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The 2020 Wild, Wild West of Diagnostics

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Regarding regulatory oversight of laboratory-developed tests (LDT) for molecular diagnostics, the Food and Drug Administration (FDA) often refers to the LDT space as the “Wild, Wild West,” making it seem like laboratories are all going rogue with respect to Clinical Laboratory Improvement Amendments (CLIA)-defined quality assurance practices. Now, with the challenges of the COVID-19 pandemic in 2020, the FDA finds themselves in a self-created Wild, Wild West regarding molecular and serologic testing for SARS-CoV-2. In December 2019, Chinese officials notified the World Health Organization of a cluster of severe pneumonia cases in Wuhan that had a suspicious origin. On January 7, 2020, the cause was identified, the novel severe acute respiratory coronavirus 2 (SARS-CoV-2), and the first death was reported in China several days later. By the end of January, cases were being reported globally, including the first case in Washington State, and travel bans were issued by some countries. The FDA released a guidance document for designing and validating molecular tests for SARS-CoV-2 and issued the first Emergency Use Authorization (EUA) for a reverse transcriptase, real-time polymerase chain reaction (RT-qPCR) assay to the Centers for Disease Control and Prevention (CDC) on February 4, 2020. The EUA specified that all diagnostic testing for SARS-CoV-2 be reviewed by the FDA, and in effect removed the option to offer testing as an LDT. This changed the landscape of molecular diagnostics for the virus and thrust the nation into a difficult situation because no assays other than the CDC RT-PCR test, available only to public health laboratories (PHLs), were accessible.

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Soon after distribution of the CDC EUA, assay laboratories noticed failed results, in part because of contaminated reagents. Remanufacturing and redistribution of tests to the PHLs significantly delayed the implementation of wide-scale national testing of symptomatic individuals. Hospital and academic laboratories capable of developing and validating their own assays were forced to do so, and the subsequent tsunami of new molecular SARS-CoV-2 tests submitted for EUA certification overwhelmed the FDA from a regulatory standpoint. One of the advantages of molecular techniques is that they are universal and flexible in their application. This, however, became a disadvantage in the current pandemic as the number of preanalytic variables, including specimen types and different collection tubes, together with the analytical variables associated with different technology platforms, generated an assortment of assays, each requiring review. In addition, the demand to increase testing to include not only well-characterized symptomatic patients but also less well-characterized symptomatic and asymptomatic individuals posed further significant concerns and challenges. To date, no tests are EUA certified for use in asymptomatic patients.

Ideally, a molecular diagnostic procedure for SARS-CoV-2 would call for a specific specimen type or types, a specific extraction method and instrument, and a defined PCR protocol and amplification instrument with published primer/probe sequences and cycling conditions. At first glance, this seems straightforward, but the breadth and depth of methods and instruments available in laboratories across the country makes this very complex; ultimately, these combinations used together in an assay must yield the same result in all laboratories and does, as illustrated by many national proficiency testing programs. The purpose of CLIA is to ensure that all results are correct, regardless of the method or instrument used. This variability was daunting for the FDA (who must remain vendor neutral) to manage through this escalating pandemic. The EUA regulatory process was challenged with increased demand from providers and institutions for more testing using alternative specimens when swabs were in short supply, transport media versus saline versus dry swabs, and multiple methods in the laboratory to ensure supplies for at least 1 EUA assay. Validation/verification data required for EUA were minimal compared with routine validation studies for LDTs or commercial assays. Demonstration of assay performance criteria, especially limit of detection studies, was challenging because of lack of well-characterized control material, as well as variability in extraction efficiencies and specimen types.

Although the FDA tried to manage the ensuing flood of assays, other federal and state agencies as well as professional societies were calling for new indications for testing of patients. None of these groups willingly recognized the fact that the FDA EUA status granted to all of these tests was for symptomatic patients and that testing beyond that indication would be in direct violation of the EUA. Some noted that there was no information to contradict that the assays should perform the same in asymptomatic versus symptomatic patients forgetting performance characteristics associated with positive and negative predictive values. Others stated that there are no authorized tests for asymptomatic testing, but the health care provider has discretion with ordering tests, and suppliers wishing to seek authorization should contact the FDA and submit a Pre-Emergency Use Authorization request. Nonetheless, the demands from providers and clinical professional societies alike were too great, and many laboratories were forced to perform this testing adding disclaimer after disclaimer to their reports. As with public protests to reopen our country, demands from providers and professional groups to increase testing across all patient populations were due in part to fear of the unknown regarding the virus and to a misunderstanding of good laboratory practices. The system had become a free-for-all.

Some take away lessons from this pandemic for the laboratory are worth mentioning. First, we must have a better, more coordinated national response network in practice, and ready for the next time that we are faced with a pandemic challenge. Second, we need a system that affords certified and licensed clinical laboratories the flexibility to rapidly engage in testing using established protocols in individual laboratories, but continuing to ensure accurate results, ideally with high-quality reference materials available to demonstrate the accuracy of the assay. Third, our supply chain must be more robust across all aspects of our health care system, including laboratory supplies. Fourth, at a time when medical school curricula are being redesigned and reinvented, this pandemic was an amazingly eye-opening experience on how poorly we are training health care providers with regards to diagnostic skills and use of laboratory information. In addition, ongoing national efforts to reduce health care expenditures that include drastic cuts to laboratory reimbursement have hobbled many laboratories. Laboratory results make up only about 2% of health care costs but determine about 80% of subsequent expenditure; modest
investment in laboratories provides better information and actually reduces the overall cost of care, as we have seen during the pandemic and in many other situations. Finally, a national mechanism to distribute not only supplies but also help with testing across state borders in support of laboratories in the hot zones is critical to our responsiveness. We have never experienced the impact of a major pandemic such as this, and the hope is that we will be much better prepared for the next one.

**DISCLOSURE**

The authors have nothing to disclose.