Laboratory-Developed Tests: A Critical Bridge During the COVID-19 Pandemic

William M. Rehrauer, PhD; David T. Yang, MD

In February 2020, it was becoming increasingly clear that a global pandemic was fomenting, and diagnostic testing for COVID-19 in the United States was woefully inadequate.[1] Under normal circumstances, diagnostic tests are developed largely by commercial manufacturers and sold to clinical laboratories. The US Food and Drug Administration (FDA) reviews these commercially available tests through an extended and bureaucratic process that manufacturers have necessarily built and staffed with infrastructure to navigate.[2] Alternatively, clinical laboratories certified to perform high-complexity testing can implement laboratory-developed tests (LDT) for use within the institution through a quicker, less bureaucratic process. As long as these tests are performed within the institution and not directly marketed to consumers, the FDA has so far exercised regulatory discretion and allowed oversight of LDTs to fall under the Clinical Laboratory Improvement Amendments (CLIA) clinical laboratory certification process managed by the Centers for Medicare and Medicaid Services (CMS).[3]

Like most clinical laboratories at academic medical centers that serve a referred population of complex and high-acuity patients, UW Health Clinical Laboratories has experience developing LDTs that fill a niche where commercial tests are either unavailable or do not meet clinical needs. Having staff with test development expertise and validation/implementation workflows in place was critical to our ability to design and operationalize a diagnostic COVID-19 LDT in 7 days. In order to appreciate the significance of this rapid implementation, it is important to recall that COVID-19 testing initially could be performed only by the Centers for Disease Control and Prevention (CDC) and local public health departments.[4] As these institutions quickly became overwhelmed with testing demands, turnaround times stretched from days to weeks.[1] Thereafter, the FDA was forced to permit clinical laboratories with high-complexity designation to develop LDTs.[5] When UW Health Clinical Laboratories began test development, essentially no COVID-19 testing was available to our patients. The implications were dire as there was no way to ration depleting stocks of personal protective equipment, reliably isolate infected patients, or implement an employee testing program. The timely implementation of local public health measures, including school closures and limiting gatherings, likely averted an impending disaster at our medical center during the interval of LDT development.[6]

> The ability to develop LDTs was not serendipitous but rather emerged out of a policy that allowed clinical laboratories to address gaps in diagnostic testing—gaps that became strikingly apparent and were pervasive...during the early days of the pandemic.

Laboratory-developed COVID-19 testing at our institution served as a critical bridge for 4 weeks until we transitioned to a high throughput commercial test whose availability was delayed due to reagent and manufacturing supply chain constraints. In addition, LDTs also provided clinical laboratories the opportunity to diversify their testing methodologies to counter these same supply chain constraints and to accommodate alternative specimen sources to meet clinical needs.[7,8] Without LDTs, it is hard to imagine the degree to which patient care may have been compromised. The ability to develop LDTs was

• • •

Author Affiliations: Department of Pathology and Laboratory Medicine, University of Wisconsin School of Medicine and Public Health and University of Wisconsin Hospitals and Clinics, Madison, Wisconsin (Rehrauer, Yang).

Corresponding Author: David T. Yang, MD, Department of Pathology and Laboratory Medicine, University of Wisconsin, B4/251b CSC, 600 Highland Ave, Madison, WI 53792; phone 608.265.5095; email dtyang@wisc.edu; ORCID ID 0000-0002-9488-1704

not serendipitous but rather emerged out of a policy that allowed clinical laboratories to address gaps in diagnostic testing – gaps that became strikingly apparent and were pervasive throughout the entire country during the early days of the pandemic.

Today, expanded regulation of LDTs is being considered in Congress through two competing bills. The Verified Innovative Testing in American Laboratories (VITAL) Act[9] proposes to keep regulatory oversight of LDTs with CMS, while the Verifying Accurate Leading-edge IVCT Development (VALID) Act[10] proposes to establish new FDA authority for regulation of LDTs. The VALID Act would add another layer of oversight and bureaucracy designed for manufacturers who sell commercial tests to be duplicatively imparted on clinical laboratories that already are subject to CMS oversight. Looking back at lessons learned from the pandemic, we reflect on how critical our ability to develop a COVID-19 LDT was and the possible consequences of legislation that might curtail a clinical laboratory's inclination to foster and support expertise in laboratory test development.

Funding/Support: None declared.

Financial Disclosures: None declared.

REFERENCES

1. Boburg S, O'Harrow R, Satija N, Goldstein A. Inside the coronavirus testing failure: alarm and dismay among the scientists who sought to help. *The Washington Post.* April 4, 2020.

2. U.S. Food and Drug Administration. Overview of IVD regulation. Updated October 18, 2021. Accessed April 11, 2023. https://www.fda.gov/medical-devices/ivd-regulatory-assistance/overview-ivd-regulation

3. U.S. Food and Drug Administration. Laboratory developed tests. Updated September 29, 2023. Accessed April 13, 2023. https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests

4. FDA takes significant step in coronavirus response efforts, issues emergency use authorization for the first 2019 novel coronavirus diagnostic: crucial milestone reached in response to this outbreak. News release. U.S. Food and Drug Administration. February 4, 2020. Accessed April 12, 2023. https://www.fda.gov/news-events/press-announcements/fda-takes-significant-step-coronavirus-response-efforts-issues-emergency-use-authorization-first

5. U.S. Food and Drug Administration. Policy for coronavirus disease-2019 tests (revised): guidance for developers and Food and Drug Administration staff. March 16, 2020. Updated January 12, 2023. Accessed April 13, 2023. https://www.fda.gov/media/135659/download

6. Public Health issues order closing schools and imposing countywide directive to stop holding gatherings of 50 or more people. News release. City of Madison. March 15, 2020. Accessed April 13, 2023. https://www.cityofmadison.com/news/public-health-issues-order-closing-schools-and-imposing-countywide-directive-to-stop-holding

7. Moran JH, Kessler L, Moylan J, et al. Modifying laboratory testing via home brew during the COVID-19 pandemic. *J Clin Transl Sci.* 2021;5(1):e93. doi: 10.1017/ctx.2021.5

8. Tsai JM, Tolan NV, Petrides AK, et al. How SARS-CoV-2 transformed the clinical laboratory: challenges and lessons learned. *J Appl Lab Med*. 2021;6(5):1338-1354. doi: 10.1093/jalm/jfab034.

9. Verified Innovative Testing in American Laboratories (VITAL) Act of 2021. S 1666, 117th Cong (2021). Accessed April 13, 2023. https://www.congress.gov/bill/117th-congress/senate-bill/1666

10. Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2021. HR 4158, 117th Cong (2021). Accessed April 13, 2023. https://www.congress.gov/bill/117th-congress/house-bill/4128/text?q=%7B%22search

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

Visit www.wmjonline.org to learn more.