been sequenced; and far more samples have been sequenced than are represented in GISAID.

In countries with a longer CST lag, the new variants may have enough time to establish themselves across a region[13] if quick tracking, tracing and actions to stop transmission are not undertaken. Therefore, this issue must receive urgent attention and bottlenecks that prevent a lower CST lag must be addressed.

Overall, an effective genomic surveillance system requires not only sequencing a major fraction of SARS-CoV-2 strains from COVID-19 patients, but also rapid genome submission to open access platforms like GISAID. This will enable researchers across the globe to track the evolved variants and their mutations, epidemiology and biological consequences, which will provide crucial inputs for appropriate and effective public health policies ❐

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The need for new test verification and regulatory support for innovative diagnostics

To the Editor — The pressing need to address the COVID-19 pandemic led to the creation of novel large-scale cooperative programs among the US government, including the US National Institutes of Health (NIH) and the US Food and Drug Administration (FDA); academia; and private industry. A case in point is the NIH's Rapid Acceleration of Diagnostics (RADx), the diagnostic testing arm of Operation Warp Speed — a public–private partnership to fast-track SARS-CoV-2 vaccines, diagnostics and therapeutics. As the name suggests, the goal of RADx is to accelerate development, verification, validation, FDA Emergency Use Authorization (EUA) and deployment of diagnostic tests to detect infection with SARS-CoV-2. Availability of fast, accurate and inexpensive testing is a key component of efforts stemming from the pandemic. RADx was created in response to our nation's declared state of emergency that caused a sharp increased demand for testing in traditional clinical laboratories, resulting in a nationwide shortage. This cascade of events motivated swift innovation of new technologies using alternative test materials and methods, and even alternative biospecimen sample types. As investigators in the RADx initiative, we gained a unique perspective on the frenetic pace of test development, performance testing and regulatory assessments in response to the COVID-19 pandemic. Consistent with an editorial recently published here in *Nature Biotechnology*[1], our experience suggests that RADx provides a high-reward approach for a relatively small investment. Furthermore, we believe the RADx model could be broadly established and applied beyond the current pandemic as a foundational resource to improve the developmental pathway for novel laboratory and point-of-care tests for all varieties of diseases.

For its RADx infrastructure, the NIH leveraged its Point-of-Care Technology Research Network (POCTRN), of which our center, the Atlanta Center for Microsystems Engineering Point-of-Care Technologies (ACME POCT), serves as the national RADx test verification hub. In this role, and in collaboration with the FDA, we provided independent and impartial verification data on the performance of COVID-19 diagnostic tests developed by private companies or academic inventors. RADx and ACME POCT also created a close working partnership with FDA leadership and regulatory experts to convey clear regulatory guidelines and processes to developers, who often had little experience in this area. RADx also provided test developers access to a network of experienced entrepreneurs to help them avoid common mistakes that could hinder innovation, evaluation and deployment of COVID diagnostics.

The ACME POCT has evaluated over 80 different diagnostic technologies for detection of SARS-CoV-2 infection. These products, which typically detect either SARS-CoV-2 antigens or SARS-CoV-2 RNA, originated from a spectrum of applicants ranging from well-established companies to small teams from academic laboratories. For test verification at the ACME POCT, each diagnostic technology was put through a battery of different evaluations to determine preliminary analytical and clinical performance (for example, limits of detection, sensitivity, specificity and cross-reactivity), repeatability and usability. Whenever possible, tests were cross-compared with one another to provide the NIH and RADx leadership the most objective performance data on which to base their decisions to fund test validation, further manufacturing,

Table 1 | Attributes of nine best-performing companies and their SARS-CoV-2 diagnostic tests evaluated at ACME-POCT as part of RADx

Company size (employees)[a]	Analyte	Location	Tested dilution of positive patient pool[b]				
			Undiluted	1:10	1:100	1:1,000	1:10,000
			2×10^6 GE ml^{-1}	2×10^5 GE ml^{-1}	2×10^4 GE ml^{-1}	2×10^3 GE ml^{-1}	2×10^2 GE ml^{-1}
>1,000	Antigen	POC	**Positive**	Negative	Nt	Nt	Nt
200–1,000	Antigen	POC	Faint	Nt	Nt	Nt	Nt
10–200	RNA	POC	**Positive**	**Positive**	**Positive**	**Positive**	Nt
10–200	RNA	POC	**Positive**	**Positive**	**Positive**	**Positive**	Nt
10–200	Antigen	POC	**Positive**	**Positive**	**Positive**	Negative	Nt
10–200	Antigen	Central lab	Nt	**Positive**	**Positive**	**Positive**	**Positive**
<10	RNA	Central lab	**Positive**	**Positive**	Negative	Negative	Nt
<10	Antigen	POC	Faint	Negative	Nt	Nt	Nt
<10	Antigen	POC	**Positive**	Negative	Nt	Nt	Nt

$n = 9$, as of 31 December 2020. POC, point of care. [a]Company names have been omitted. [b]The analytical sensitivity was determined using the same pool of nasopharyngeal patient samples positive for SARS-CoV-2 RNA via RT-PCR. The applied dilution and resulting genome equivalents (GE) per milliliter are listed, as are the test results interpreted according to guidelines provided by each company: 'Positive', clearly positive; 'Faint', likely positive; 'Negative', negative; 'Nt', not tested.

scale-up and deployment on an accelerated timescale to meet the public health need.

Table 1 highlights a selection of the nine best performing technologies that were evaluated for detecting SARS-CoV-2 virus in the same positive patient pool at serial dilutions (just one of the battery of tests applied). As such, each of these diagnostic technologies analyzed the identical patient biospecimen, enabling a true 'apples to apples' comparison between different tests. The table also reports company size, analyte and clinical use case location, which was either point of care or a centralized laboratory.

Many of the testing technologies evaluated by ACME POCT are now either on the market or on track for expanded production and manufacturing to provide the US public with more and better testing. For example, owing in large part to the successful test verification studies conducted by the ACME POCT, the NIH accelerated the development and scale-up of a rapid antigen test (Ellume USA), which recently became the first COVID-19 home test to receive an over-the-counter EUA from the FDA. Those tests with less robust performance were either dropped from the RADx portfolio or were assigned to a separate pathway in which ACME POCT worked closely with the developers to iteratively improve their tests so they could be reevaluated in the RADx process.

Recently, Jeffrey Shuren, the FDA's director of the Center for Devices and Radiological Health, and Timothy Stenzel, the FDA's director of the Office of In Vitro Diagnostics and Radiological Health, described lessons learned while evaluating the flood of new COVID-19 tests developed in response to the global pandemic[2]. They also suggested much-needed changes in our country's approach to diagnostics, including more effective sharing of clinical specimens for test validation and improved education on appropriate test utilization and interpretation. In addition, we believe the innovative RADx test verification model could substantially accelerate diagnostic test development not only in response to future pandemics, but also for non-emergency public health issues.

This notion is guided by our observations in RADx that many smaller companies and academic groups with little experience in bringing clinical diagnostics to market have jumped into the pandemic response to translate their novel ideas into clinically useful tests for COVID-19 diagnosis. Indeed, our RADx experience has demonstrated that the innovative leaps required for rapid, accurate and low-cost tests are more likely to come from smaller companies and startups. In fact, of the over 50 tests we have evaluated so far, the four that showed the best combination of analytical sensitivity and specificity were developed by companies with fewer than 200 employees (Table 1). Yet great technology is not enough. Most of these smaller companies and startups have limited regulatory experience, and their novel technologies could be viewed as risky from the perspective of potential investors and acquirers of the said technology. By providing support with our objective third-party assessments and test verification, which were designed in collaboration with the FDA itself, the RADx program has helped several of these companies navigate regulatory requirements and successfully obtain FDA authorization in an expedited manner. In the proposed structure, if it were more broadly applied, this type of evaluation could be efficiently and immediately reviewed by the FDA alongside other performance and clinical data required for regulatory submissions for each test and thereby accelerate and de-risk diagnostics innovation overall.

To this end, we propose the creation of a federally funded programs in which academic or private laboratories, individual investigators or teams of scientists can compete for funding to create a distributed system of impartial third-party evaluators who work hand in hand with the FDA to assess new clinical diagnostic tests. Similarly, we suggest a European Union-funded system to help companies achieve a CE mark with European Union regulatory authorities. Like the ACME POCT, those selected centers would serve as independent testing laboratories to provide the critical objective data needed by the regulatory agency to evaluate new tests with higher confidence, even if they originate from recent startup ventures or individual investigators. By leveraging the multidisciplinary setting of a research university, academically based centers like the ACME POCT, with collective expertise in the basic sciences, biomedical engineering and clinical medicine, have the capability to nimbly bring in, on demand, researchers with specific skill sets relevant to the technology at hand.

For example, ACME POCT has most recently added academic researchers with expertise in aerosol chemistry and

analysis to help conduct test verification of COVID-19 breath tests that are moving through the RADx pipeline. Including academic laboratories in this network opens the possibility of agile collaborative interactions with test developers to improve technologically immature tests to the point where they merit FDA EUA, clearance or approval. Such cooperative initiatives would not only substantially improve the nation's ability to implement new diagnostic tests in response to the next pandemic or public health emergency, but could facilitate development of better tests for common chronic conditions in the United States, such as heart disease, cancer and diabetes.

What about established diagnostics companies? On the one hand, these firms did not nimbly respond to COVID-19 with the new types of game-changing innovations, such as highly sensitive, fluorescent nanoparticle-enabled rapid antigen tests for home use or disposable point-of-care PCR test kits that were desperately needed for contact tracing programs at the very beginning of the pandemic. On the other hand, they do play important roles in the response to public health emergencies through their substantial R&D, regulatory, production and distribution teams and long histories of FDA interactions. Larger companies can also develop tests rapidly for distribution in platforms already available in laboratories around the country and can manufacture assay reagents at large scale.

One other issue we would like to raise is that the data packages submitted on diagnostic products for regulatory review are produced either internally or through subcontracts; these tests typically do not undergo third-party verification studies before they undergo FDA review. Thus, we propose applying the RADx test verification approach to assays from large companies and small organizations (for example, academic groups or medtech startups) alike, as it would support impartial FDA evaluations and could also level the playing field for diagnostics entities of all sizes.

The challenges the FDA faced in responding to the pandemic were herculean, particularly the need to balance test availability and test supply shortages with comprehensive performance characterization during an avalanche of submissions for EUA of molecular, antigen and serology tests in a short period of time. The RADx program has paved a path forward for small- and medium-sized diagnostics companies with innovative ideas and novel technologies to help meet public health challenges and compete in the marketplace. A funded network of agile academic or private laboratories that can objectively evaluate novel clinical tests, whether they originate from the largest diagnostics companies or new startups, can provide impartial and cost-effective third-party assessments of test performance to facilitate FDA decision making. We believe this test verification model could be used to not only verify better performing, more innovative and less expensive diagnostic tests for SARS-CoV-2, fulfilling the RADx vision to "speed innovation in the development, commercialization, and implementation of technologies for COVID-19 testing," but also serve healthcare needs and shape test verification in the diagnostic testing landscape as a whole. ❐

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Check for updates

A Python-based programming language for high-performance computational genomics

To the Editor — The vast growth of next-generation sequencing data has provided us with a new understanding of many biological phenomena. As sequencing technologies evolve, sequencing datatypes (such as standard Illumina short reads, PacBio long reads or 10x Genomics barcoded reads) typically require new implementations of corresponding computational analysis techniques, necessitating software that is not only computationally efficient, but also quick to develop and easy to maintain so as to enable rapid adaptations to new kinds of data.

However, developing an efficient software tool requires domain expertise in performance engineering, computational modeling, and the ability to translate