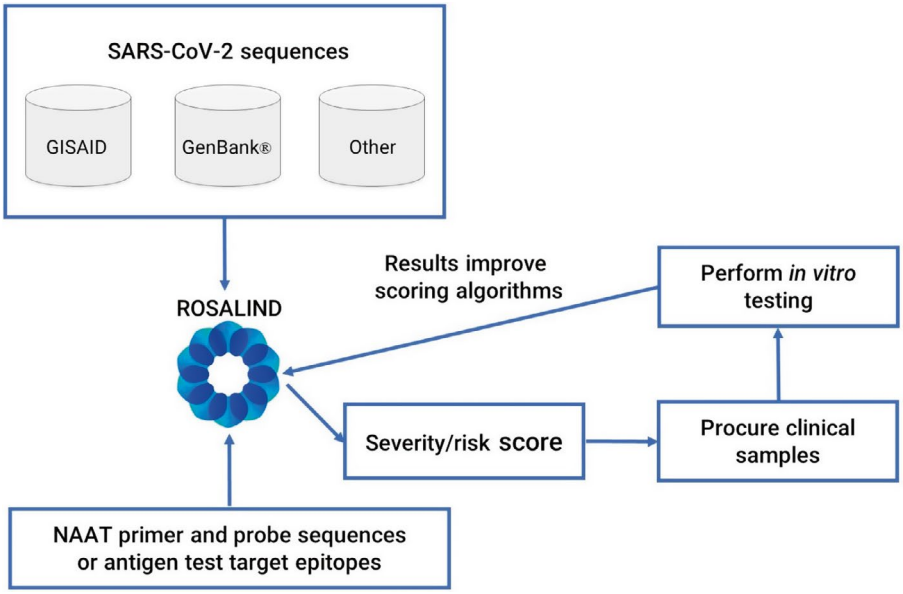

Fig. 9 RADx Variant Task Force program for assessing the impact of variants on SARS-CoV-2 molecular and antigen tests. (Creager et al. 2021; CC BY 4.0)

at home under the guidance of a smartphone app. The app interprets the test result as being positive, shares the result with the state public health department, and leverages digital contact tracing to automatically notify other phones that were in close proximity in recent days. Two weeks pass, and the person recovers from COVID-19 and self-administers another test that yields a negative result. The testing app issues a digital testing passport, allowing the person to board a plane for vacation. While this scenario is not currently possible, it may be an element of future pandemic response.

2.8 Monitoring and Anticipating Viral Variants

The emergence of the COVID-19 Delta variant in 2021 underscored the importance of ongoing monitoring and quality control of test sensitivity. The NIH, CDC, and FDA developed a collaborative strategy to address this challenge. The CDC established a nationwide genomic surveillance program, engaging multiple high-throughput laboratories to perform whole-genome sequencing on up to 100,000 SARS-CoV-2 samples per week. The NIH and the FDA jointly created the RADx Variants Task Force (VTF), which brought together RADx Tech's test verification and bioinformatics cores and the FDA's Center for Devices and Radiological Health. The mission of the VTF was to ensure that testing technologies supported by RADx Tech would accurately and comprehensively detect SARS-CoV-2 variants. This was a critical aspect of nationwide access to an array of effective COVID-19 tests.

The VTF carried out its work through a combination of computational and laboratory approaches. The computational aspect centered on continuous processing of viral genomes deposited into the global genetic database GISAID[2] and public sequence databases to track the distribution of viral lineages and identify lineage-specific mutations (Fig. 9). These mutations were compared to known primer probes of molecular tests and known epitopes of antigen tests to evaluate whether loss of affinity or signal was likely.

2 Originally called the Global Initiative on Sharing Avian Influenza Data.

All tests computationally identified as being at risk for loss of sensitivity were referred to the Test Verification Core for laboratory follow up.

The laboratory component of the VTF effort relied on collection of viral samples from partner laboratories. Only samples that were fully characterized through whole-genome sequencing were collected. The emphasis was on samples of variants that could lead to loss of sensitivity, although a representative library of SARS-CoV-2 lineages was maintained whenever possible. Existing tests computationally shown to be at risk for sensitivity loss were evaluated against variants in a laboratory setting, with the outcome guiding potential adjustment of either the test or the accompanying label. Experts from the FDA participated in the design and evaluation of both computational and laboratory metrics, enabling test developers to use the VTF data as part of their EUA or other regulatory submission. Administration officials overseeing pandemic response were briefed when emerging SARS-CoV-2 variants seemed likely to reduce the sensitivity of any test when used in a meaningful new market, as well as on the outcome of ensuing validation or remediation.

3 Summary of Key Lessons Learned

The RADx Tech Program has demonstrated the value of active NIH engagement across scientific, technical, operational, and commercial boundaries during a health emergency. RADx Tech compressed the timeline and increased the success rate for innovative biomedical technology development and commercialization. The urgency of the pandemic and declaration of a public health emergency provided the opportunity to speed up program implementation, fund at-risk activities in parallel with de-risking work, explicitly support product development and commercialization through direct partnerships with experienced industry consultants, and collaborate freely and intensively with other government agencies and departments. Shared, urgent goals in a public health crisis underscored the value of combining complementary capabilities from government, industry, and academia to solve interdisciplinary challenges. These experiences will likely have a lasting impact on how NIH, and by extension the U.S. Government (USG), approaches biomedical technology development.

3.1 Scientific and Technological

Investment in diverse diagnostic platforms is essential to ensuring that different use cases can be met successfully. RADx Tech supported a diverse portfolio of diagnostic assays and platform technologies; these ranged from hand-held RT-PCR devices with isothermal amplification to CRISPR-based (clustered regularly interspaced short palindromic repeats) assays to lateral flow assays utilizing quantum dot technology, to name a few. Multiplexed platforms, analyte concentration reagents that increase assay sensitivity, and injection-molded plastic nasal swabs are additional innovations developed with RADx Tech support. By spreading its investments across a variety of detection approaches targeting diverse viral genomic sequences and antigens, the potential that SARS-CoV-2 variants could evade tests across the diagnostic portfolio was reduced. Similarly, the impact of supply chain disruptions was diminished when tests utilized different components, from buffers to reagent enzymes to swab types. This scientific and technological heterogeneity was a critical design component of RADx Tech's approach to accelerating diagnostic innovation, and has had the secondary benefit of supporting many small businesses and diversifying the program's positive economic impact.

Another scientific and technological advance was the establishment of VTF with experimental analysis from the Test Verification Core (TVC). Building diagnostic resilience against the arrival of SARS-CoV-2 variants required resources to monitor their emergence and measure impact on test performance. The VTF and TVC built their sample collection, inventory, and storage management capabilities and assay protocols to ana-

lyze test sensitivity quickly and quantitatively as variants emerged. Again, the diversity of molecular and viral tests receiving RADx Tech support was critical as the ability to adapt testing technologies to viral variants is not uniform across diagnostic platforms. Rapid antigen tests tend to design robustness against variants into the initial selection of antibody/antigen pairs but require laboratory or real-world analysis to demonstrate continued accuracy, while nucleic acid amplification-based tests can more rapidly be modified with new primers that identify mutated sequences based on computational analysis of binding affinity.

Overall, the technologies accelerated through the innovation funnel are likely catalyzing a fundamental shift in the diagnostic testing ecosystem, away from the dominance of laboratory assays to further integration of rapid POC and at-home tests powered by cutting-edge analytical science and digital health technologies. The acceptability of and demand for access to facile, on-demand testing is growing, and continued diagnostic innovation will be needed to meet that demand. This is a story that continues to unfold, and the relevance of in vitro diagnostic testing, both in a health crisis and in the larger context of healthcare and personalized medicine going forward, was captured in a recent *Nature Biotechnology* editorial stating, "[the] combination of RADx technologies, together with structural changes to healthcare during the pandemic, has the potential to radically change diagnostics, opening up the point of care (POC), at-home and community testing settings" (Radical solutions 2021).

3.2 Operational

A critical programmatic tool NIH has used to bring scientific discoveries into the clinic to positively impact human health is public–private partnerships. NIH has a substantial record of achievement in supporting research that leads to the development of technologies for basic science and clinical applications. However, NIH has traditionally not provided active support for development and commercialization activities that follow the research phase of technology development. That work has historically been regarded as the province of industry, though the significant challenges of moving technologies from laboratory prototype to commercial product are many. While NIH encourages the licensing and commercialization of products originating in agency-funded research, direct support for commercialization has been limited.

RADx Tech, building on the POCTRN operational model and further expanding industry partnerships, provides a roadmap for NIH success in the acceleration of technology development, preparation for regulatory submissions, and commercialization of impactful health technologies. The success of RADx Tech demonstrates that urgency and willingness to step beyond the traditional NIH approach to technology development can significantly accelerate the transition from concept to proven product. Engaging a large cadre of consultants with significant industry experience proved critical. This includes leadership for rapidly growing companies, navigating a complex, rapidly evolving regulatory process, and solving problems in supply chain, cash flow, marketing, and sales, among other tasks. The availability of experts with practical experience and a network of industry contacts has been essential. Industry insiders have been able to establish connections, build trust, and mentor emerging companies. Under a typical industry-funded development pathway, it usually takes 5–7 years to get a new medical device cleared by the FDA. RADx Tech has proven that with an all-hands-on deck approach and the investment of sufficient resources this can be reduced to as little as 12 months.

For a program like RADx Tech to be successful, it requires decision-making that extends beyond technical and scientific assessment. Investment decisions must also consider the capabilities of the company and its ability to execute the plans proposed. RADx Tech includes mechanisms to evaluate that larger picture. The team has had to learn to recognize warning signs of failure and be willing to move on when a diagnostic in development does not meet its performance metrics. Test

developers supported by RADx Tech face many hurdles, and not every company with an attractive technology platform has been able to fully act on the regulatory guidance and production assistance developed through the program. A clear-eyed appreciation that not every project will succeed must be tempered with the patience to see a promising project through the crises that are inherent in development and commercialization—problems different from the routine setbacks that scientists encounter in their research.

New collaborative arrangements with industry partners were not the only operational innovation; the success of the RADx Tech program would not have been possible without active partnerships across government. The urgency of addressing a global pandemic gave formal and informal networks among departments and operating divisions new importance and legitimacy. Those networks have addressed problems as diverse as expediting the movement of research materials through ports of entry, finding alternative suppliers for critical parts, developing novel approaches to rapid approval of tests already available outside the United States without diminishing the rigor of the regulatory review process, and ensuring that support for test development by different agencies is complementary rather than duplicative.

Government agencies have innovated together not just to accelerate processes but to improve them and increase confidence in outcomes. Sustaining these collaborative networks going forward has the potential to institutionalize a level of communication and cooperation that will not only impact ongoing technology development but also provide a warm base for action in subsequent public health crises.

RADx Tech has also leveraged the public health emergency-authorized flexibilities in federal procurement to award Phase 2 and other contracts at a rate commensurate with urgency of expanding COVID-19 testing while ensuring proper stewardship of federal funds. Prior to the pandemic, most large NIH contracts required an average of a full year to go from initial solicitation to final award. RADx Tech staff reduced this timeline down to a range of 10 days to 4 weeks. Another unique capability utilized by the program were "letter contracts," which support efforts with loosely defined objectives that are not guaranteed to achieve their deliverables or may not even be needed by the time the deliverable is completed. A key element has been to balance the need to act swiftly and decisively while maintaining good practices for government procurement. An important lesson as the country emerges from the pandemic will be to maintain the degree of flexibility appropriate for inherently risky activities like technology development directed at a moving target.

The approaches outlined above can be applied to other opportunities no less urgent but with a narrower impact than the COVID-19 pandemic, such as diseases with similar or worse consequences but affecting fewer individuals, building on NIH investments in the development of therapies for understudied and rare diseases.

3.3 Regulatory

The RADx Tech program has provided an opportunity to better understand how agencies with complementary missions such as NIH and FDA can collaborate while maintaining their autonomous decision authority. Facile communication between agencies has allowed NIH and the RADx Tech program to support participating test developers more effectively. It has also ensured that FDA has the necessary information for expedited review and issuance of EUAs. One example is the bi-weekly meetings that have shared awareness of trends, cross-cutting issues, and specific product issues among trusted interlocutors. A good example of what can result is the "universal" protocol RADx Tech developed with the FDA for clinical product evaluation, a protocol that provides more consistency in regulatory submissions for different products and reduces review time.

In the current healthcare regulatory paradigm, it is not the responsibility of the U.S. government to validate an individual product or monitor its market performance. Currently,

the FDA does not have authorization or appropriations to build analytical software or perform independent laboratory or clinical validation of performance and safety data submitted by test developers. In response, RADx Tech utilized the resources it had available to experimentally validate data from diagnostic products not associated with government-funded programs and build extensive analytical software to collect, manage, and store this data.

Initially, little effort was put into verifying shelf life, though as the pandemic progressed it became apparent that waves of infection would continue, and shelf life would be an important criterion. Given the relative immaturity of most POC and OTC technologies, the FDA has required "real-time" shelf-life evaluation, where sample products must sit on a shelf in typical storage conditions for the entire duration of the shelf-life claim being sought in order to demonstrate its viability.

Although genome sequences fulfill many functions that required physical samples until recently, this is not true of diagnostic validation. In the current state of uncertainty about sample sharing in international law, cross-border sample acquisition has rarely been possible during the last few years (Halabi 2019). This leaves diagnostic validation weeks behind the emergence of new variant strains since the strain must first spread to the United States, be detected domestically, sequenced, and sent to NIBIB or other labs in sufficient quantity to validate the performance of both authorized and pending products. In addition, during a lull in SARS-CoV-2 transmission, it became very difficult to collect enough positive samples domestically to support EUA claims.

3.4 Manufacturing and Supply Chain

The unpredictable ups and downs of the pandemic have led to further volatility in the changing diagnostic market, complicating a highly competitive and fragile supply chain for test components. It has been an iterative process to learn which supply chain items have a long manufacturing ramp-up that cannot be accelerated, and which can. This introduces additional risk, as items that require a long time to produce may be highly customized and usable only for one product—one that may have failed by the time the component is ready. Automated manufacturing equipment has been a perpetual challenge as it is expensive, usually highly customized, specific to a product, cannot be built quickly, and must be ordered and paid for before the product has been validated.

This led to a very challenging situation in the fall of 2021 as various market forces collided. The demand for COVID-19 testing had decreased compared to the previous summer, and most testing companies did not project enough long-term demand to maintain manufacturing capacity. Meanwhile, the global economy had begun to return to catch up on a year-long backlog in the supply chain. When the emergence of the Delta variant sparked demand for additional testing, there was intense competition across all market segments for commodity items such as semiconductor chips and other electronic components. Given the volatile behavior of the diagnostics market, most suppliers gave preference to their steady nondiagnostic customers. This left most POC and high-end OTC diagnostic products in short supply.

Talent and human resources have also been a severe constraint at various junctures. Many products went through an initial phase of production by manual or semi-automated assembly, both of which require short-term technicians to be hired and trained quickly. For lab-based tests, this shortage is even more critical given the training and certifications required. As one industry member put it, skilled and trained labor "cannot be stockpiled."

There has been constant tension between leveraging foreign manufacturing capacity to ramp up quickly versus the more sustained investment to build domestic capacity. Domestic manufacturing is ultimately more responsive to national needs and addresses national security concerns. However, domestic production costs are higher, which affects price, public access to testing, and long-term market competitiveness.

The key lesson learned, however, is that if the federal government wishes small businesses to build and develop new products quickly for a market that had not previously existed, then the government needs to provide key resources. For example, a half dozen industry experts were brought on board to coordinate RADx Tech supply chain activities. They provided a single RADx Tech point of contact with suppliers to support multiple products, and a small team to monitor ongoing and potential supply constraints.

3.5 Implementation

A key chicken-and-egg problem for RADx has been bringing new companies with new products to a new market. In several cases, it has been challenging to garner enough attention to get these small businesses over the hump. For example, a new medical product might need the same swab as an established diagnostic manufacturer. As there has never been an oversupply of swabs, the small company is usually unable to get the swabs they need for a comparative clinical evaluation prior to entering the market to compete with the established company.

On another note, the Centers for Medicare & Medicaid Services (CMS) has not been deeply involved in RADx activities, since Congress mandated that they pay for all *diagnostic* tests. The lack of reimbursement for anything other than *medical* diagnosis has put a massive crimp in national surveillance and early detection. While CDC and state departments of health have funded some efforts, other organizations (e.g., schools and businesses) must be subsidized (e.g., the joint DoD and HHS Operation Expanded Testing) or make difficult business decisions about whether to pay for testing as a proactive measure to detect and avoid COVID-19 transmission. Moreover, day-care and pre-kindergarten settings, falling outside of the usual K-12 structure, have been a blind spot in testing policy and economics.

Another difficulty has been ensuring that all test results are reported to a public health authority. Since reporting is not required by the FDA or CMS and costs time and money, there is little incentive for reporting. This is particularly critical for cost-sensitive POC and OTC tests. But it goes both ways. On several occasions, county-scale efforts to distribute tests with reporting built in were rebuffed by the local department of health as they lacked data processing capacity. Logistics for transporting finished products from the site of manufacture to the end-user has been an underdeveloped component of the national strategy, particularly as logistics may account for up to two-thirds of the cost of a test. This was compounded for some time starting in the fall of 2021 by the severe backlog of ships waiting to unload at seaports.

Finally, the national testing strategy has primarily been reactive to changing conditions. While vaccines and therapeutics have been supported proactively through deployment and implementation, emphasis and resources have been provided to testing only as need arises. Further, perceptions regarding the need for and value of testing have fluctuated as diagnostics (relative to vaccines and therapeutics) grows into its role in that triad. Given the months-long ramp-up time to manufacture new tests and get them to market, testing capacity has frequently lagged demand. This on-demand approach has led to some very high-profile and unfortunate situations where manufacturers have ceased production or eliminated their capacity (Fink 2021). As the nation prepares for SARS-CoV-2 to become an endemic disease with new waves as variants emerge, and as global health attention shifts to negotiating a preparedness instrument for the next pandemic (WHO 2022), it is incumbent upon us to ensure that diagnostics does not become the weak leg of the disease response tripod.

3.6 Digital Health Technologies

Digital health platforms should empower individuals to manage their healthcare data, make better-informed decisions for themselves and their families, facilitate communi-

cation with their healthcare providers, and support public health response when needed. With home-use diagnostics, data may be generated and collected in disparate systems. For example, an individual may use one device to collect heart rate data, a separate device to check blood pressure, and a third device to monitor blood oxygenation. Platforms that aggregate these data are needed and will be central to the digital health connectivity of the future. Systems such as Apple Health are early entrants into this market, and others are being developed. These platforms must adhere to principles of patient accessibility, patient control, and patient empowerment (Layman 2020). The public would be best served with a choice of such platforms that compete for market share by providing the best services for the best value, yet they must provide data to a unified healthcare platform for advanced applications to be developed to provide personal guidance to patients.

To support such data aggregation, devices need to collect, store, and transmit diagnostic data in standard formats. This will enable the data generated by tests and devices of different manufacturers to be stored in a variety of personal health records. The standards must also allow exchange of information between an individual and other electronic health records, including public health systems. Such communications should be bidirectional, allowing a diabetic patient, for example, to share results of home blood glucose tests with their primary care physician, and allowing that same patient to obtain electronic copies of lab results residing in the physician's electronic medical record. Results of home COVID-19 tests sent to public health departments could help inform state and federal responses to a public health emergency. Health Level Seven International Version 2 (HL7v2) has been a tried and tested communications standard for decades, one that continues to evolve and adapt to meet new requirements such as remote diagnostics. The Fast Healthcare Interoperability Resource (FHIR) is an emerging communications standard compatible with HL7 that may be well suited for the mobile applications associated with remote diagnostics but requires wider adoption and development to reach its full potential.

Discussion Questions

1. How can government research and development institutions best design and implement programs to catalyze diagnostic innovation in the face of an infectious disease emergency?
2. What are some attributes of the RADx Tech program that provide lessons for future infectious disease outbreaks? What elements of RADx Tech could be improved?
3. Note some barriers to the development and deployment of POC and OTC tests during the COVID-19 pandemic. Consider issues in various domains, for example, scientific, technological, clinical, regulatory, and commercial. Propose an approach to overcoming one or more barriers in the future.
4. How might the proliferation and utilization of self-tests for at-home SARS-CoV-2 testing affect how we detect and diagnose other diseases, both infectious and noncommunicable, moving forward?

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