Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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GUEST EDITORIAL

Laboratories and Pandemic Preparedness

A Framework for Collaboration and Oversight

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The coronavirus pandemic of 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 was first detected in Wuhan, China, in December 2019 and spread globally during the early part of 2020. As of May 11, 2020, >4 million cases have been confirmed worldwide, with >1.3 million cases in the United States (*https://coronavirus.jhu.edu/map.html*, last accessed May 11, 2020). The United States now has the most confirmed cases and confirmed deaths worldwide. The key to slowing the spread of this disease is widespread testing so that patients can be quickly identified and isolated. The publication of the first viral sequence in mid-January made the design of PCR assays for SARS-CoV-2 possible (*https://www.ncbi.nlm.nih.gov/genbank/sars-cov-2-seqs*).

A variety of laboratories across the United States have the expertise and capability to test for pathogens that are a threat to public health, such as SARS-CoV-2. Certified public health laboratories working with the CDC are often first to begin testing, and provide an important epidemiologic role, but these laboratories lack sufficient testing capacity to serve in a significant clinical role. In contrast, hospital laboratories are on the frontlines, supporting patient care during an epidemic. Hospital laboratories need to provide rapid and accurate results to help care for patients, make rapid decisions about isolation of infected patients, guide use of personal protective equipment, and protect health care workers. A third source of testing is the referral, or commercial, laboratories. These centralized laboratories have large testing capacity, but are located remotely, and are not able to produce results with sufficient speed to facilitate care of an acutely ill or emergency department patient. As we have seen with the current pandemic, these laboratories may be most useful for evaluation of mildly ill outpatients who may not require hospitalization. However, those patients whose disease worsens may later find themselves at their hospital emergency department while still awaiting the results of their commercial laboratory COVID-19 PCR test. Ideally, all these testing resources must be working in a coordinated manner to optimize national testing needs and provide the best patient care.

The public health laboratories initiated testing using the CDC RT-PCR assay, released on February 4, 2020 (*https://www.cdc.gov/coronavirus/2019-ncov/lab/rt-pcr-panel-primer-probes.html*); this assay was only available to certified public health laboratories at the time of this outbreak. Subsequently, a number of hospital and health system laboratories capable of developing high-quality laboratory-developed procedures did so, and many submitted to the US Food and Drug Administration (FDA) for Emergency Use Authorization (EUA; *https://www.cdc.gov/coronavirus/2019-ncov/lab/rt-pcr-panel-primer-probes.html*, last accessed April 28, 2020). These clinical laboratories needed to provide testing for their institutions, physicians, and patients, who desperately needed clinical results at a time no other testing was available. Many of these laboratories based their PCR assays on the CDC model, whereas others replicated the World Health Organization and other assay designs. In time, a third wave of assay development was seen, as numerous commercial companies brought their assay kits to market following EUA certification by the FDA. This allowed expansion of testing to include hospital laboratories not able to develop an in-house PCR test, as well as multiple reference laboratories. EUA certification is not as comprehensive as the usual FDA review process and, as a result, there is some degree of variation in the performance of these assays. Thus, laboratories must complete more significant

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evaluations than usually necessary when implementing a new kit-based assay and verifying its performance, placing significant additional burden on laboratories during this difficult time. Hospital and university laboratories often had to make decisions about commercial assays with little or no performance data provided, were asked to sign purchase agreements to be prioritized for later reagent allocations, and then often were left without testing equipment, materials, or reagents when allocations were redirected to other facilities. It has been a challenging several weeks.

We all recognize the critical shortfall in our testing capacity, and how it affected readiness to contain this virus. Several steps would have allowed the United States to put together a more coordinated and effective response to the testing needs for COVID- 19. These actions would leverage the high potential capacity for testing across the country and facilitate a more rapid response in the future.

First, public health, clinical, and reference laboratories must have collaborative relationships and a formal communication strategy in place before a pandemic occurs. The ability to share early alerts and coordinate testing efforts and expectations would be a first step to rapidly scale a laboratory response across the country. High-quality, CLIA-accredited laboratories constitute a significant resource for testing during a pandemic, essential in their designated role testing their patients as part of health care delivery.[1,2] We should formalize a framework that capitalizes on this laboratory capacity and talent, in addition to public health and commercial laboratories. This approach and coordination would have rapidly increased our testing capacity for COVID-19 during recent months. A network of preapproved and interconnected laboratories also avoids the need to build such communication and quality certification systems during the heat of a growing pandemic. Information technology connectivity between the public health, hospital, and commercial laboratories would also facilitate the ability to transfer samples to fill available laboratory capacity, without inefficient, expensive, and error-prone manual entry of patient data at a testing site.

A coordinated laboratory network could be valuable in vetting laboratory tests suitable for broad deployment. Such a laboratory network could rapidly and broadly validate new assays, provide consolidated data on quality and performance, and watch for issues that might compromise results. For example, minor sequence variations that occur in a viral genome can interfere with the binding of PCR primers and subsequent amplification; such issues rendered some PCR assays for H1N1 2009 influenza ineffective in 2010.[3] Ongoing assessment of assay performance would be valuable, and reportable, through such a network. We are already seeing sequence differences in the genomes of separate isolates of the SARS-CoV-2 virus that correlates with the geographic origin of the virus, and may be associated with variations in virulence.[4]

The FDA may have a role in approval of tests, and should contribute further quality measures, even during an emergency situation. The need to rapidly make diagnostic tests available during a crisis necessitates adjustments to the regulatory oversight. The EUA declaration streamlines the usual FDA oversight, requiring little more than analytic validation of the assay performance. As such, the process requires less data than are collected during the validation of a laboratory-developed procedure under CLIA guidelines. Consequently, significant variability in performance between EUA-certified assays has been reported[5,6] (personal observations). This is a disadvantage for laboratories, which must make decisions and investments in reagents and instruments without complete knowledge of test accuracy. Although time is of the essence during an emergency, basic performance standards for diagnostic assays could be quickly defined and used to guide EUA decisions regarding suitability for clinical use. For example, an assay not achieving a minimal limit of detection (LOD) should not be approved, even for EUA purposes. Preventing inadequate tests from reaching the clinical market would improve patient care and prevent laboratories from wasting time and resources on suboptimal assays. Basic performance requirements for diagnostic assays should be defined by a team of qualified laboratory professionals representing a variety of stakeholders and could be based on available data. Using COVID-19 as an example, such a group could have quickly defined a suitable viral copy number detection target based on experience elsewhere in the world, the CDC assay, and possibly information from other coronaviruses. It is interesting that the FDA required some minimal performance standards for review of serologic assays for COVID-19, but not for RT-PCR assays. In time, a retrospective review of the value of the FDA EUA program during this pandemic should be performed, and adjustments and improvements made before EUA is enacted again in the future.

Initially, it was difficult for laboratories to obtain the reference materials needed to validate assays for SARS-CoV-2. Quantitative viral or RNA standards were not available commercially, so laboratories worked together informally to share samples to allow other laboratories to verify and validate assays rapidly. A centralized source of quantitative viral standards available early would enhance assay validation, and allow laboratories and manufacturers alike to demonstrate the ability of their test to detect the required viral LOD. In addition, a validation panel of blinded negative and positive samples (across a range of positivity levels) would be invaluable to laboratories and manufacturers seeking to demonstrate the accuracy, sensitivity, and specificity of their tests. In addition, such materials should be used to demonstrate ongoing proficiency and performance of diagnostic tests.

As the United States begins to look forward to a post−COVID-19 pandemic world with more normal hospital activities and reduced social distancing, we also must learn from this unprecedented experience. We have encountered infectious threats with increasing frequency in recent years (swine influenza 2009, SARS, Middle East

respiratory syndrome, and ebolavirus) and will be certainly threatened again. The time to prepare for a crisis is not as the crisis is escalating; we must plan and put in place the necessary infrastructure to prepare us for the next pandemic. Hopefully, the above points will serve to initiate further discussions and actions. We encourage professional laboratory organizations, physician associations, commercial reference laboratories, and federal, state, and local agencies to collectively formulate effective planning to prepare for future infectious disease outbreaks.

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