

Laboratory-Developed Tests: The Need for Regulation

Laboratory-developed tests (LDTs) are a type of in vitro clinical test (IVCT) that are developed and used in a single laboratory, distinguishing them from other IVCTs that are used by multiple laboratories and conventionally manufactured as medical devices.¹ LDTs are “send out” tests, meaning a sample is collected in one facility and sent to another to be tested, instead of collecting and testing a sample in the same facility.² Reliable LDTs are crucial, as inaccurate tests can lead, on the one hand, to failure to diagnose critical diseases or conditions and, on the other, to inappropriate treatment.

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Food and Drug Administration (FDA) has the authority to review medical devices, including LDTs, to ensure they are safe and effective before they are marketed.³ However, to date FDA has not used this authority to regulate LDTs, allowing the devices to enter the market without premarket approval.

The number of inaccurate LDTs is a growing problem and may lead to misdiagnoses of common diseases.

In the 1970s, there were a limited number of LDTs and they were generally used to diagnose rare diseases and conditions in a small number of patients.¹ Advances in science and technology have enabled greater availability and complexity of tests that can be used to diagnose serious medical conditions like cancer, heart disease, and, more recently, COVID-19.^{1,4} The field of medicine is evolving, including a new focus on Precision Medicine, which tailors disease prevention and treatment to individuals by accounting for individual factors like genetic variation.⁵ Development of accurate and clinically meaningful tests is crucial to support these advances.

In the absence of FDA oversight, labs offering LDTs are regulated by the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA).¹ CMS regulates labs themselves, including the process of testing, but does not regulate the safety and effectiveness of tests directly.⁶ CMS requires labs to have documentation of their tests’ analytical validity, which determines if a test can detect the target of interest reliably. CMS does not require clinical validity data: the accuracy with which tests identify a particular disease or susceptibility to a disease in a patient. For example, if a blood test measuring proteins shed by pancreatic cancer cells is used to diagnose pancreatic cancer, CMS would only assess whether the test accurately detects the proteins, not whether the detection of the proteins is a reliable way to diagnose pancreatic cancer. By contrast, if LDTs were reviewed as medical devices, clinical and analytical validity would be assessed by the FDA, which would carry out a more comprehensive assessment with a focus on test safety and effectiveness prior to reaching

patients.¹ Regulating LDTs under the CLIA, rather than by FDA, therefore leaves critical gaps that allow inaccurate LDTs to be marketed to consumers without adequate independent oversight. And examples of inaccurate LDTs abound.

In 2015, the FDA published a report that presented 20 case studies of problematic LDTs that caused or may have caused real harm to patients.¹ In some cases, patients were told they had conditions they did not have (false-positives); in others, patients' life-threatening conditions were not identified (false-negatives). The biomarkers measured in other tests had no proven relevance to the diseases that tests claimed to detect, or their associated treatments. The case studies included tests for a variety of conditions, such as Lyme disease, vitamin D deficiency, autism, fetal genetic abnormalities, heart disease, and various types of cancer.¹ The situation has only been exacerbated since the report was published, with many more LDTs being developed and used on an increasing number of patients, all without premarket review.⁷ Some additional recent examples follow.

Prenatal tests

- Genetic non-invasive prenatal screening (NIPS) tests analyze small pieces of fetal DNA in the maternal circulation to assess the risk for genetic abnormalities in a fetus.⁸ All are LDTs and are widely used by providers. These are screening tests, but patients have terminated their pregnancies based on test results without further diagnostic testing.⁸ Although companies claim their tests are highly accurate, some genetic abnormalities like microdeletions are so rare that false positives are common (they have low "positive predictive values").⁸ FDA recently released a safety communication warning patients and providers about the risks of inaccurate results from NIPS tests.⁸

Theranos blood tests

- The company claimed it could deliver cheap and convenient tests, which were LDTs, to diagnose common conditions like diabetes, cancer, and cardiovascular disease using a single finger prick and a few drops of blood.^{9,10} It capitalized on the LDT loophole, allowing it to circumvent FDA regulation and market tests that were inaccurate. For example, unreliable results led one consumer to believe she was HIV+ when she was not, and another was informed she was miscarrying when she had a healthy pregnancy.^{11,12} Luckily, both women retested with different providers and learned the truth, but these results could have led to unnecessary treatment for HIV or the termination of a healthy pregnancy.

COVID-19 tests

- In February 2020, FDA allowed COVID-19 diagnostic tests (which were LDTs) to remain on the market until FDA had a chance to review their applications for emergency use authorization.¹³ By eluding review under the EUA provision, which would otherwise have required at least some premarket review, these LDTs were in essence regulated like all LDTs – without premarket review. The agency subsequently discovered validation or design issues in over 65% of a sample of 125 tests submitted for authorization.¹³

Inaccurate results from these tests may have led to unnecessary quarantining due to false positives or to additional virus spread due to false negatives.

Reform is needed to ensure adequate oversight of LDTs.

FDA is aware of the public health risks posed by unregulated LDTs and has proposed regulation in the past. In 2014, it released a draft guidance³ that outlined a risk-based approach to premarket review of LDTs and a process for notifying FDA of such tests. This elicited a strong response from industry, including academic medical centers (AMCs), and pressure from Congress led FDA to suspend work on its proposed regulation.^{14,15} In 2017, the agency released a discussion paper¹⁵ that synthesized stakeholder feedback on the draft guidance but made clear it would not implement this policy change through its current authorities, leaving it to Congress to address the issue. In August 2020, the U.S. Department of Health and Human Services (HHS) announced that FDA would be required to regulate each LDT by individual regulation, which in effect meant that LDTs would be unregulated.^{16,17} HHS has since reversed this policy,¹⁸ but still left LDTs unregulated.

Negotiations around LDT regulation resulted in the introduction of the Verifying Accurate Leading-edge IVCT Development Act of 2020, “VALID”,¹⁹ which was revised and reintroduced in 2021.²⁰ VALID amends the FD&C Act to create a uniform regulatory framework for all IVCTs, including both LDTs and non-LDT IVCTs, that are currently regulated as medical devices. The bill was modified and included in legislation that reauthorizes user fees for drugs, biologics, and devices (the Food and Drug Administration Safety and Landmark Advancements Act of 2022, “FDASLA”).²¹ However, it was stripped from the FDASLA before it passed.²² The VALID Act of 2023 has since been introduced in the House.²³

FDA should act within its existing authority if Congress does not.

FDA has the authority to regulate all IVCTs as medical devices, but only non-LDT IVCTs are currently following device approval requirements. For example, an application for the MissLan® Pregnancy Rapid Test, a moderate-risk over-the-counter non-LDT pregnancy test, was submitted and granted approval from FDA in early 2023.²⁴ In the event that legislation addressing LDTs is not forthcoming, FDA is working on a proposed rule²⁵ that would clarify that LDTs are devices under the FD&C Act and, presumably, establish a risk-based regulatory approach to LDT regulation. This proposal is now under review at the Office of Management and Budget.

Congress can offer a more comprehensive regulatory framework for IVCTs and LDTs.

An ideal regulatory framework for LDTs should include a tiered approach, as incorporated into most versions of VALID and supported by FDA:

1. **Full premarket review:** Individual high-risk tests, or those where an undetected inaccurate result is reasonably likely to result in serious or irreversible harm or death to patients or is reasonably likely to result in the absence or delay of necessary medical treatment would be subject to the most stringent scrutiny. Such tests would undergo premarket review of their proposed labeling, submit raw data showing the test is safe and analytically and clinically valid for its intended use, and submit quality requirement (QR) documentation.
2. **Exempt from premarket review:** Tests that qualify as exempt do not undergo any premarket review. Exempted products may include low-risk tests (those where an undetected inaccurate result would cause minimal or immediately reversible harm with only a remote risk of harm to patients); custom tests (those used to diagnose a unique condition for which no other IVCT is available); low-volume tests; and grandfathered tests (those on the market prior to the bill's enactment).
3. **Abbreviated premarket review:** Moderate-risk tests, or those that do not meet the criteria for high-risk or low-risk tests, require review of only the proposed labeling and summary data demonstrating the test is safe and analytically and clinically valid for its intended use. No QR documentation or raw data would be required unless requested by the Secretary.

Regulation should also consider the following issues:

Resources: FDA should be provided adequate funding to regulate LDTs through appropriations and user fees. There should be no cap on user fees collected by FDA; the agency must have the ability to negotiate such fees without restriction every five years according to its resource needs.

AMCs: Only about 5% of the roughly 267,000 labs in the U.S. offer LDTs, but AMCs, which typically develop such tests, have been some of the most vociferous opponents of LDT regulation by FDA.²⁶ AMCs may oppose regulation partly because commercialized technologies with intellectual property patents provide substantial revenue.²⁷ A risk-based approach would preserve AMCs' ability to generate revenue from innovations while still protecting patient safety and increasing transparency. All LDTs, regardless of the organization that creates them, should be held to the same risk-based regulatory approach as an inaccurate test is a problem regardless of who produces it.

Technology certification: One proposal to help FDA handle the large number of tests that would be reviewed is a pathway called technology certification. This allows eligible developers of moderate- or low-risk tests to develop and modify tests within a single technology type without individual review of each test. Developers would submit a representative test for FDA to review and submit information to show that tests within the scope of the certification conform to the procedures for analytical and clinical validity and those for establishing that tests are safe. All tests approved under a technology certification should be required to not differ significantly in their indication or analytical and clinical validity and FDA must be given

the authority to define the circumstances in which a developer could receive a technology certification that covers multiple technologies through regulation or guidance.

Grandfathered tests: Tests on the market prior to the passage of regulation or legislation may be exempt from premarket review, due to the burden of reviewing the thousands of tests already on the market, but FDA should be given the authority to request information from a developer any time it has concerns about a test’s analytical or clinical validity, claims, or safety. Test developers should be required to maintain documentation supporting their tests’ analytical and clinical validity, evidence proving their marketing claims are not false or misleading, and data establishing that their tests will not contribute to serious adverse health consequences and provide these to the agency on request.

Postmarket authorities: A tiered approach to review would exempt most tests from premarket review, shifting the majority of test oversight to the postmarket setting. FDA should have the authority to require postmarket surveillance for any test when the agency determines that such review is necessary to protect the public health or to provide data supporting analytical or clinical validity. Adverse event reporting by manufacturers should be required for all adverse events associated with the use of a developer’s test.

Exemptions: Exemptions from premarket review should be narrowly tailored to ensure that critical categories are not excluded. For example, exemptions meant to cover grandfathering LDTs and custom or low-volume LDTs should not be drafted to cover all IVCTs, which currently undergo premarket review as devices.

For more information, please contact the Center for Science in the Public Interest at policy@cspinet.org.

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¹ U.S. Food and Drug Administration. *The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies*. 2015. [https://www.nila-usa.org/images/nila/The%20Public%20Health%20Case%20for%20FDA%20Oversight%20of%20LDTs%20110915\(2\)_508ed%20\(1\).pdf](https://www.nila-usa.org/images/nila/The%20Public%20Health%20Case%20for%20FDA%20Oversight%20of%20LDTs%20110915(2)_508ed%20(1).pdf).

² National Academies of Sciences, Engineering, and Medicine. *Challenges and Opportunities for Precision and Personalized Nutrition: Proceedings of a Workshop*. 2022. <https://nap.nationalacademies.org/catalog/26299/challenges-and-opportunities-for-precision-and-personalized-nutrition-proceedings-of>.

³ U.S. Food and Drug Administration. *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*. 2014. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/framework-regulatory-oversight-laboratory-developed-tests-ldts>.

⁴ Adashi EY, Cohen GC. SARS-CoV-2 Laboratory-Developed Tests Integrity Restored. *JAMA*. 2022;327(13):1229-1230.

⁵ Ginsburg GS, Phillips KA. Precision Medicine: From Science to Value. *Health Aff*. 2018;37(5):694-701.

⁶ 42 C.F.R U.S.C. § 493.1253. Standard: Establishment and Verification of Performance Specifications.

⁷ The PEW Charitable Trusts. *What are In Vitro Diagnostic Tests, and How are They Regulated? Oversight May Not be Keeping Pace with Changes in the Diagnostics Market*. 2019. <https://www.pewtrusts.org/-/media/assets/2019/05/what-are-in-vitro-diagnostic-tests-and-how-are-they-regulated.pdf>.

⁸ U.S. Food and Drug Administration. *Genetic Non-Invasive Prenatal Screening Tests May Have False Results: FDA Safety Communication*. 2022. <https://www.fda.gov/medical-devices/safety-communications/genetic-non-invasive-prenatal-screening-tests-may-have-false-results-fda-safety-communication>.

⁹ Carreyrou J. Hot Startup Theranos Has Struggled with its Blood-Test Technology. *The Wall Street Journal*. October 16, 2015. <https://www.wsj.com/articles/theranos-has-struggled-with-blood-tests-1444881901>.

¹⁰ Richardson L. *The Theranos Problem Congress Must Still Solve – Patients Need Protection*. The PEW Charitable Trusts. 2022. <https://www.pewtrusts.org/en/about/news-room/opinion/2022/01/12/the-theranos-problem-congress-must-still-solve-patients-need-protection>.

¹¹ Randazzo S. Patient Tells Jury about False-Positive HIV Test Result from Theranos. *The Wall Street Journal*. November 17, 2021. <https://www.wsj.com/livecoverage/elizabeth-holmes-trial-theranos/card/ABdQ1bsOguzWRNwGA3LP>.

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- ¹² Randazzo S. The Elizabeth Holmes Trial: Jurors Hear First Patient Testimony about Theranos Blood Tests. *The Wall Street Journal*. September 21, 2021. <https://www.wsj.com/articles/the-elizabeth-holmes-trial-jurors-hear-first-patient-testimony-about-theranos-blood-tests-11632266549>.
- ¹³ Shuren J, Stenzel T. Covid-19 Molecular Diagnostic Testing – Lessons Learned. *N Engl J Med*. 2020;383(17):e97(1)-e97(3).
- ¹⁴ Genzen JR, Mohlman JS, Lynch JL, et al. Laboratory-Developed Tests: A Legislative and Regulatory Review. *Clin Chem*. 2017;63(10):1575-1584.
- ¹⁵ U.S. Food and Drug Administration. *Discussion Paper on Laboratory Developed Tests (LDTs)*. 2017. <https://www.fda.gov/media/102367/download>.
- ¹⁶ Cancryn A, Owerhohle S. HHS Chief Overrode FDA Officials to Ease Testing Rules. *Politico*. September 15, 2020. <https://www.politico.com/news/2020/09/15/hhs-alex-azar-overrode-fda-testing-rules-415400>.
- ¹⁷ Lurie P. *The Turning of the Political Screw*. Center for Science in the Public Interest. 2020. <https://www.cspinet.org/news/beyond-the-curve/political-interference-fda-and-cdc>.
- ¹⁸ Mezher M. *FDA Revises COVID Test Approach after HHS Reverses Trump-Era LDT Directive*. Regulatory Affairs Professionals Society. 2021. <https://www.raps.org/news-and-articles/news-articles/2021/11/fda-revises-covid-test-approach-after-hhs-reverses>.
- ¹⁹ H.R.6102/S.3404. VALID Act of 2020.
- ²⁰ H.R.4128/S.2209. VALID Act of 2021.
- ²¹ Food and Drug Administration Safety and Landmark Advancements Act of 2022, introduced version.
- ²² Association of American Medical Colleges. *Congress Avoids Shutdown, Approves Continuing Resolution Through Mid-December*. 2022. <https://www.aamc.org/advocacy-policy/washington-highlights/congress-avoids-shutdown-approves-continuing-resolution-through-mid-december>.
- ²³ H.R.2369. VALID Act of 2023.
- ²⁴ U.S. Food and Drug Administration. *510(k) Substantial Equivalence Determination Decision Summary (Miss Lan® Pregnancy Rapid Test)*. 2023. https://www.accessdata.fda.gov/cdrh_docs/reviews/K230038.pdf.
- ²⁵ HHS/FDA. *Medical Devices; Laboratory Developed Tests*. (proposed Spring 2023) (to be codified at 21 C.F.R. 809).
- ²⁶ The PEW Charitable Trusts. *The Role of Lab-Developed Tests in the In Vitro Diagnostics Market*. October 22, 2021. <https://www.pewtrusts.org/en/research-and-analysis/reports/2021/10/the-role-of-lab-developed-tests-in-the-in-vitro-diagnostics-market>. Accessed June 22, 2023.
- ²⁷ Brown M, et al. *Innovative Revenue Streams for Academic Medical Centers– Reaching Beyond Patient Care: Part Two*. American Health Law Association. 2022. https://www.pyapc.com/wp-content/uploads/2022/08/AHLA_AMCTH_Briefing_7-25-22_Brown_Cent_Beane_Vernaglia.pdf.