

COMMENTARY

Covid-19 will not “magically disappear”: Why access to widespread testing is paramount

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Since the beginning of the current pandemic, Covid-19 has infiltrated all aspects of biomedicine. As the associations between mortality risk and chronic illness became evident, the field of hematology has played a front-line role in combating this global public health emergency, with a particular focus on patients with hematologic malignancies, immunodeficiencies, and sickle cell disease (SCD). Hematologists have been key in elucidating the pathophysiology of the microthromboses that occur with infection of the SARS-CoV-2 virus while determining the most effective anticoagulation regimens, in unraveling the mechanisms of the multisystem inflammatory syndrome in children, and in characterizing the development of neutralizing antibodies.¹⁻⁴ Accordingly, improving Covid-19 diagnostic testing - performance, capacity, availability, accessibility - has become a major collective goal of the biomedical community with hematologists heavily involved at the forefront of these efforts.

To achieve this goal, on April 24, 2020, Congress appropriated \$1.5 billion for the National Institutes of Health (NIH) to support SARS-CoV-2 development and expansion of testing. Within days, the NIH launched the Rapid Acceleration of Diagnostics (RADx) Tech initiative to develop innovative technologies and speed them to market, with the goals of (1) deploying millions of Covid-19 tests per week by December 2020 and (2) enabling Americans to return safely to school and work.⁵ The ambitious agenda of RADx Tech, as the name indicates, includes clinical evaluation, manufacturing scale up, and widespread deployment of tests to detect the presence of SARS-CoV-2 virus.

1 | RADX TECH: NOVEL PARTNERSHIPS TO ACCELERATE INNOVATION

Through RADx Tech, the NIH has undertaken a truly unprecedented plan to compress the typical medical diagnostic prototype-to-product launch timeline from years to weeks. Overseen by the NIH's National Institute of Biomedical Imaging and Bioengineering (NIBIB), the RADx Tech program formed a unique public-private partnership involving hundreds of civil servants, academic researchers, and industry consultants. The NIBIB solicited applications from diverse scientific entities that were developing Covid-19 diagnostic tests, including established medical device companies, startups, and academic research laboratories. Project applications were evaluated using a fast track, multi-staged review process including (1) initial evaluation by a team with wide-ranging clinical and scientific expertise; (2) a weeklong intensive review process, dubbed a "shark tank" by U.S. Senators Lamar Alexander (R-TN) and Roy Blunt (R-MO); and (3) a month-long, milestone-based clinical evaluation of all technologies deemed meritorious during the "shark tank". Technologies judged to be successful in this final stage received substantial financial assistance (tens of millions of

dollars) from the NIH and federal government to initiate rapid scale-up and deployment.

Honing in on the third stage above, one of the key objectives of RADx-Tech is to rapidly yet comprehensively evaluate technologies that successfully exit the "shark tank" via an independent and objective approach. To that end, the NIH leveraged the multi-institutional, U54-funded Atlanta Center for Microsystems-Engineered Point-of-Care Technologies (ACME POCT), an integral part of the NIBIB's longstanding Point-of-Care Technologies Research Network (POCTRN), to function as the national Test Validation Core for RADx-Tech. Based at Emory University, Georgia Institute of Technology and Children's Healthcare of Atlanta, ACME POCT is comprised of physicians, engineers, and basic scientists dedicated to fostering the development, clinical translation, and implementation of new diagnostic technologies, and is directed by a clinical researcher and pulmonologist, a micro/nanosystems engineer, and a pediatric hematologist/oncologist and biomedical engineer (an author of this commentary - Wilbur A. Lam).

With an infusion of \$50 000 000 from the NIH, the ACME POCT RADx Tech Center quickly established a program to efficiently verify the performance of Covid-19 diagnostic tests, focusing on their sensitivity, specificity, limit of detection (LOD), and cross-reactivity. The Center established an infrastructure comprised of bio-safety level three virology laboratories, clinical bio-banks of Covid-19 patient specimens (including nasopharyngeal, nasal, and saliva samples), and community-based collection sites for prospective testing to compare novel diagnostic technologies with the gold standard RT-PCR tests. This test validation model, which entails objective, third party validation using multiple methodologies, allows for go/no-go decision-making to force "fast failure" of underperforming technologies, while rapidly advancing meritorious ones. This model also enables "apples to apples" comparisons of the different RADx technologies by using the same protocols, personnel, and often the same patient samples. The Center's test evaluations are then incorporated into the NIH's ultimate decision-making process regarding whether or not to devote millions of additional dollars to scale-up manufacturing of those technologies towards making them rapidly available to the public.

In "testing the tests," the ACME POCT RADx Center has assessed a wide array of diagnostic technologies that have entered the RADx Tech pipeline. In general, Covid-19 diagnostic technologies fall into two major categories - *nucleic acid tests* that identify the RNA of the SARS-CoV-2 virus, and *antigen tests* that detect unique biochemical structures of the virus (eg, spike and nucleocapsid proteins). The underlying molecular biology of the nucleic acid tests in the RADx Tech program varies from standard RT-PCR, to loop-mediated isothermal amplification (LAMP), to CRISPR-based technologies. The

intended uses of these tests vary widely, from point-of-care (POC) settings (hospitals, clinics and environments such as businesses and schools) to moderate-to-high complexity clinical laboratories that support much higher throughput and capacity than existing PCR-based diagnostics. The antigen tests being evaluated by RADx Tech program are typically designed for POC use, speed of result, and ideally are simple and user-friendly, similar to the visual, color-based readout of home pregnancy tests. They should also be cost-effective, faster than PCR-based approaches, and without sophisticated instrumentation. Although, nucleic acid tests tend to have higher sensitivity (fewer false negatives) than antigen tests, the latter offer simplicity and ease-of-use, often not requiring any additional equipment other than the assay device itself. From the vantage point of the RADx Center, to date no single test/approach “has it all” and we predict that each successful RADx Tech Covid-19 diagnostic test will occupy a unique niche in clinical use and the marketplace.

To date, over 700 RADx Tech applications have been completed and submitted, approximately 150 “shark tank” sessions have taken place, and the ACME POCT Test Validation Center has been involved in the assessment of >50 different technologies, more than 20 of which are now being scaled up by the NIH for deployment. Indeed, several Covid-19 diagnostic tests have recently entered the marketplace and are steadily increasing their user and patient base.

2 | LEADERSHIP ROLE FOR HEMATOLOGISTS IN THE COVID-19 PANDEMIC

Panel A

Recommendations for President-elect Biden's COVID-19 Task Force

On November 9, 2020, President-elect Biden announced an advisory board of scientists and health experts to guide the new administration's approach to managing the Covid-19 pandemic. With the burden being carried by hematology patients in mind, we present specific recommendations for this advisory board:

1. The federal government should continue and expand upon the support for programs such as RADx Tech; as new testing technologies rapidly come to market, it is imperative to have ongoing, unbiased evaluation in a controlled and standardized fashion.
2. Covid-19 tests are not uniform and have different appropriate clinical use-cases given different venues' (eg, hospital vs school) unique testing needs and variable underlying test properties (eg, highly sensitive vs highly specific). Thus, the advisory board should include

specialists to help oversee and provide recommendations on and direct Covid-19 tests to their appropriate settings.

3. Guaranteed coverage for Covid-19 tests should be extended to include asymptomatic screening for general workplace and school safety.
4. Where feasible, schools should offer “Covid-safe” classrooms, which require periodic, asymptomatic Covid-19 testing for students and teachers, whose members do not interact with untested classrooms, and to which students and teachers can opt in or out.

With 240 000+ reported deaths from Covid-19, a winter wave of cases threatening the United States, and no national plan for containment from the current administration, the call to action is clear: healthcare workers must step in as advocates for their patients. This call is especially true for hematologists as many patients with blood disorders, given underlying immune dysfunction and other co-morbidities, are at high risk for severe Covid-19. In addition, many hematologic diseases disproportionately affect minorities and people of low socioeconomic status, two populations that remain especially impacted by Covid-19. Reinforcing this imperative, the Centers for Disease Control and Prevention (CDC) state that adults with cancer or SCD are at increased risk of severe Covid-19, and adults and children who are immunocompromised may also be at increased risk.⁶

Thus, the pandemic has changed the way hematologists deliver care. Frequent testing has become standard practice upon admission to the hospital and/or prior to delivery of immunosuppressive therapies and will likely be required until the pandemic is under control. Though it is well established that asymptomatic carriage of Covid-19 is common, hematologists face additional diagnostic challenges as symptomatic Covid-19 can mimic many common presentations of hematologic diseases.⁷ Anemia can complicate the presence of Covid-19-associated fatigue, chemotherapy-related dysgeusia may mask loss of taste and smell, and in patients with SCD, pain may be the only presenting symptom of Covid-19.⁸ Active hematologic malignancies are associated with worse Covid-19 outcomes.⁹ As a result, hematology patients can be tested multiple times per month, and thus are one group that will substantially benefit from innovations in testing modalities such as those evaluated by RADx Tech. As seen in Figure 1, the availability of broader testing at our center coincided with identification of substantially more patients with Covid-19. While some of the increased infections could be attributed to increasing community spread and/or loosening of social distancing behaviors, more frequent testing has enabled our clinicians to initiate more effective treatment and improve infection containment of spread through counseling on quarantine and isolation. Regardless of the underlying situation, increased testing leads

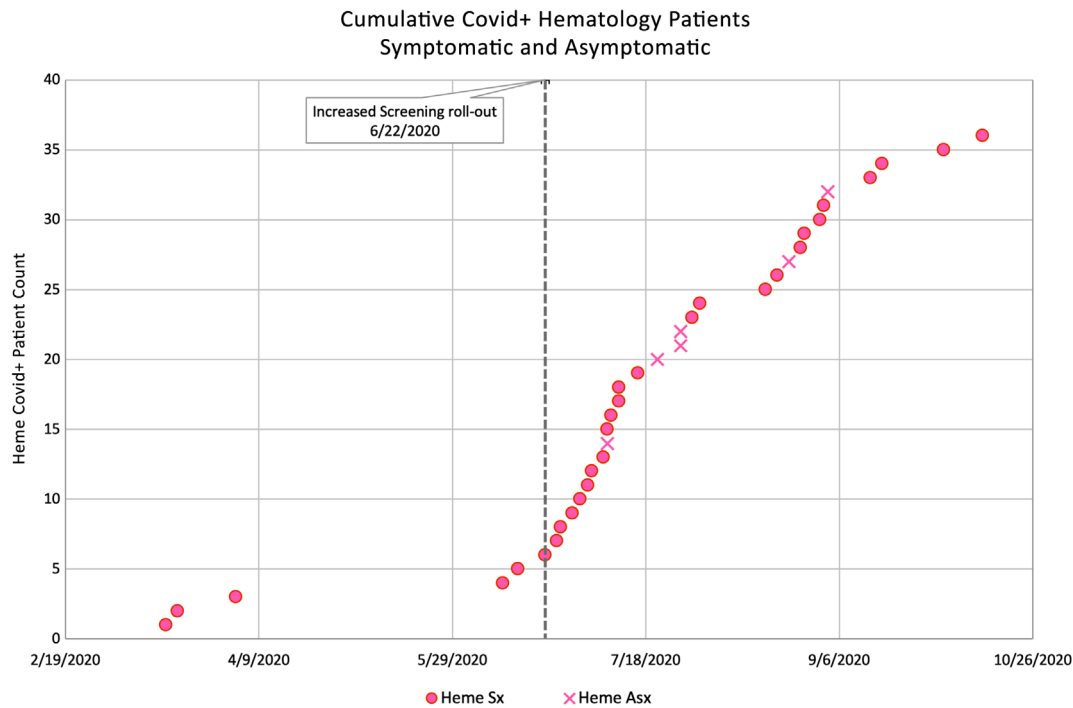


FIGURE 1 As testing capacity increased, Children's Healthcare of Atlanta (CHOA) changed testing policy to include asymptomatic (Heme Asx) testing prior to surgery and symptomatic (Heme sx) testing of patients with atypical Covid-19 presentations such as fever and neutropenia or admission for a sickle cell crisis [Color figure can be viewed at wileyonlinelibrary.com]

to more Covid-19 diagnoses and therefore appropriate treatment and preventative measures for patients.

Given the vulnerability of some patient populations, including those with hematologic diseases or immunocompromise, the lack of free and widely available testing puts patients and their families in challenging situations. While the Families First Coronavirus Response Act and subsequent Coronavirus Aid, Relief, and Economic Security Act require that most insurance plans (ie, those participating in Medicare, Medicaid, and the Federally Facilitated Exchanges) cover FDA-authorized Covid-19 tests and certain related services, there is no regulation of pricing for private insurance, enabling significantly disparate prices for similar tests. Furthermore, the congressionally mandated coverage does not include asymptomatic testing for return to work or school that, in conjunction with high test costs, can discourage such screening. Alternatively, widespread, inexpensive Covid-19 screening of students and teachers could provide a safer school environment, increasing productivity and well-being. For example, as pediatric hematologists, several authors of this commentary have noted that parents of children with SCD, knowing their immunocompromised status, often chose to keep their child at home rather than risk exposure to a school environment that lacks aggressive testing and isolation of infected children, potentially worsening the known education gap between Caucasian and African-American children. An immunosuppressed adult might have to make the unfair choice of exposing himself to asymptomatic co-workers and risking his life vs staying safe at home and losing his job. Thus, this incomplete patchwork of

regulations and coverage again disproportionately affects high-risk patients, including those with hematologic illnesses and hematologists must advocate for policies that help ease this unfair burden. With a new President-elect and administration that has stated addressing the Covid-19 pandemic as its top priority, there are opportunities for advocacy for improvement in testing and related policies and we have included specific recommendations with the above issues in mind (Panel A).

The RADx Tech program, through unprecedented action towards the development of novel, rapid, and accurate Covid-19 testing, has demonstrated the integral role of the federal government and the NIH in combating the Covid-19 pandemic and has provided significant benefits to patients, including to those with blood disorders. However, early political and technical failures as well as ongoing uncertainty regarding Covid-19 test availability and payment threaten the nation's health and safety. Therefore, while the country awaits the development and widespread dissemination and uptake of the Covid-19 vaccines, testing remains a key element in curbing the pandemic and hematologists must continue to advocate for funding, policies, and programs that will ensure effective and available Covid-19 tests.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

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