



# The Role of Lab-Developed Tests in the In Vitro Diagnostics Market

As lab-developed tests grow increasingly complicated, federal oversight has lagged

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**The Pew Charitable Trusts** is driven by the power of knowledge to solve today's most challenging problems. Pew applies a rigorous, analytical approach to improve public policy, inform the public, and invigorate civic life.

# Overview

In vitro diagnostic (IVD) tests—which use blood, saliva, and other human samples to detect the presence or risk of certain diseases—are a pillar of modern medicine. Doctors and patients rely on them to guide life-or-death medical decisions, from choosing a cancer treatment<sup>1</sup> to managing a pregnancy.<sup>2</sup> They also have been critical tools in the fight against COVID-19.

Although the U.S. Food and Drug Administration approves or clears many IVDs before they reach patients, an unknown number of a type of IVD—lab-developed tests (LDTs)—enter the market without FDA review or any other independent regulatory review, simply because they are created and used in the same facility. The Centers for Medicare & Medicaid Services (CMS) regulates labs but has limited insight into the quality, reliability, or usefulness of LDTs, including whether patients have been harmed as a result of their use. (See Figure 1.)

To inform policymakers' efforts to strengthen diagnostics oversight, The Pew Charitable Trusts commissioned research to measure how many tests are run every year using LDTs, and how, when, and why laboratories use these kinds of tests. No database encompasses all available LDTs, so any attempt to characterize the market must rely on estimates built on certain assumptions and be refined with additional data. This study leveraged multiple data sources to provide a current snapshot of the diagnostics market. (See Methodology.) The research—based on insurance claims data, a nonprobability web survey of 195 lab managers, and 20 interviews with executives from clinical labs and diagnostic manufacturers—yielded several findings.

First, because LDTs are not centrally registered or tracked, no one knows precisely how many of them are on the market, when and why they are used, or how their performance compares with FDA-reviewed diagnostics.

- An estimated 3.3 billion in vitro diagnostic tests—both FDA-reviewed and LDTs—are run every year. Although it is clear that LDTs are commonly deployed in many labs, it is not clear exactly how often they are used or for what clinical purposes. Insurance claims and electronic health records do not distinguish between LDTs and FDA-reviewed diagnostics, and there are no comprehensive databases of all LDTs in use.
- When surveyed, even seasoned clinical lab managers demonstrated confusion over what constitutes an LDT. For example, some survey respondents did not realize that anytime a lab makes a change to an FDA-reviewed test—such as altering how specimens are handled—it has effectively created an LDT.
- Lab managers generally expressed a preference for using diagnostics that have undergone FDA review because they are often simpler to use. However, labs often rely on LDTs in cases where an FDA-reviewed test is unavailable or needs modifications for use in a particular population. Interviewees said they may also run LDTs to reduce costs or improve the speed or efficiency of the testing process.

Second, LDTs have changed considerably since Congress established the current regulatory framework for diagnostics in 1976, and the regulatory gaps now present unnecessary risks to patients.

- Today, labs run far more complex and high-risk tests for a wider range of uses than in 1976. Lab managers reported using LDTs more commonly in certain areas such as oncology and rare and infectious diseases—fields that rely heavily on genetic testing and other sophisticated methods, or where scientific understanding is evolving quickly. In these fields, inaccurate results can cause significant harm because providers and patients often rely heavily on test results to determine treatment plans. For example, false positives for cancer-causing mutations can lead patients to have surgery they do not need, whereas a false negative test result for an infection can cause patients to forgo potentially lifesaving treatment or spread that infection to others.
- When FDA was originally granted oversight of medical devices, most LDTs served a limited number of

patients—typically those living near the labs that developed them—but today they can reach millions of people. For example, there are many direct-to-consumer genetic tests that claim to determine an individual’s risk of developing cancer and other diseases, and that can easily be shipped to consumers without a doctor’s prescription. However, FDA has reviewed very few;<sup>3</sup> the rest are unapproved LDTs.

Third, increased transparency of the diagnostics market and a risk-based approach to LDT regulation would enable clinicians and patients to make more-informed decisions about diagnostics without disrupting their access to the tests.

- Many in the clinical laboratory industry and in academic medical centers have opposed recent efforts by lawmakers, FDA, public health advocates, and other stakeholders to strengthen FDA oversight, saying it would impede innovation, increase costs, and disrupt patient care. Although lab managers interviewed for this report echoed those concerns, they also generally agreed that appropriately structured FDA oversight could improve patient safety and increase the scientific rigor and quality of the tests on the market.

FDA, Congress, public health advocates, and other stakeholders have debated how best to modernize IVD regulation for more than a decade. The most recent and most comprehensive proposal to date is the bipartisan Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2021, which would direct FDA to regulate all diagnostics, including LDTs, based on their risk to patients if tests give the wrong result, rather than on where they are created and used. However, there is still disagreement among these key stakeholders over whether the bill adequately balances patient safety protections with the need to bring innovative tests to market quickly.

As federal policymakers consider approaches to strengthening oversight of in vitro diagnostics, this research and the following principles can help guide their thinking:

- To effectively regulate these products, FDA must have a clear picture of what tests are in use and be able to collect sufficient information on how they are performing. At a minimum, this should include a requirement that all tests be registered with the agency; developers report adverse events related to their diagnostics; and the agency be empowered to request information regarding the validity and performance of those products when it has concerns.
- Given the large yet unknown number of LDTs currently on the market, any reform will need to include a mechanism for bringing these tests into compliance with FDA regulations in a way that minimizes disruptions to patient care. Two options that policymakers could consider are phasing in FDA reviews of LDTs or exempting these tests from premarket review while ensuring that the agency has sufficient postmarket authority to require data on their performance and take enforcement action when necessary to protect patients.<sup>4</sup> (See Appendix E.)
- In vitro diagnostics are regularly modified or adapted to address patient needs and to respond to advances in scientific understanding. Any new regulatory approach for diagnostics must be flexible enough to allow developers to modify tests or develop new ones in order to meet patient need without undue delay. However, adequate safeguards must be in place to ensure that tests are valid, reliable, and of high quality. Again, as with any medical product, regulatory oversight should be proportional to the associated risks.
- The lack of a shared definition of what constitutes an LDT—even among laboratory experts—highlights the broader lack of familiarity of many labs with FDA regulations. Bringing LDT developers under FDA oversight will require a transition period that allows labs adequate time to come into compliance. It will also require extensive outreach and education after reform is passed to ensure a common understanding of FDA regulations and what compliance will entail.
- FDA, in turn, will also need adequate time and additional funding to develop new guidance documents and regulations and to implement them by conducting more reviews and inspections of labs.

Figure 1

## Key Public Health Protections Missing From Federal Oversight of Lab-Developed Tests

Despite similarities, LDTs and FDA-reviewed tests are not held to the same standards

	FDA-reviewed in vitro diagnostics	Lab-developed tests
Moderate- and high-risk tests are reviewed externally before use on patients	✓	✗
Tests are registered in a public database	✓	✗
Public reporting of adverse events related to an incorrect test result is mandatory	✓	✗
Product labeling is reviewed and approved to ensure that it is comprehensive and accurate	✓	✗
Marketing claims must be supported by evidence and approved before use in a clinical setting	✓	✗
Oversight body is able to recall faulty tests	✓	✗

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## Regulatory background and history

FDA has regulated medical devices since the passage of the Medical Device Amendments of 1976, including products “intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease.”<sup>5</sup> As such, the agency has authority over in vitro diagnostic (IVD) tests and their components. In vitro diagnostic refers to any clinical test that analyzes samples taken from the human body. Under the current regulatory regime, IVDs developed for the commercial market are subject to regulatory requirements set by the agency to ensure safety and effectiveness.

FDA has historically exempted tests made and used in a single laboratory from nearly all regulatory requirements under the Food, Drug, and Cosmetic Act because the agency has generally viewed LDTs as posing a lower risk to patients than IVDs manufactured at commercial scale and sold to labs. When FDA was originally granted oversight over medical devices in 1976, most LDTs were relatively simple, or they provided customized tests for rare conditions that could not be assessed with commercially available IVDs. Although some LDTs continue to be developed at a small scale and used locally, others, particularly those that are modified versions of commercial IVDs, may run at significant volumes—especially in a large commercial lab that processes thousands of samples a day. LDTs have also become more complex, are used for a wider range of conditions that affect many more people, and are sometimes marketed nationwide.

As LDTs have grown in use and complexity, FDA regulations have not kept pace. Instead, LDTs are principally regulated by CMS under separate regulations known as Clinical Laboratory Improvement Amendments (CLIA). CLIA oversight focuses on laboratory operations and staff training but does not assess the validity of individual tests in a lab. Because LDTs have not been required to meet FDA review standards, their number and the extent of their use is unknown. In 2014, FDA estimated that 650 U.S. laboratories developed and deployed LDTs,<sup>6</sup> while the American Clinical Laboratory Association maintained that the 11,633 labs that were certified at that time to develop such tests did so.<sup>7</sup>

CLIA standards differ from those applied during FDA premarket review. FDA regulates IVDs as medical devices and classifies these tests based on the level of risk that potentially inaccurate results pose to patients and public health. During the premarket review process, a developer must provide evidence demonstrating that a test is both analytically and clinically valid, which are key concepts in assessing a test’s reliability and accuracy. (See box below.)

**Analytical validity** refers to how well a test performs in detecting or measuring the presence of a given chemical compound, hormone, or genetic marker in a given sample. Analytically valid tests are precise (they provide a high degree of specificity), accurate (they measure or detect what they are intended to), and reliable (they regularly reproduce the same results).

**Clinical validity** refers to how accurately a test predicts the presence of, or risk for, a given condition. A genetic test intending to detect the presence of a genetic mutation is clinically valid for a particular cancer if a meaningful association between that mutation and the incidence of the disease has been demonstrated.

For those laboratories administering tests that have not received FDA clearance or approval, CLIA regulations do not allow the release of any test results until the laboratory demonstrates its ability to analytically validate the tests it performs. However, unlike FDA’s review of IVDs, a determination of analytical validity for a laboratory regulated under CLIA cannot be extrapolated to other sites or patient populations. In addition, a laboratory’s analytical validation is reviewed as part of a survey that takes place every two years—meaning that an unreliable test might not be caught for two years.<sup>8</sup> FDA review of analytical validation, in comparison, is performed before a test is marketed for use in patients, and is more comprehensive and focused on a test’s safety and effectiveness.<sup>9</sup> CLIA is also not intended to assess the clinical validity of the tests performed in that lab—this type of validation is left to the labs themselves.<sup>10</sup>

Table 1

## Federal Oversight of Diagnostic Tests Is Fragmented<sup>11</sup>

Tests are regulated according to where they are developed and used, not the risks posed to patients

	FDA	CMS
<b>Primary statutory authority</b>	Food, Drug, and Cosmetic Act, as amended by the Medical Device Amendments of 1976	Public Health Services Act, as amended by the Clinical Laboratory Improvement Amendments (CLIA) of 1988
<b>Oversight</b>	All IVDs (including LDTs and reagents) are categorized as medical devices, but FDA has historically not exercised its regulatory authority with respect to LDTs.	Labs conducting tests on human samples. Inspectors evaluate the qualifications of lab personnel and testing processes and review their analytical validation processes for all tests, whether LDT or IVD.
<b>Validation requirements</b>	Analytical validity Clinical validity	Analytical validity

	FDA	CMS
<b>How are tests validated?</b>	Through premarket review, manufacturers of moderate- and high-risk IVDs must establish that a test detects or measures the intended analyte with appropriate precision and accuracy. Human studies are typically required to demonstrate the test's ability to predict a disease or condition as intended.	Labs performing tests that are not subject to FDA clearance or approval must establish performance characteristics of that test ("an analysis of accuracy, precision, analytical sensitivity, analytical specificity, reportable range, reference interval").
<b>When are tests reviewed?</b>	At various points before the legal marketing of that test.	During inspections every two years (may be up to two years after an LDT is first performed).
<b>Adverse event reporting</b>	Mandatory reporting of adverse events by manufacturers, device user facilities (hospitals, nursing homes, etc.), and importers. Providers and patients may also voluntarily report serious adverse events.*	Not required. No mechanism exists to collect such information.
<b>Recall authority?</b>	Yes	No

\* U.S. Food and Drug Administration, "Medical Device Reporting (MDR): How to Report Medical Device Problems," <https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems>.

Source: As governed by Public Law 94-295, Public Law 100-578, and associated implementing regulations; Centers for Medicare & Medicaid Services.

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This fragmented oversight system, whereby tests are regulated according to where they are developed and used rather than their risk to patients, can pose dangers to public health. Given that CLIA's regulatory system does not require a laboratory to demonstrate an LDT's clinical validity, the chance that an inaccurate test will be introduced into the market increases. Inaccurate tests can expose patients to harm, including false-positive results, which could lead them to pursue unnecessary treatments or delay the timely diagnosis of underlying conditions. Similarly, false-negative results can delay or prevent patients from receiving proper treatment, potentially allowing the disease or condition to progress unchecked. For example, many direct-to-consumer genetic tests—such as genetic health risk tests, which predict a person's risk for developing diseases such as cancer or Alzheimer's—are developed and used as LDTs. The clinical validity of some of these tests is uncertain, as there is ongoing scientific disagreement about the role that genetic variants may play in contributing to many diseases. A positive result from a test that is not clinically valid, therefore, might cause unnecessary emotional distress to a patient.

Furthermore, unlike FDA standards, CLIA regulations do not require makers of LDTs to publicly report adverse events that may stem from the use of their tests, nor is there a system in place to track these events. Therefore, if an inaccurate LDT was used, the number of patients affected and how they were affected might never be known. For example, a test called OvaSure was marketed as an LDT by LabCorp to detect ovarian cancer in high-risk populations. It was later discovered that only 1 out of every 15 positive results was a true positive, potentially leading patients to undergo unnecessary, dangerous, and invasive surgeries.<sup>12</sup> FDA sent LabCorp a warning letter, and the test was removed from the market within months, but because there is no mechanism for adverse event reporting for LDTs, the full scale of that test's impact remains unclear.

Over the years, as testing technologies have become more complex, clinicians' use of these tests has presented greater risks to patient and public health. (See "What Can Happen When Patients Are Exposed to Unreliable Tests?") However, although FDA maintains that LDTs are medical devices and fall under its jurisdiction, many

LDT developers have thwarted attempts to bring them under the agency's oversight, arguing that these tests are procedures that fall under the practice of medicine. For years, policymakers on both sides of the aisle have debated how best to reform the current system of oversight. (See Appendix C for a timeline of key events in this long-standing discussion.) In 2010, FDA announced its intention to reconsider its policy of enforcement discretion over LDTs and held a two-day public meeting to solicit input from stakeholders. This led to the development of draft guidance that was published in 2014 bringing LDTs under the agency's existing regulatory framework.<sup>13</sup> However, this proposal met with significant pushback from many in the laboratory industry and within academic medical centers.<sup>14</sup> As a result, the agency announced that it would not issue final guidance,<sup>15</sup> and reform discussions then shifted to Congress, where negotiations eventually culminated in the Verifying Accurate Leading-edge IVCT Development (VALID) Act, which was introduced in March 2020.<sup>16</sup>

### What Can Happen When Patients Are Exposed to Unreliable Tests?

Some categories of tests illustrate just how little oversight there is for even widely marketed LDTs and how risky inaccurate test results can be when patients are relying on their results to guide medical decisions around everything from pregnancy to cancer treatment.<sup>17</sup>

- **Noninvasive prenatal testing** is a method of determining the risk that a fetus will be born with certain genetic abnormalities, such as Down, Edwards, and Patau syndromes. These tests help parents make critical decisions about a pregnancy and, as such, need to be carefully designed, administered, and marketed. Of the more than 40 noninvasive prenatal tests, all are LDTs;<sup>18</sup> none have been cleared or approved by FDA. Some companies advertise these tests for use in populations where their accuracy is less established, or to diagnose a broader range of conditions despite the limited evidence for those uses.<sup>19</sup>
  - **Risk:** Expectant parents may be misled about the risk that a pregnancy has a chromosomal abnormality.
- **Direct-to-consumer (DTC) genetic tests** are, with relatively few exceptions, LDTs and not FDA-approved.<sup>20</sup> One study estimated that more than 26 million people had taken a DTC genetic health or ancestry test as of January 2019, with the number expected to reach 100 million by the end of 2021.<sup>21</sup> There is variable quality among manufacturers, however.<sup>22</sup> One small study examined 49 patients who had taken a DTC genetic test and subsequently received follow-up testing. The authors found that 40% of the harmful variants reported back to those patients were false positives, indicating that the patients did not actually have those genetic variants.<sup>23</sup>
  - **Risk:** These incorrect results can lead to stress and unnecessary medical procedures.
- **Companion diagnostics** guide the safe and effective use of a particular therapy and are often a key factor in treatment decisions, increasing the risks to patients if the results are incorrect. In some cases, after FDA approves one companion diagnostic, labs create follow-on versions of those tests that they claim can identify the same mutation.<sup>24</sup> However, individual labs often have different approaches to analyzing samples. And some LDT developers claim to test for additional mutations that have not been adequately reviewed to predict drug response.<sup>25</sup>
  - **Risk:** The same patient may get different results depending on the LDT used,<sup>26</sup> receive ineffective therapies for a condition, or miss out on more beneficial ones. And many cancer treatments have serious side effects of their own, which can compound the harm for patients who receive an inappropriate therapy.<sup>27</sup>

The onset of the COVID-19 pandemic has only underscored the need for regulatory clarity. When a public health emergency was declared in January 2020,<sup>28</sup> FDA subsequently announced that it would require any test used as part of the pandemic response to apply for emergency use authorization (EUA), just as it had done for prior emergencies.<sup>29</sup> To further speed expansion of COVID-19 testing, FDA in March 2020 began allowing labs to bring a test to market immediately, provided that they apply for an EUA within 15 days.<sup>30</sup>

EUAs allow FDA to temporarily authorize urgently needed medical products while ensuring that the potential benefits to patients outweigh the risks. This quality check from the agency is crucial in ensuring that tests on the market meet baseline standards for accuracy and reliability before they are used on patients. The EUA process also allows the agency to track tests once on the market and to know how they are performing in the real world, issuing safety announcements<sup>31</sup> and even revoking authorizations where necessary.<sup>32</sup>

However, in August 2020, the Department of Health and Human Services (HHS) declared that FDA could not require premarket review for any LDT—whether developed for COVID-19 or any other condition—unless the agency first went through a time-consuming rule-making process.<sup>33</sup> This announcement did not state whether any of FDA’s other emergency authorities, such as the ability to recall faulty tests, were still in effect. HHS subsequently declared that LDTs for use in a national public health emergency remain subject to appropriate FDA regulations under the Public Health Service Act in order “to prevent the introduction, transmission, or spread of communicable diseases.” However, because most of the agency’s authority over diagnostic tests stems from the Food, Drug, and Cosmetic Act, FDA’s power to regulate LDTs—whether during a public health emergency or not—remains unclear.<sup>34</sup>

Legislators are still considering how to reform IVD oversight in a way that ensures that all tests are held to risk-based standards of review while providing pathways for developers to bring innovative tests to market without undue delay. However, an incomplete understanding of the scale and complexity of the diagnostics market has impeded these discussions. Research assessing the size of the testing industry, its structure, and the role of LDTs within the market is essential to inform discussions about reform and to tailor new oversight mechanisms and resources to the risks of those tests.

## Understanding the role of LDTs in the diagnostics market

Pew’s study found that an estimated 3.3 billion IVD tests are performed in the U.S. every year. Interviews with lab professionals suggested that LDTs account for a significant portion of this total, but our analysis did not produce a reliable estimate of this part of the overall testing market. No single database tracks all LDTs currently in use, and claims data—which is typically used to estimate testing volume—does not distinguish between tests run as LDTs and those run as IVDs. Responses to our survey indicated that lab managers lack a widely shared definition for LDTs, further challenging efforts to characterize the market.

### Who makes LDTs

Not all clinical labs develop LDTs. Of the approximately 267,000 lab facilities in the U.S., the vast majority are simple operations set up to run conventional, easy-to-use blood tests and other low-risk tests without the need for specially trained laboratory personnel.<sup>35</sup> These tests—collectively referred to as “CLIA-waived” because they can be run outside a CLIA-certified setting—include those that can be performed anywhere, from the back of an ambulance to a school nurse’s office, pharmacy, physician’s office, or hospital.<sup>36</sup>

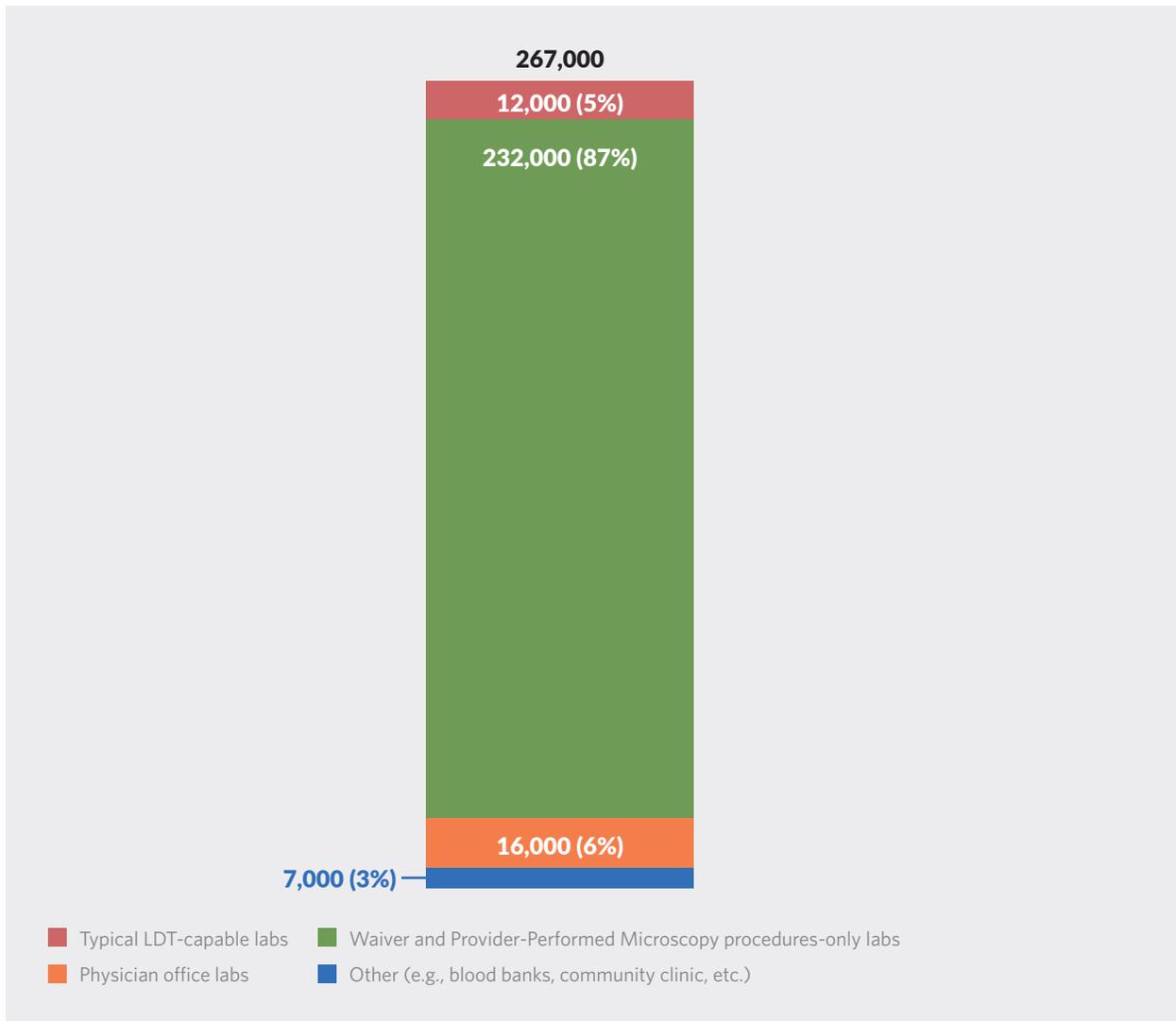
Developing a safe and effective test from scratch is a complex undertaking that involves significant training, reliable controls, and substantial investment in analytical equipment. For the most part, only labs certified by CLIA as high-complexity labs can develop and deploy LDTs, and an estimated 12,000 such laboratories were

registered with CMS as of March 2020.<sup>37</sup> (See Figure 2.) Although this number is a small proportion of the approximately 267,000 labs in the U.S., it still makes up a considerable segment of the overall testing landscape, as many of these labs are large and process thousands of patient samples a day.

Figure 2

## Only Certain Laboratories Develop LDTs

Of approximately 267,000 lab facilities in the U.S., an estimated 12,000 are likely to use LDTs



Source: BCG analysis of the Quality Improvement and Evaluation System (QIES) database

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Qualified labs may create a new LDT in four basic ways (see Figure 3):

- Starting from scratch, assembling relevant testing reagents and other FDA-reviewed testing components.
- Combining elements of FDA-reviewed test kits with components made or separately acquired by the lab.
- Obtaining the protocol for a test developed as an LDT by another facility.
- Altering an FDA-cleared or -approved IVD by, for instance, enabling the product to analyze patient specimens that have been stored longer than the test's labeling allows.

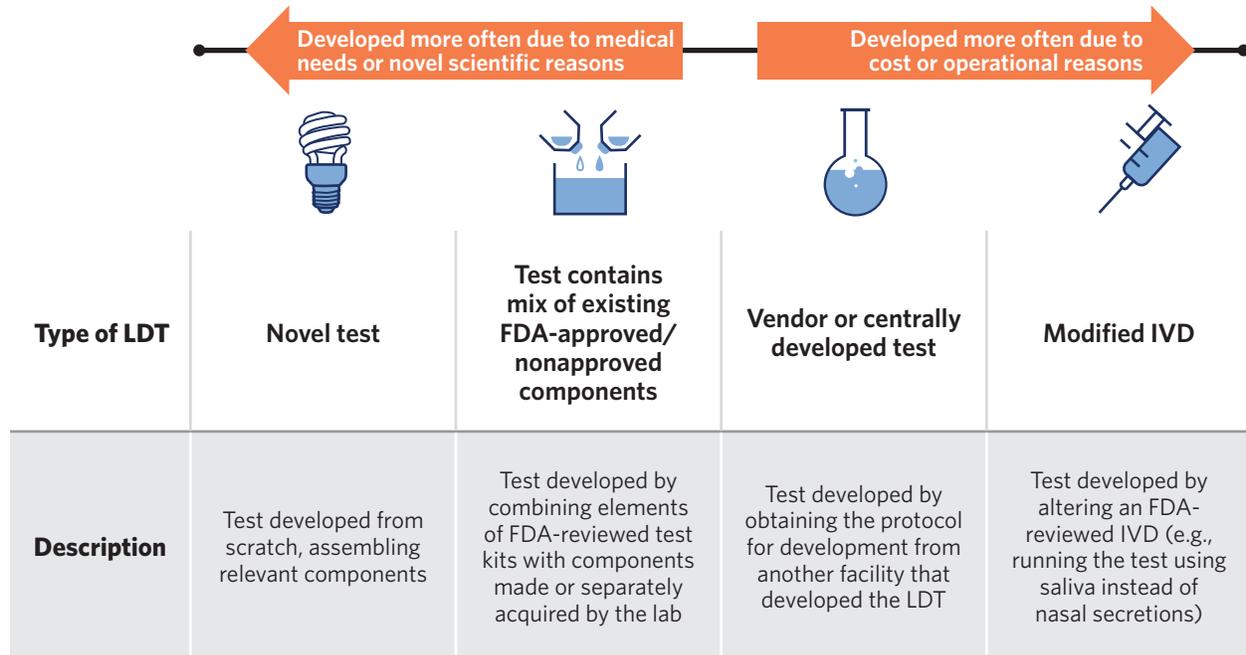
### **Considerations for reform**

Although it is difficult to know precisely how many LDTs are on the market, or to accurately estimate the volume of tests that are run using LDTs, they are clearly common, and many labs rely on them in some capacity. This poses a challenge for policymakers considering reform, because a mechanism will be needed for bringing these tests under a new regulatory framework in a way that minimizes disruptions to patient care and critical laboratory services. There are two potential options that could be considered. Policymakers could adopt a risk-based, phased-in approach that would transition all existing tests under the new regulatory framework within some specified time frame, similar to what FDA proposed in its 2014 draft guidance on LDT regulation.<sup>38</sup> Alternatively, policymakers could issue a blanket regulatory exemption for tests that are on the market before a particular date, much as they have in past cases where FDA has been granted new authorities over an existing market.<sup>39</sup> However, this approach poses public health risks, because it would exempt from review many moderate- and high-risk tests that are currently driving the need for reform.

One solution to this issue would be to allow FDA broad authority to request data on these “pre-reform” tests and to require a full premarket review if it was deemed necessary to protect public health. Pre-reform tests should also be subject to the same registration and reporting requirements that apply to new tests entering the market, including adverse event reporting. To ensure that all pre-reform tests are accounted for and subject to FDA enforcement, developers should also be required to register them with the agency. A central registry would be a key tool for oversight and could also serve as an important public resource.

Figure 3

## LDTs range from wholly lab-developed to slight modifications of IVDs



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### Why labs develop LDTs

Lab managers interviewed for this study noted that they prefer to use FDA-reviewed commercial IVDs when those are available. They cited several reasons, including their relative ease of use and efficiency compared with LDTs. Some also noted that commercial IVDs are generally more reliable and are of high quality. Relying on commercial IVDs also reduces labs' potential liability if there is a problem with the test. However, they all noted that LDTs are sometimes necessary or preferable.

In many cases, labs may develop a test if FDA has not approved a suitable IVD. There are many scenarios in which this might be the case. There might be a limited commercial incentive to develop a test that will go through FDA review—for example, for certain rare diseases or conditions. Alternatively, an LDT might represent the prototype of a diagnostic test that will ultimately be submitted for FDA approval. In other cases, the test in question is evolving rapidly in response to emerging science, and developers might perceive FDA review as being too slow to keep pace. (See Figure 4.) Approximately half of our nonprobability survey respondents stated that they used LDTs when no IVD was commercially available.

Figure 4

## Reasons an FDA-Reviewed IVD Might Not Be Available for a Particular Use

Lab managers cite lack of market incentives, the rapid pace of test innovation, and regulatory costs as key drivers of LDT development

Question: For tests where no FDA-approved IVD exists for the testing indication and an LDT is utilized, what are the most common reasons why no IVD exists? Percentage of respondents selecting in Top 3.

	Total
Test is too low-volume to warrant filing for IVD	46%
Novel test—will eventually become IVD	45%
Test is evolving quickly (e.g., new markers)	43%
Test is instrument- and interpretation-based (e.g., mass spec, flow cytometry, immunohistochemistry)	35%
Filing for IVD would be too expensive	28%
Test is specific to a single lab/lab company and no desire currently exists to market it outside of lab/lab company	23%
Other	1%

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The survey also sought deeper insight into why lab managers would choose to employ an LDT. Open responses to offer the “top reasons” for using LDTs tended to fall into four broad categories: patient need, clinical workflow, rapid access, and cost.

- Patient need**—When a disease such as COVID-19 emerges or spreads, the spike in demand for testing can outstrip the available supply of IVDs from device manufacturers. In such cases, clinical laboratories with the requisite equipment, supplies, and expertise can step in to provide additional testing, much as they have during the current pandemic. In other cases, a test may be altered in some way to make it less invasive or easier to perform—for example, changed to run on saliva instead of a sample taken from deep in a patient’s nasal cavity. In oncology, tests that are validated in one type of cancer may be adapted for use in another type of cancer. For example, no FDA-approved IVDs exist for the KRAS gene mutation in pancreatic cancer, but clinicians sometimes modify an available IVD test for KRAS in colorectal cancer, thereby creating an LDT.
- Clinical workflow**—Any deviation from a manufacturer’s instructions for administering an IVD creates an LDT. For instance, an IVD may be approved for use with samples taken within the past 48 hours. However, a reference lab performing thousands of these tests across a broad geographical area may require more time to receive and process the samples. In such cases, the lab can perform an analysis to determine whether the delay has any bearing on the validity of the test and document the results for inspectors.
- Rapid access**—IVDs can take considerable time to gain FDA approval and reach the market. However, the

speed of scientific research and technological development in the diagnostics market can outpace FDA review, particularly in rapidly evolving fields such as genetic testing. In those contexts, an LDT may be developed as an early prototype and then transformed into a standardized, FDA-approved IVD once it has been refined through experimentation and the developer has accumulated enough data to demonstrate that it meets FDA standards for safety and effectiveness. Alternatively, some tests, such as those that rely on next-generation sequencing technology, may be highly complex to run and require specific training to interpret, both of which are factors that can make a test more difficult to standardize and produce at a commercial scale for use in many labs.<sup>40</sup> In these cases, the developer may prefer to maintain the test as an LDT.

- **Cost**—All IVDs include components designed to make their systems resilient under a range of procedural and handling conditions. However, a sophisticated and well-equipped clinical lab might consider these safeguards both unnecessary and expensive, so it could modify the test to save money. For example, labs might substitute reagents or other components that can be purchased at a lower cost, then validate those modifications to ensure that the test still works as expected. In this way, some labs might reduce their operating expenses. Examples of this phenomenon are common, especially with large laboratory chains with multiple sites that often substitute LDTs for IVDs such as complete blood count testing kits.

### Considerations for reform

Given the important role that IVDs—including LDTs—play in the health care system, any new regulatory framework will need to balance several competing public health priorities. For example, it must be flexible enough to allow laboratory professionals to address legitimate clinical needs, such as developing tests for rare diseases, in response to disease outbreaks, or to address areas with limited commercial incentive. In addition, it should be flexible in allowing labs to develop their own tests to increase the speed of the tests, reduce costs, and improve the efficiency of lab processes. As with any medical product, however, all clinical tests should be subject to the same system of oversight, and regulatory scrutiny should be proportional to the risk that a test poses to patients or to public health if it is inaccurate.

### How and where LDTs are used

Previous studies have found that LDTs are used most frequently in molecular diagnostics, which includes genetic testing as well as tests targeting a range of other molecules.<sup>41</sup> Common applications include oncology and inherited diseases, but widespread use is also observed across a range of other applications, including toxicology or blood coagulation.<sup>42</sup> The lab managers who responded to our survey and participated in interviews generally echoed these findings. The concentration in oncology speaks to the increased trend toward targeted therapy, in which individual tumors are tested for specific cancer mutations, such as the BRAF gene in melanoma, to identify patients who are more likely to benefit from a particular therapy. So-called companion diagnostics are developed and marketed as IVDs by device companies. However, once these tests are approved by FDA, LDT developers often create follow-on co-diagnostic tests that they claim will identify the same mutations.<sup>43</sup> In some cases, this may not pose risks to patients.<sup>44</sup> However, because individual labs may have different approaches to analyzing samples—particularly for newer, more complex tests—the same patient may get different results depending on the LDT used.<sup>45</sup> And because many labs do not operate under an FDA-regulated quality system, there is less assurance that the test will not change over time.

Genetic testing for inherited conditions—including many screening tests that are administered to all newborns—and prenatal tests to detect fetal abnormalities also have a high level of LDT use. In fact, none of the more than 40 noninvasive prenatal tests on the market are FDA-reviewed.<sup>46</sup> As genetic research expands and more therapies are developed, the need for companion diagnostics will probably continue to rise—potentially resulting

in either greater LDT volumes across a broad range of conditions or a higher number of applications for FDA to review.<sup>47</sup>

Other types of testing, particularly those that rely on well-established technologies and have been on the market for years, tend to have lower LDT use. Interviewees cited general chemistry tests, hematology tests, and certain well-established microbiology tests in this group.

Interviewees also noted that different types of labs tend to have varying approaches to LDT development. Academic medical centers and specialty labs that focus on particular disease areas or technologies, for example, are more likely to develop novel tests from scratch, and tend to do so to meet specific medical needs or as part of their ongoing research. Large reference labs, by contrast, are more likely to develop LDTs to make work more efficient or to reduce operating costs. For example, testing for sexually transmitted and other infectious diseases generates large test volumes that are often sent through large commercial reference labs. Although the labs may process these samples using a commercially available IVD, internal processes designed to improve efficiency may deviate from FDA-approved guidelines. Under CLIA rules, if the lab can document that its procedures do not alter the validity of the diagnostic, it is free to amend the procedure. In doing so, however, the lab creates an LDT.

Interviewees noted that public health labs—which include the CDC’s as well as state and local labs—also rely on LDTs for a range of uses, including responding to local outbreaks of particular pathogens, conducting surveillance testing, and, notably, responding to public health emergencies such as COVID-19. However, smaller public health labs typically do not have the resources to develop novel tests from scratch; rather, they may be more likely to modify a commercial IVD or to use a test protocol developed elsewhere that they then validate in their own lab.

LDT use is also more common in technologies that rely on manual interpretation or are highly adaptable and can be used in a broad range of clinical contexts. This includes mass spectrometry and next-generation sequencing, which are testing methods that rely on sophisticated instrumentation and expert interpretation. Both have high rates of LDT use, and relatively few IVDs that rely on these methods are commercially available.

### **Considerations for reform**

As these findings illustrate, LDTs are used in a variety of settings and for a broad range of purposes. However, they are particularly common in fields where inaccurate results can lead to serious, even life-threatening consequences, such as oncology and other fields that rely heavily on genetic testing. They are also frequently used in certain contexts where the science is rapidly evolving, and where tests must be quickly adapted to reflect new learning. Although any new regulatory framework will need to allow for this sort of ongoing innovation, it must also provide a baseline assurance of both analytical and clinical validity. The stakes for clinical validity are especially high in cases where a clinical decision is based entirely or primarily on the result of an IVD, such as companion diagnostics that are used to screen cancer patients to receive certain drugs.

### **Common misconceptions about LDTs**

Pew’s survey results revealed that even highly experienced laboratory professionals may not realize when they are using an LDT. Many respondents, for instance, claimed that all or a significant proportion of their mass spectrometry and next-generation sequencing tests were FDA-reviewed IVDs. However, there are relatively few FDA-approved mass spectrometry or next-generation sequencing tests. This points to a broader lack of understanding of the boundary between an LDT and an IVD.

Subsequent interviews revealed that many respondents did not realize that every time they deviate from an FDA-reviewed test’s protocol, they effectively create an LDT. Alternatively, some appeared to think that using FDA-reviewed test components as part of a more complex testing procedure means that the test is FDA-approved.

However, this is not the case. Components and tools may help lab technicians and researchers with their analysis, but the test itself—which may be a multistep procedure generating an output interpreted by a laboratory professional—is considered an LDT.

Previous estimates of LDT use have varied widely for these reasons. For example, FDA suggested that 11,000 LDTs developed in 650 labs were in use during consideration of the agency’s proposed guidance framework in 2014.<sup>48</sup> In contrast, researchers studying the market for genetic tests estimated that 75,000 such IVDs were in use in 2018, with the vast majority being LDTs.<sup>49</sup>

### **Considerations for reform**

These misconceptions highlight the general lack of familiarity that many laboratory professionals have with FDA and its regulations, which could pose a challenge for the agency as it attempts to exert its authority over the LDT market. Bringing these developers under FDA regulation will require a transition period that will allow the lab community adequate time to come into compliance. It will also require extensive outreach and education after reform is passed to ensure a common understanding of those regulations and what compliance will entail. Such a transition period will also be necessary for FDA, which will need to write new regulations and guidance documents on how it will implement these reforms, and to hire staff to handle the influx of new applications and conduct the necessary inspections. These activities will necessarily require additional funding from Congress, and potentially user fees paid by test developers.

### **Lessons from COVID-19**

The COVID-19 pandemic took hold in the middle of our research and offered a unique window into the impact of LDTs on public health. In our interviews and survey, labs’ ability to ramp up testing was an important topic that highlighted the role that LDTs play in driving innovation in the market. Eighty-one percent of lab managers surveyed said they either offered or planned to offer COVID testing, with 21% of respondents saying their lab deployed an LDT COVID-19 test (versus a commercially manufactured EUA test that FDA reviewed). Furthermore, 59% of respondents said that without an LDT option, their ability to ramp up testing would have been further delayed. While not perfect, many LDTs filled a critical role in the early management of the pandemic and continued to provide additional testing capacity throughout 2020.

However, FDA plays a critical role in ensuring the quality and reliability of COVID-19 testing. The value of FDA review was made clear early in the pandemic when the agency briefly allowed COVID-19 antibody tests to come to market without undergoing the EUA process. Antibody tests are used to screen for past infection and can be an important tool in tracking outbreaks and developing mitigation strategies. However, many of these tests proved unreliable in practice, leading the agency to reverse its policy within weeks.<sup>50</sup> FDA also conducted a review of the EUA submissions it received from labs that had developed diagnostic tests aimed at identifying active COVID-19 cases. Of the 125 EUA requests it reviewed, 82 had design or validation issues that required correction, and some were denied authorization altogether. In many cases, the agency was able to work with the labs to resolve problems so that tests could eventually be used.<sup>51</sup>

### **Considerations for reform**

As these examples illustrate, FDA review serves as a critical check on tests entering the market. It also ensures that the agency has a clear picture of the tests on the market and can receive information on how those tests are performing in the real world, including the incidence of false positives or false negatives, as well as documentation of patient harm. This in turn allows it to update the public when it becomes aware of a problem and pull a test from the market when necessary.

## Implications for regulatory reform

The current diagnostic testing regulatory system—in which tests are regulated according to where they are developed and used, rather than the risk they pose if they are inaccurate—creates double standards and potential loopholes that undermine public health objectives. Although labs that make LDTs are subject to CMS regulation, they are not required to demonstrate clinical validity or report cases of patient harm from their products—requirements that FDA applies to manufacturers that develop and sell IVDs for use in multiple facilities. They are also not held to the same quality standards that device manufacturers must meet.

As the diagnostics market has evolved and the role of LDTs has changed, diagnostics manufacturers, public health groups, patient advocates, and FDA have raised concerns about the public health effects of excluding thousands of tests—many of which have significant implications for patient care—from FDA review.

Over the past decade, there has been significant, sustained debate on how best to harmonize the regulatory pathway for IVDs and LDTs. Achieving consensus will require substantial public dialogue, with input from these key stakeholders as well as the health care researchers and professionals who rely on their output. As legislators evaluate the best path forward, the following guidelines may help guide their thinking:

- To effectively regulate these products, FDA must have a clear picture of what tests are in use and be able to collect sufficient information on how they are performing. At a minimum, this should include a requirement that all tests be registered with the agency; developers report adverse events related to their diagnostics; and the agency be empowered to request information regarding the validity and performance of those products when it has concerns.
- Given the large yet unknown number of LDTs currently on the market, any reform will need to include a mechanism for bringing these tests into compliance with FDA regulations in a way that minimizes disruptions to patient care. Two options that policymakers could consider are phasing in FDA reviews of LDTs or exempting LDTs from premarket review while ensuring that the agency has sufficient postmarket authority to require data on their performance and take enforcement action when necessary to protect patients.<sup>52</sup> (See Appendix E.)
- IVDs are regularly modified or adapted to address patient need and to respond to advances in scientific understanding. Any new regulatory approach for diagnostics must be flexible enough to allow test developers to modify tests or develop new ones in order to meet patient need without undue delay. However, adequate guardrails must be in place to ensure that these tests are valid, reliable, and of high quality. Again, as with any medical product, regulatory oversight should be proportional to the associated risks.
- The lack of a shared definition of what constitutes an LDT—even among laboratory experts—highlights the broader lack of familiarity of many labs with FDA regulations. Bringing LDT developers under FDA regulation will require a transition period that allows labs adequate time to come into compliance. It will also require extensive outreach and education after reform is passed to ensure a common understanding of FDA regulations and what compliance will entail.
- FDA, in turn, will need adequate time and additional funding to develop new guidance documents and regulations and to implement them by conducting more reviews and inspections of labs.

## Conclusion

Clinical diagnostics play an essential role in the U.S. health care system. Our research demonstrates that roughly 3.3 billion diagnostic tests are performed in the country each year. Although most of these tests are run on FDA-approved IVD kits, an unknown but probably sizable number follow a different path to market as LDTs. Although both categories of tests are used for similar clinical purposes, CLIA oversight of LDTs provides only an indirect review of test validity. Although the LDT regulatory process offers labs significant flexibility and enables a more rapid response to public health needs when no FDA-cleared or -approved test exists, the relative lack of oversight for LDTs puts the health of patients at risk.

LDTs were once more limited in scope, but changes in technology and industry practices have led to far greater numbers of patients being routinely exposed to tests—even high-risk ones—that undergo no premarket review. IVDs are subject to FDA standards for analytical and clinical validity, postmarket surveillance requirements, and adverse event reporting designed to identify, rectify, or recall problem tests. But no equivalent requirements are imposed upon LDTs, even though they may be used similarly to IVDs on patients. This is particularly concerning in fields that rely heavily on genetic testing, such as oncology, where test results may be the deciding factor in whether a patient receives a particular treatment.

Although regulatory harmonization has been discussed for decades, the current dual system—and the public health vulnerabilities that it perpetuates—remains in force. The COVID-19 pandemic only underscores the need to establish a unified regulatory framework that ensures the safe and effective use of all tests. The findings outlined in this report can help guide policy discussion about how to establish a risk-based oversight system that enables innovation while ensuring patient safety.

# Glossary

**Analyte.** A substance whose chemical constituents are being identified or measured.

**Analytical validity.** A measure of how well a test performs in detecting or measuring the presence of a particular analyte.

**CDC.** Centers for Disease Control and Prevention.

**CLIA.** Clinical Laboratory Improvement Amendments, a section of the CMS authorization pertaining to regulation of U.S. laboratory testing.

**Clinical validity.** A measure of how accurately a test predicts the presence of, or risk for, a given condition.

**CMS.** Centers for Medicare & Medicaid Services.

**CPT.** Current Procedural Terminology, the medical code set used to report medical, surgical, and diagnostic procedures.

**EUA.** Emergency use authorization, a premarket notification classification used to obtain FDA permission to market a medical product without undergoing normal approval procedures because of a health crisis such as the COVID-19 pandemic.

**FDA.** Food and Drug Administration.

**FFS.** Fee-for-service, a method of payment for health care services also known as “traditional Medicare” when used in the context of Medicare health insurance.

**Flow cytometry.** A scientific method for measuring the number, size, and nucleic content of cells using an instrument in which cells flow in a narrow stream through a beam of light.

**G-codes.** Temporary codes used to identify health care procedures and services that have not yet been assigned CPT codes.

**HCPCS.** Healthcare Common Procedure Coding System, a standardized coding system used by medical providers to submit health care claims to Medicare and other providers.

**IVD.** In vitro diagnostic; includes any test that analyzes a human sample for a clinical purpose.

**LDT.** Laboratory-developed test; IVDs that are developed and used within the same laboratory.

**Mass spectrometry.** An analytical technique that measures the ratio of an ion’s mass to its charge to obtain a unique isotopic signature that helps to identify the chemical identity or structure of molecules and compounds.

**NGS.** Next-generation sequencing, a DNA sequencing technology that uses massively parallel systems to query the entire genome to identify specific sequences that correspond to known pathologies.

**Sensitivity.** The term used to describe how often a test correctly identifies a positive result, or the “true positive” rate.

**Specificity.** The term used to describe how often a test correctly identifies a negative result, or the “true negative” rate.

## Methodology

All FDA-reviewed tests are listed in a publicly available database maintained by the agency, but no database—public or private—encompasses all available lab-developed tests. Nor does any central repository capture the billions of clinician orders for tests that are performed on millions of patients in tens of thousands of settings each year and paid for through many different funding streams. Therefore, any attempt to characterize the LDT market must rely on estimation built on certain assumptions, and these estimates must be refined with additional data. This study leveraged multiple data sources to provide a current snapshot of the diagnostics market.

**Market size.** To estimate the number of IVDs run annually, Boston Consulting Group (BCG) used 2017 Current Procedural Terminology (CPT) data from the CMS fee-for-service claims database. CPT codes allow us to identify common diagnostic tests for various medical conditions and applications. BCG also reviewed information from a large data aggregator, which includes electronic health records (EHRs) without patient identifying information for approximately 6% of the total U.S. market. Using observed differences between the Medicare-eligible and overall U.S. population, BCG extrapolated the data to arrive at a clinical diagnostic market size for the entire country. Appendix A contains a more detailed review of the market sizing methodology, data sources, and key assumptions.

**LDT usage.** To better understand the nature of LDT use and factors contributing to this usage, the BCG team began with qualitative research anchored by 20 market interviews with lab directors and diagnostic testing professionals and executives, followed by a nonprobability web survey and a round of five in-depth follow-up qualitative interviews with respondents to the nonprobability survey. To ensure the quality of the survey, the questions were pretested with five potential survey respondents. The survey questions and responses were discussed in depth with each pretest participant to verify that respondents had interpreted the questions in the manner intended. Appendix B includes a more detailed review of the online LDT market survey, as well as the respondents, survey design, and interview questions. The team then reviewed published literature and market analyses by third parties to help interpret the survey and interview findings. These sources are cited throughout the document.

**Limitations.** It is difficult to make inferences about the LDT market because it is poorly tracked and highly fragmented. As mentioned, we used a nonprobability sample, meaning that the labs we surveyed are not representative of the industry at large. We used this approach because it was cost-effective and timely, but more importantly because the incomplete picture of the market makes it impossible for researchers to ensure that a given sample reflects the real composition of the market. This also means that confidence intervals to measure the degree of certainty around the market's use of LDTs cannot be constructed. We have attempted to ensure that the different sectors of the laboratory industry were represented in the sample and have conducted a series of comparisons and checks (see Appendix B for details) to ensure confidence in and lend credibility to the analysis. However, the lack of transparency in this market precludes any guarantee of precision in how survey respondents estimate the operations and in views of the industry, and ultimately prevented us from making reliable quantitative estimates about LDT use.

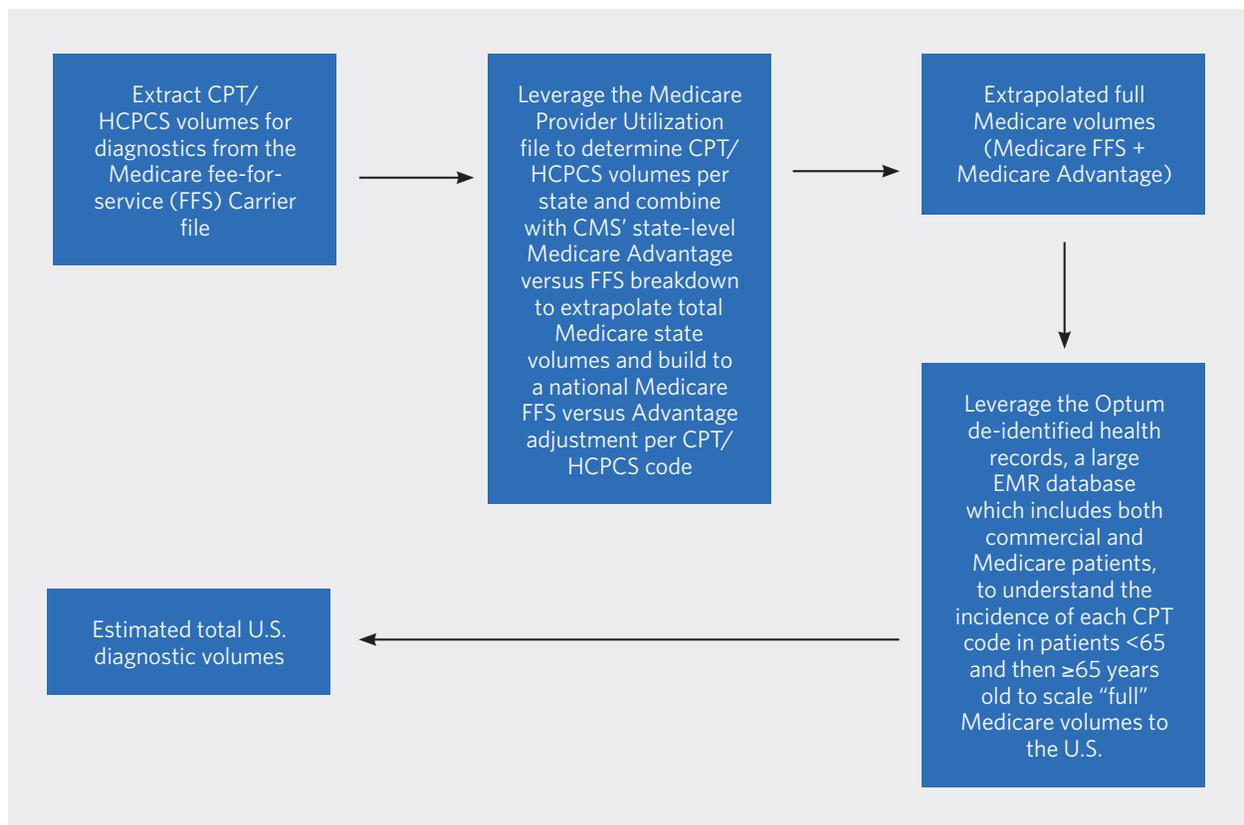
# Appendix A

## Methodology Detail—Market Sizing

Because the health care landscape is fragmented, there is no single source of diagnostic test volume across the U.S. Instead, diagnostic utilization data exists in silos at various hospitals and insurance companies, as well as CMS. Neither medical orders nor reimbursement systems require any documentation of whether the test is an IVD or LDT, and health care claim codes—Current Procedural Terminology/Healthcare Common Procedure Coding System (CPT/HCPCS)—may not provide insight into the specific modality used. Any attempt to estimate overall U.S. diagnostic test volume, therefore, requires a triangulation between insurance claims and EHRs, supplemented by published literature and expert input.

Figure A.1

### Overview of Process to Estimate Market Size



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Our estimation followed this general path, using Medicare claims from CMS and EHRs from the private health care company Optum. The results were compared with prior estimates in the public literature and discussed with 20 industry experts (lab managers, equipment manufacturers, clinicians, researchers, and others) who reviewed our approach and validated our analytical assumptions.

To provide further detail on the approach used and the specific sources, our first task was to identify the relevant CPT/HCPCS codes that pertain to diagnostics in key disease areas and modalities. The team evaluated

CPT codes between CPT 80047 and CPT 89398, which consist of 1,400 individual “pathology and laboratory procedures” as well as specific “G-codes”—which track services and procedures under review before being assigned to the CPT coding system—that could potentially be identified as laboratory tests.

The 2014-18 available Medicare fee-for-service (FFS) Carrier Files were used as the foundation for market volumes with the Medicare FFS Provider Utilization file used for adjustment. Both datasets are publicly available. A few notes on these data sources for context: Medicare FFS contains 70% of Medicare data; the remaining 30% of Medicare volume flows through an array of private insurance companies through the Medicare Advantage (“MA”) managed care program. CMS publishes the share of MA versus traditional Medicare per state. The Carrier file provides an aggregate assessment of CPT and G-code billings within a calendar year and contains claims submitted by all providers regardless of national provider identifier (NPI) status including physicians, nurse practitioners, clinical laboratories, ambulance services, suppliers, and stand-alone ambulatory surgical centers. This file has no geographic breakdown. The provider file includes only billings by physicians and suppliers with valid NPIs and therefore often has a lower volume than the Carrier file. This file does have a state breakdown allowing for more granular geographic analysis.

To extrapolate the full U.S. Medicare volumes, we used the following process:

1. Each CPT code in the provider file was aggregated on a state level and then grossed up by the share of MA in each state to determine the total state volumes.
2. These state values were then aggregated to form a national view.
3. The extrapolated total U.S. volume was then compared with the original provider file volume to determine the required percentage adjustment for each CPT code.
4. This factor was then applied to the Carrier file to give a more refined view of the MA adjustment compared with using the national breakdown of traditional Medicare versus MA.
5. For CPT codes that were underrepresented in the provider file (i.e., identified by only a limited number of states reporting in the provider file), the average percentage of Medicare Advantage across CPT codes with complete data (i.e., 50 states found in the provider file) was applied. This underrepresentation was variable and probably the result of differences in data capture in the Medicare Provider Utilization Data file, which analyzes only select providers, and the Carrier file, which is an all-comers report. Overall, this adjustment resulted in a gross up of testing volumes by 43% to 52%.

Because Medicare data covers only the population over 65 and certain specific groups (e.g., end-stage renal disease patients), Medicare test volume is skewed and is only part of the puzzle. To adjust for non-Medicare test volumes, the team utilized Optum de-identified EHRs (2007 to March 2018), a patient-level database that standardizes and integrates multiple U.S.-based EHR data systems. The longitudinal clinical repository is one of the largest in the U.S. and is derived from more than 50 health care provider organizations, including more than 2,000 hospitals and 7,000 clinics. The data is sourced from both the ambulatory and inpatient settings and includes ICD 9/10 and HCPCS diagnosis and procedure codes. The Optum cohort used for this study included 122,421,485 lab records. We used only data from 2017 as that was the most current full year of data and thus captured newer tests.

Optum was used to calculate the incidence rate of each CPT/HCPCS code for patients under 65 and then over 65. That ratio was used to scale Medicare data to full U.S. volumes to give a more tailored approach to scaling to the non-Medicare population (and better include tests exclusive to patients under 65). This methodology produced a national estimate of 3.3 billion tests. However, there are geographic and demographic biases to acknowledge with Optum. Compared with the U.S., Optum is overrepresented for those over 65 (22% of the patients in Optum versus 17% of the U.S. population) and underrepresented for those under 18 (16% in Optum

versus 23% of the U.S.). All other age groups align with the U.S. population breakdown. Optum also mirrors the U.S. in terms of gender distribution (54% female in Optum versus 53% in the U.S.). Geographically, Optum is overrepresented in the Midwest (41% of patients in Optum versus 21% in the U.S.) and underweighted in the West (13% in Optum versus 24% in the U.S.) and the Northeast (11% in Optum versus 18% in the U.S.). As this data comes from health care systems, there is no specific insurance bias in Optum, unlike Medicare. These breakdowns are current for the years used and do not apply for any later revisions of the database.

Three approaches were used to triangulate this market number. The first scaled Medicare total volumes to the U.S. population using the share of Medicare of the total population as published in the Census Bureau's American Community Survey by the Kaiser Family Foundation. This approach produced an estimate of 3.8 billion tests, which probably overestimates testing intensity because the 65-plus population has a higher overall utilization of diagnostic testing than younger populations. The second approach directly extrapolated Optum incidence rates per CPT code to the full U.S. population. This approach suggested a total of 2 billion tests, which was considered a lower bound as Optum is underrepresented in key geographies. Our final estimate of 3.3 billion tests uses age adjustment based on observed differences in the over-65 and under-65 age cohorts observed in the two datasets. The results of this analysis were compared with six other estimates in the available literature, and our estimates fall well within the range.

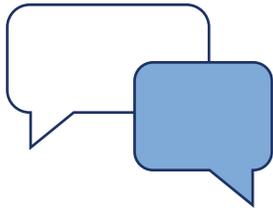
Finally, there are a number of important limitations to the methodology that should be acknowledged. The CMS data (Carrier and provider file) covers less than 20% of the U.S. and is primarily for individuals 65-plus and therefore does not represent testing patterns for younger age cohorts. Likewise, the Optum EHR dataset covers less than about 10% of the U.S. population—with a regional bias—and thus is not fully representative of the U.S. population. Moreover, diagnostic testing that occurs during inpatient admission into a hospital could be underrepresented in both datasets. Nonetheless, the usage of multiple datasets and comparisons with public research should help mitigate the limitations and provide confidence in the final estimates.

## Appendix B

### Methodology Detail—Primary Market Research

Figure B.1

#### Overview of Interviews and Survey Research



##### 1. 20 interviews

- Lab directors and diagnostics industry professionals and executives
- Data analyzed qualitatively
- Questions addressed include:
  - What are the typical reasons your lab utilizes LDTs for?
  - What are the positives/negatives of using LDTs versus IVDs?
  - What trends in LDT use do you see?



##### 2. Nonprobabilistic web survey n=195

- Current and recent former lab managers
- Data analyzed quantitatively
- Questions addressed include:
  - Do you use LDTs in your lab? For what reasons?
  - Are you aware of the pending VALID legislation?
  - Are you using LDTs for COVID diagnosis?



##### 3. 5 follow-up deep dives

- Current and recent former lab managers
- Data analyzed qualitatively
- Questions addressed include:
  - How did you interpret the survey questions?
  - Were there any questions that did not make sense?
  - Are there any other additional comments you'd like to add?

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### Methodology Detail—Market Nonprobability Survey

Available datasets contain little information on the type of diagnostic test used in various laboratory settings, the extent of LDT usage, and the main drivers of that usage. Accordingly, we constructed a market survey to shed light on these topics. To provide additional depth and to characterize the data, the team conducted market interviews with 20 laboratory managers and industry professionals.

The vast majority of diagnostic tests used by U.S. health care professionals are considered simple diagnostics conducted under a CLIA waiver. These tests are granted waived status once FDA and CDC have determined that they are relatively simple to perform and interpret. Because our focus was on the role of LDTs and such waived tests require FDA review, the team sought to exclude these simple tests from consideration in our segmentation. Based on input from industry experts and lab managers as well as a review of the medical literature, we created a list of disease applications and technologies that are most likely to involve moderate to complex diagnostics, as indicated below:

Figure B.2  
**Applications and Technologies**

Application	Technology
1. Oncology	1. Immunoassays
i. CDx (companion diagnostics)	
ii. Genomic sequencing and other	
2. Genetic disorders/inherited disease	2. Hematology and coagulation
3. Infectious and parasitic diseases*	3. Molecular diagnostics^
i. STI (sexually transmitted infection)	i. PCR (polymerase chain reaction)
ii. Viral	ii. NGS (next-generation sequencing)
iii. HAI (hospital acquired infection)	iii. Other
iv. Respiratory and other	
4. Immunology	4. Microbiology
5. Endocrine, nutritional, and metabolic diseases	5. Clinical chemistry
6. Cardiology	6. Histology/cytology
7. Mental/behavioral disorders	7. Flow cytometry
8. Reproductive, prenatal, and newborn testing	8. Mass spectrometry
9. Pediatrics-specific testing	9. Other
10. Hematology/general blood testing	
11. Bodily fluids analysis (e.g., urine, saliva)	
12. Toxicology	
13. Other diseases	

\* Infectious disease requires additional breakdown as it is a large and diverse application area

^ Molecular diagnostics requires additional breakdown due to the higher share and variability of LDT usage across application areas

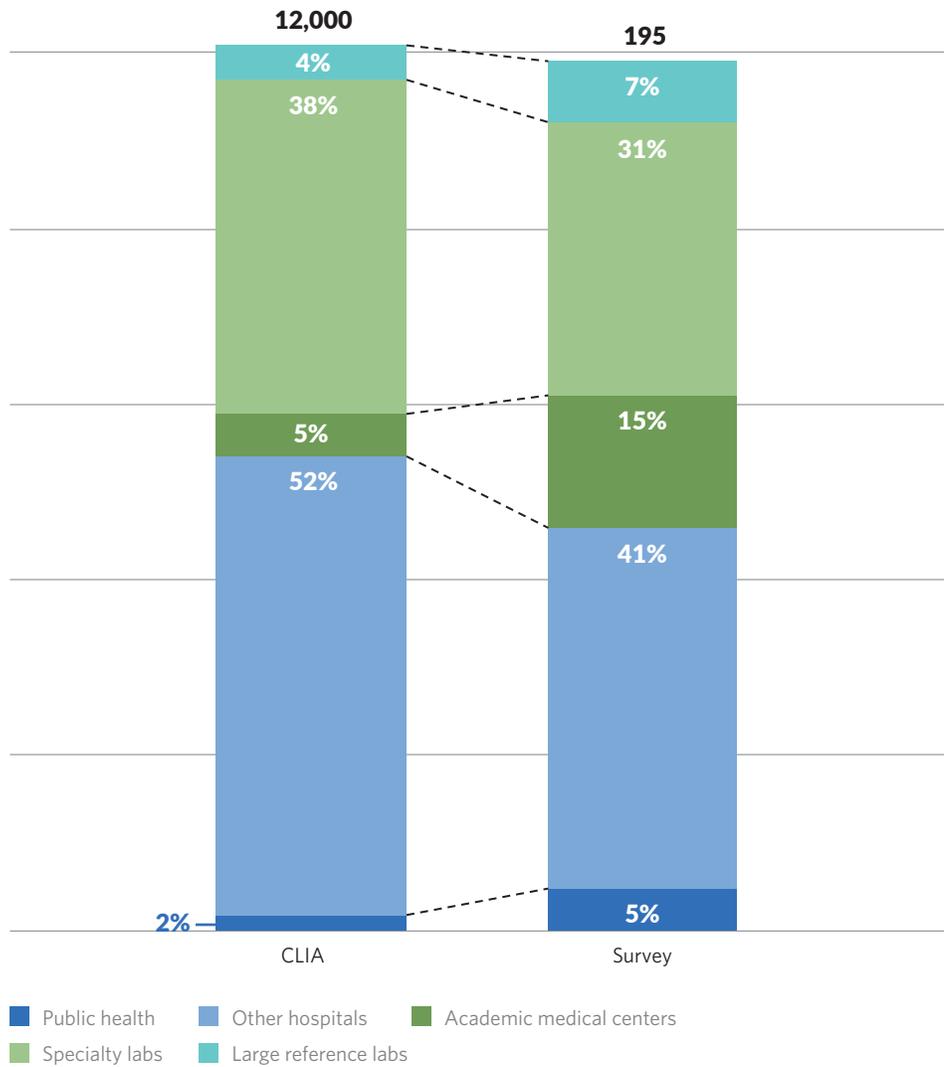
The team performed a nonprobability survey and a series of qualitative interviews, both directed at laboratory managers. The nonprobability survey was used to provide insights into moderate-to-complex diagnostic testing volume by laboratory type, technology used, and disease or therapeutic area focus. In addition, the survey asked respondents to indicate the percentage of tests performed with LDTs versus IVDs, as well as their general rationale for LDT usage. Qualitative interviews were used to supplement the survey and specifically explore tradeoffs between IVD and LDT options.

The web-based survey began with a screening tool to ensure appropriate representation across lab types and geographies, and to verify that each respondent had appropriate background and knowledge about their labs' testing volume. The actual survey consisted of 40 questions covering the areas described above. Our survey sought to reach 200 qualifying responses, with a specific breakdown into seven laboratory types: large reference labs; independent and specialty labs; academic medical center labs; labs at large hospitals (more than 400 beds), medium-sized hospitals (100-400 beds), and small hospitals (fewer than 100 beds); and public health labs. The three nonacademic hospital lab segments were later grouped together to generate a final list of five laboratory types for our analysis, with each type assigned a quota based on the mix of laboratories accredited or approved to develop and deploy LDTs.

Figure B.3

### CLIA vs. Survey Data by Lab Category<sup>53</sup>

Survey quota roughly aligned to federally published CMS data on certified labs



Note: Academic medical centers, large reference labs, and public health labs were oversampled compared with CLIA

Source: BCG analysis of CLIA data (assessed via QIES database); Centers for Medicare & Medicaid Services

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The survey was provided to a subset of the laboratory population sourced through third-party market research companies Dynata, Gerson Lehrman Group, and Guidepoint on April 16-28, 2020. These companies maintain specialty lists of experts for targeted surveys that allow researchers to qualify prospective respondents using employment history, responsibilities, and a full range of demographic dimensions.

The survey was distributed to 30,356 potential survey takers. The vast majority were invited via email (more than 30,000). To ensure adequate representation from all segments of the industry, other recruits were targeted via text message and through a portal where regular survey respondents could access available surveys. Those who did not respond received up to three reminders, one to five days after initial outreach.

Among those invited to take the survey, there was a 10% response rate, with survey administrators observing a 5-10% bounce-back rate for their email outreach. Respondents were then screened to qualify by being a current or recent (less than five years) lab manager, director, or supervisor with knowledge of their lab's volume of tests, types of tests performed, split of IVD and LDT, and the rationale for selecting each type of test. Among those who responded to the outreach, 31% were deemed eligible after this initial screening. Each of the 195 qualified respondents was offered a financial incentive (less than \$200) to complete the questionnaire, in accordance with market rates.

There are several limitations to the approach. Our survey specifically excluded testing sites that perform only waived tests, which constitute the vast majority of labs in the U.S. Waived tests represent about 1.5 billion of the approximately 3.3 billion tests performed in the U.S. Because our survey deliberately skewed toward higher-volume and more specialized labs considered more likely to develop and use LDTs in the course of their business, it is not representative of the complete U.S. diagnostic laboratory sector.

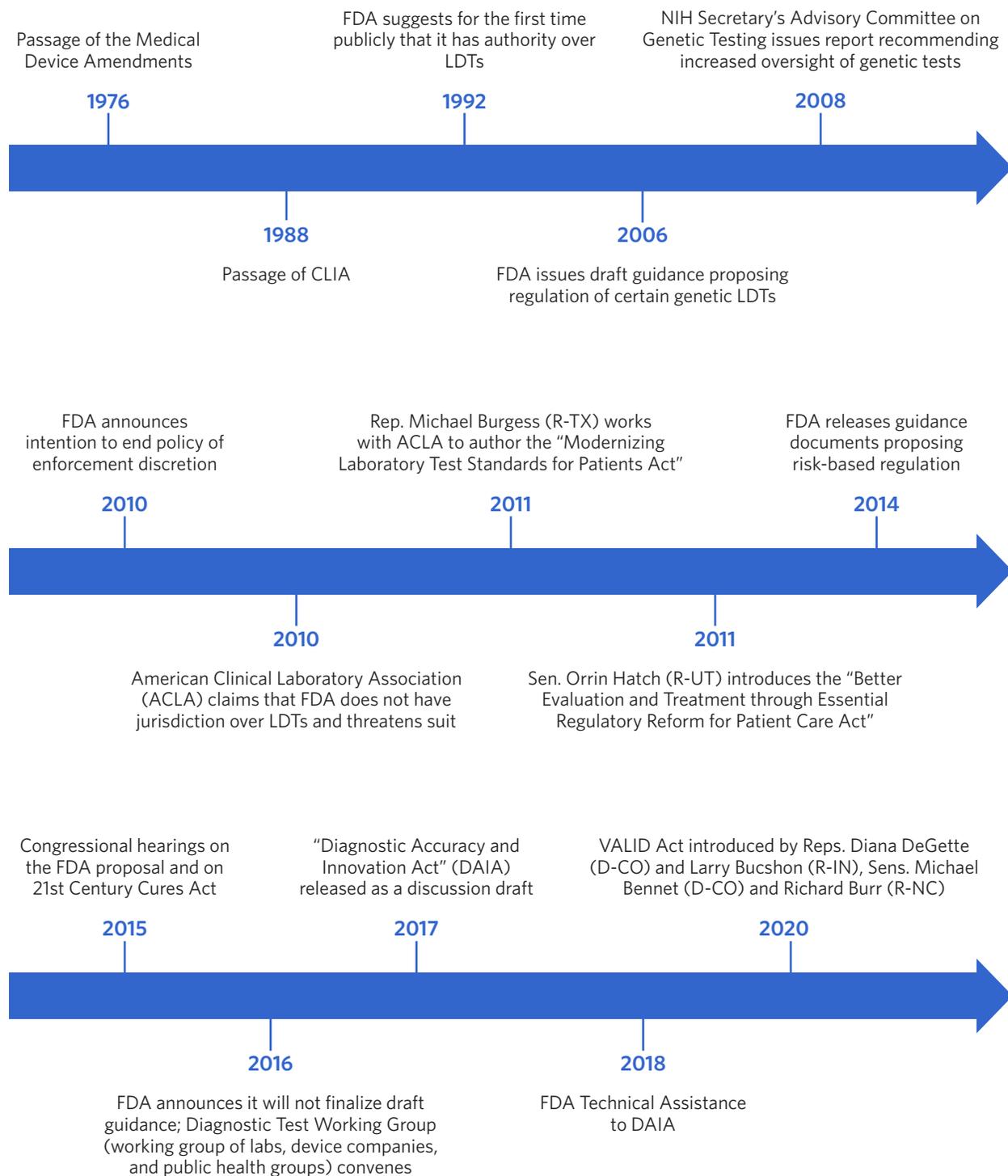
Moreover, the fragmented regulation of this market has created trickle-down effects that make research in this area particularly challenging. This was reflected in apparent inconsistencies in the definition of common terms—primarily the terms “test” and “LDT.” There was apparent confusion as to whether intermediate steps in the performance of a test (e.g., sample processing) could be defined as a discrete test, and whether modifications to IVDs would be defined as LDTs. Although respondents were provided with definitions of these terms and provided with appropriate context and guidance, the survey output suggested that some responses reflected different understandings of these terms.

Although detecting this issue presented a research finding of significance to policymakers, this lack of uniform understanding of common terms did introduce measurement error, which confounded attempts to estimate LDT use at the market level. Furthermore, for this reason, our survey can provide only directional information about how and why frequent users of LDTs employ tests of this type.

The overall number of respondents covered 195 sites out of thousands of labs that may perform at least some LDTs. However, our survey quotas were deliberately selected to reflect the composition of the reference laboratory sector, which consists of facilities that are approved under CLIA guidelines to develop and deploy LDTs. Even with a skew toward heavy LDT users, the team was obliged to review survey responses to ensure a consistent interpretation of a “diagnostic test,” which is often misconstrued to apply to individual components of a single test. To mitigate against overcounting, the team took the precaution of conducting follow-up interviews and checking individual responses for significant outliers. The team also reviewed the list of respondents to avoid duplication of responses for individual labs.

## Appendix C

### Timeline of Diagnostics Regulation



# Appendix D

## Lab Manager Survey

### Based on all respondents

**S0.** Which of the following describes your occupation? Select all that apply.

Dentist

Registered Nurse

Director or Manager at a diagnostic testing lab

Lab technician or scientist (nonmanagement)

Student

Retired

Other

### Based on all respondents

**S1.** Which of the following describes your current role and relation to diagnostic lab testing?

Lab Director / Manager / Operations Manager of a CLIA-certified (or exempt) U.S. clinical testing lab or clinical testing services

Associate or Assistant Lab Director / Manager / Operations Manager of a CLIA-certified (or exempt) U.S. clinical testing lab or clinical testing services

Former Lab Director / Manager / Operations Manager of a CLIA-certified (or exempt) U.S. clinical testing lab or clinical testing services (no longer in role)

None of the above

### Based on respondents who are former lab directors

**S1A.** How long ago was your most recent experience as a Lab Director / Manager / Operations Manager?

Less than 1 year ago

1-3 years ago

4-5 years ago

More than 5 years ago

Note: Percentage less than 0.5 printed as \*.

### Based on respondents who are former lab directors

**S1B.** What is your current role?

Senior executive or leader (e.g., CEO, CMO, COO, SVP, VP) for a diagnostic lab company or test manufacturer

Other role within diagnostic lab testing industry (e.g., for a test device manufacturer, or R&D for a hospital system)

Full-time professor / teaching

Full-time policy / regulatory

Retired

Other

**Based on all respondents**

S3. Where is your current or most recent lab located?
Alabama
Alaska
Arizona
Arkansas
California
Colorado
Connecticut
Delaware
Florida
Georgia
Hawaii
Idaho
Illinois
Indiana
Iowa
Kansas
Kentucky
Louisiana
Maine
Maryland
Massachusetts
Michigan
Minnesota
Mississippi
Missouri
Montana
Nebraska
Nevada
New Hampshire
New Jersey
New Mexico
New York
North Carolina
North Dakota
Ohio
Oklahoma
Oregon
Pennsylvania
Rhode Island

**S3. Where is your current or most recent lab located?**

South Carolina

South Dakota

Tennessee

Texas

Utah

Vermont

Virginia

Washington

West Virginia

Wisconsin

Wyoming

American Samoa

District of Columbia

Federated States of Micronesia

Guam

Marshall Islands

Northern Mariana Islands

Palau

Puerto Rico

Virgin Islands

Outside of U.S.

**Based on all respondents**

**S3A. What is the type of your current or most recent lab?**

Major reference lab within the Quest or LabCorp network

Other independent reference lab (single lab, part of smaller/regional network, or a specialty lab—e.g., ARUP, DaVita, Bio-Reference, etc.)

Lab affiliated with a hospital or hospital network

Public health lab

Physician office lab

Other

**Based on respondents affiliated with hospitals**

**S3B. What is the size of your hospital?**

Very Large (>700 beds)

Large (400-700 beds)

Medium (100-399 beds)

Small (<100 beds)

**Based on respondents affiliated with hospitals**

**S3C.** Is your lab associated with an academic medical center?

Yes

No

**Based on all respondents**

**S4.** What is the annual testing volume of your lab?

<100,000 tests annually

100,000 - 499,999 tests annually

500,000 - 999,999 tests annually

1 - 5 million tests annually

5 - 9 million tests annually

10 - 19 million tests annually

20 - 29 million tests annually

30 - 39 million tests annually

40 - 49 million tests annually

50+ million tests annually

**Based on all respondents**

**S5.** Please select the types of diagnostic tests that your lab runs. Select all that apply.

Lab-Developed Tests (LDTs)

In-Vitro Diagnostics tests (IVDs) - FDA Certified

Research Use Only (RUOs)

Other

**Based on all respondents**

**S6.** Which of the following disease application areas does your lab conduct testing for? Select all that apply.

Oncology - genomic sequencing and other

Oncology - companion diagnostics

Genetic disorders / inherited disease

Infectious diseases - STIs

Infectious diseases - viral

Infectious diseases - hospital-acquired infections (HAIs)

Infectious diseases - respiratory and other

Immunology

Endocrine, nutritional, and metabolic diseases

Cardiology

Mental / behavioral disorders

S6. Which of the following disease application areas does your lab conduct testing for? Select all that apply.

Reproductive, prenatal and newborn testing

General blood testing / hematology

Bodily fluids analysis (e.g., urine, saliva, etc.)

Toxicology

Pediatrics-specific testing

Other diseases

#### Based on all respondents

S7. Which of the following testing primary technologies does your lab use? Select all that apply.

Immunoassays

Hematology and coagulation

Molecular - PCR

Molecular - NGS

Molecular - other

Microbiology - culture and other

General and clinical chemistry

Histology / cytology

Flow cytometry

Mass spectrometry

Other

#### Based on all respondents

S8. Have you taken a survey on LDT vs. IVD testing in the United States in the past 2 weeks?

Yes

No

#### Based on respondents utilizing LDTs

R1. What types of LDTs does your lab utilize? Select all that apply.

Novel LDTs utilizing all-new reagents, components, or equipment that are not FDA-approved (e.g., developed by lab, RUO, etc.)

New tests that combine both FDA-approved components (e.g., ASR reagents, stains, etc.) and equipment with non FDA-approved components (e.g., RUO reagents) and equipment

New tests that combine only one or more FDA-approved / IVD components (e.g., ASR reagents, stains, etc.) and equipment for a new use case

Modification of existing FDA-approved IVD (e.g., throughput, temperature, specimen age, etc.)

Off-label use of existing FDA-approved IVD (e.g., different clinical use case)

Other

### Based on respondents utilizing LDTs

**R1D.** How are your lab's LDTs typically developed? Select all that apply.

Wholly developed within your lab from scratch (by R&D resources from your lab, for example)

Mostly or partly developed at another lab (e.g., corporate R&D lab, academic or research lab, partner, etc.), brought in and validated by your lab

Mostly or partly developed by a non-IVD vendor, brought in and validated by your lab

Developed in conjunction with an IVD vendor (e.g., Roche, Thermo Fisher, etc.)

Modifying an existing IVD

Other

### Based on respondents utilizing LDTs

**R3.** What are the most important rationales for your lab's utilization of LDTs?

Patient access to new clinical need (e.g., new or emerging medical care standard)

Nature of test is highly manual or interpretive

Emergency access (e.g., COVID)

Quality or performance of test (e.g., better version of test - more precise, etc.)

Cost

Confirmatory testing / validation

Speed to market

Operational or workflow optimization (e.g., higher throughput, more flexibility with sample age)

Extend test offering on currently installed hardware

Other

### Based on respondents utilizing LDTs

**R4.** If an IVD was introduced for a current LDT where no IVD exists for the testing indication, would your lab most likely:

Definitely switch to the IVD

Switch to the IVD only if the IVD is at least as good as your current LDT (e.g., of at least a similar efficacy and not significantly more costly)

Switch to the IVD only if the IVD is significantly better than your current LDT (e.g., IVD has a significant efficacy or cost advantage)

Not switch to the IVD in any case

Other

### Based on respondents utilizing LDTs

**R4B.** What are the most important advantages of utilizing an IVD over an LDT? Rank top five.

Liability protection for lab

Requires fewer development resources from lab

Requires less validation work from lab

Ease-of-use / requires fewer operational resources from lab

Higher accuracy / efficacy / quality than LDT

**R4B.** What are the most important advantages of utilizing an IVD over an LDT? Rank top five.

Higher trust in test from customer

Lower cost

Medical need

Ease of successful reimbursement

Other

#### Based on respondents utilizing LDTs

**R5.** For tests where no FDA-approved IVD exists for the testing indication and an LDT is utilized, what are the most common reasons why no IVD exists? Select all that apply.

Novel test - will eventually become IVD

Test is too low volume to warrant filing for IVD

Filing for IVD would be too expensive

Test is evolving quickly (e.g., new markers)

Test is instrument and interpretation based (e.g., mass spec, flow cytometry, immunohistochemistry)

Test is specific to a single lab / lab company and no desire currently exists to market it outside of lab / lab company

Other

#### Based on all respondents

**R8.** How has your lab's relative use of LDTs (compared to total testing volume and IVDs) trended in the past 5 years?

My lab uses more LDTs

My lab uses fewer LDTs

My lab uses the same number of LDTs

I don't know / prefer not to answer

#### Based on all respondents

**R8B.** How do you anticipate your lab's usage of LDTs to evolve over the next 5 years?

I expect my lab to use more LDTs over time

I expect my lab to use fewer LDTs over time

I expect my lab to use the same number of LDTs over time

I don't know / prefer not to answer

**Based on respondents utilizing IVDs and not LDTs**

**R9. What are the most important advantages of utilizing an IVD over an LDT? Rank top five.**

Liability protection for lab

Requires fewer development resources from lab

Requires less validation work from lab

Ease-of-use / requires fewer operational resources from lab

Higher accuracy / efficacy / quality than LDT

Higher trust in test from customer

Lower cost

Medical need

Ease of successful reimbursement

Other

**Based on all respondents**

**C1. Does your lab currently or will your lab offer a COVID-19 test?**

Currently offer COVID-19 test

Planning to launch COVID-19 test

Do not plan to offer COVID-19 test

**Based on respondents currently offering or planning to launch a COVID-19 test**

**C1B. What type of COVID-19 testing will your lab offer under EUA (Emergency Use Authorization)? Select all that apply.**

IVD or kitted test offered manufacturer (e.g., Roche Cobas, Hologic Panther Fusion, ThermoFisher TaqPath, CDC kit)

LDT

Other

**Based on respondents currently offering or planning to launch a COVID-19 test**

**C1C. What type of detection method will your COVID-19 testing utilize? Select all that apply.**

Molecular (viral genome)

Immune response (antibody)

Other

**Based on respondents offering LDTs and COVID-19 test(s)**

**C2. If your lab did not conduct LDTs, would you have been able to offer a COVID-19 test under a similar timeline?**

Yes

No

### Based all respondents

P1. Are you aware of the proposed VALID (Verifying Accurate and Leading-Edge IVCT Development) Act?

Yes

No

### Based on all respondents

P3. What are the most important potential positive impacts you would expect from added regulation and FDA oversight of LDTs? Rank top five.

Scientific rigor and test quality

Patient results and outcomes

Patient access to testing

Patient safety

Burden on labs for development and validation

Operational burden on labs for conducting tests

Timeline to introduce new tests (speed to market)

Ability to scale up testing

Cost of testing

Personalized or physician-preference based testing

Innovation and research

Other

Note: The total is greater than 100% because respondents selected more than one impact.

### Based on all respondents

P3D. What are the most important potential negative impacts you would expect from added regulation and FDA oversight of LDTs? Rank top five.

Scientific rigor and test quality (worsen)

Patient results and outcomes (worsen)

Patient access to testing (worsen)

Patient safety (worsen)

Burden on labs for development and validation (increase)

Operational burden on labs for conducting tests (increase)

Timeline to introduce new tests (speed to market) (increase)

Ability to scale up testing (decrease)

Cost of testing (increase)

Personalized or physician-preference based testing (worsen)

Innovation and research (worsen)

Other

## Appendix E

### Example of a Risk-Based, Phased-In Approach to Bringing LDTs Through FDA Review

In 2014, FDA issued draft guidance outlining how it proposed to apply medical device regulations to LDTs, which had historically not been required to meet FDA quality standards or undergo premarket review.<sup>54</sup> The approach was meant to give clinical laboratories that were unfamiliar with FDA regulations enough time to adapt to the requirements while also allowing the agency to prioritize review of higher-risk tests. This guidance was ultimately withdrawn, but it provides an example of how LDTs could be brought under FDA review through legislative reform.

Per the draft guidance, FDA proposed grouping all LDTs into one of three risk-based categories, in consultation with test developers who would help to classify each test. Tests in the first category would continue to receive enforcement discretion—that is, FDA would not require them to meet agency standards. This included LDTs used solely for forensic purposes and certain LDTs used for transplantation. Tests in the second category would be registered with the agency and subject to adverse event report requirements but would not be required to undergo premarket review or meet FDA quality system requirements. This category would have encompassed lower-risk LDTs, including those for rare diseases, those that served an unmet clinical need, or those that met the definition of a “traditional LDT” (referring to the type of LDT that existed when enforcement discretion was initially applied).

The third category included all other moderate- and high-risk LDTs, which would have been subject to all applicable regulatory requirements, including registration and listing, adverse event reporting, premarket review, and quality system requirements. However, test developers would not be immediately subject to these requirements. Instead, the agency proposed a nine-year phase-in process for implementation:<sup>55</sup>

- Low-risk LDTs (Class I devices), LDTs for rare diseases, traditional LDTs, LDTs for unmet needs
  - **Six months after guidance is finalized:** Manufacturers must notify FDA that they are running an LDT, provide basic information about that test, and begin adverse event reporting.
- Moderate-risk LDTs (Class II devices)
  - **Six months after guidance is finalized:** Manufacturers must formally register and list their tests with FDA, pay a registration fee, and begin adverse event reporting.
  - **Five years after guidance is finalized (when high-risk LDTs are completely phased in):** Premarket review requirements begin, and phase-in occurs over four years. Nine years after the guidance was finalized, all moderate-risk LDTs would be reviewed and fully subject to FDA standards.
- High-risk LDTs (Class III medical devices)
  - **Six months after guidance is finalized:** Manufacturers must formally register and list their tests with FDA, pay a registration fee, and begin adverse event reporting.
  - **One year after guidance is finalized:** Premarket review requirements for highest-risk devices begin, and phase-in occurs over four years. The agency would prioritize for review those LDTs with the same intended use as a cleared or approved companion diagnostic, those with the same intended use as an FDA-approved Class III medical device, and certain LDTs for determining the safety or efficacy of blood or blood products. Five years after the guidance was finalized, all high-risk LDTs would be reviewed and fully subject to FDA standards.

## Endnotes

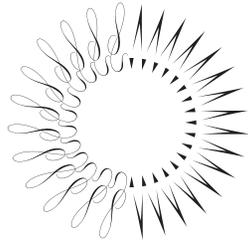
- 1 L. Buchen, "Cancer: Missing the Mark," *Nature* 471 (2011): 428-32, <https://www.nature.com/news/2011/110323/full/471428a.html>; M.H. Greene, Z. Feng, and M.H. Gail, "The Importance of Test Positive Predictive Value in Ovarian Cancer Screening," *Clinical Cancer Research* 14, no. 22 (2008), <https://clincancerres.aacrjournals.org/content/14/22/7574.2>; M. Boesen, "I Got a Double Mastectomy After a Genetic Test. Then I Learned the Results Were Wrong," *HuffPost*, Feb. 1, 2021, [https://www.huffpost.com/entry/bcr-genetic-testing-mastectomy\\_n\\_5c6c39f4b012225acd80d3](https://www.huffpost.com/entry/bcr-genetic-testing-mastectomy_n_5c6c39f4b012225acd80d3).
- 2 A. Schuessler, "Mother Speaks Up About Risks of Prenatal Testing," *The Daily Journal*, Feb. 25, 2019, [https://www.smdailyjournal.com/news/local/mother-speaks-up-about-risks-of-prenatal-testing/article\\_5739d5ca-38ab-11e9-a7bf-675355c57802.html](https://www.smdailyjournal.com/news/local/mother-speaks-up-about-risks-of-prenatal-testing/article_5739d5ca-38ab-11e9-a7bf-675355c57802.html); B. Daley, "Oversold Prenatal Tests Spur Some to Choose Abortions," *The Boston Globe*, Dec. 14, 2014, <https://www3.bostonglobe.com/metro/2014/12/14/oversold-and-unregulated-flawed-prenatal-tests-leading-abortions-healthy-fetuses/aKFAOCP5N0Kr8S1HirL7EN/story.html?arc404=true>.
- 3 U.S. Food and Drug Administration, "Lists of Direct-to-Consumer Tests With Marketing Authorization," last modified Dec. 20, 2019, <https://www.fda.gov/medical-devices/in-vitro-diagnostics/direct-consumer-tests#list>.
- 4 S. Gottlieb, M.D., former commissioner, Food and Drug Administration, "Blueprint for Breakthroughs—Charting the Course for Precision Medicine" (presentation, Friends of Cancer Research 7th Annual Blueprint for Breakthrough Forum, Sept. 13, 2018), <https://www.fda.gov/news-events/speeches-fda-officials/blueprint-breakthroughs-charting-course-precision-medicine-09132018>.
- 5 Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 321h, <https://www.govinfo.gov/app/details/USCODE-2010-title21/USCODE-2010-title21-chap9-subchapII-sec321>; U.S. Food and Drug Administration, "Classification of Products as Drugs and Devices and Additional Product Classification Issues," 2017, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/classification-products-drugs-and-devices-and-additional-product-classification-issues>.
- 6 Food and Drug Administration Notification and Medical Device Reporting for Laboratory Developed Tests; Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Availability, 79 Fed. Reg. 59779-82 (Oct. 3, 2014), <https://www.federalregister.gov/documents/2014/10/03/2014-23586/food-and-drug-administration-notification-and-medical-device-reporting-for-laboratory-developed>.
- 7 American Clinical Laboratory Association, "ACLA Written Statement for 21st Century Cures Hearing on LDT Regulation," Sept. 9, 2014, <https://www.acla.com/acla-written-statement-for-21st-century-cures-hearing-on-ldt-regulation/>.
- 8 Centers for Medicare & Medicaid Services, "CLIA Overview" (2013), [https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA\\_FAQs.pdf](https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf).
- 9 *Ibid.*
- 10 *Ibid.*
- 11 As governed by Public Law 94-295, Public Law 100-578, and associated implementing regulations. United States Public Law 94-295: Medical Device Amendments of 1976 (1976), <https://www.govinfo.gov/content/pkg/STATUTE-90/pdf/STATUTE-90-Pg539.pdf>; United States Public Law 100-578: Clinical Laboratory Improvement Amendments of 1988 (1988), <https://www.govinfo.gov/content/pkg/STATUTE-102/pdf/STATUTE-102-Pg2903.pdf#page=1>; Centers for Medicare & Medicaid Services, "CLIA Overview."
- 12 Buchen, "Cancer: Missing the Mark"; Greene, Feng, and Gail, "The Importance of Test Positive Predictive Value."
- 13 U.S. Food and Drug Administration, "Laboratory Developed Tests," last modified Sept. 27, 2018, <https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests>; U.S. Department of Health and Human Services et al., "Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories" (2014), <https://www.fda.gov/media/89841/download>.
- 14 American Clinical Laboratory Association, "ACLA Joins Physicians, Hospitals and Provider Stakeholders in AMA Letter Requesting FDA Withdraw Proposed Draft Guidance to Regulate Laboratory Developed Tests (LDTs)," news release, Nov. 19, 2014, <https://www.acla.com/acla-joins-physicians-hospitals-and-provider-stakeholders-in-ama-letter-requesting-fda-withdraw-proposed-draft-guidance-to-regulate-laboratory-developed-tests-ldts/>; Association for Molecular Pathology, "AMP Submits Written Comments to FDA on Proposed Regulation of Laboratory Developed Tests," news release, Feb. 2, 2015, [https://www.amp.org/AMP/assets/File/pressreleases/2015/1-29-15\\_AMPSubmitsCommentsToFDAonLDTRegulation.pdf](https://www.amp.org/AMP/assets/File/pressreleases/2015/1-29-15_AMPSubmitsCommentsToFDAonLDTRegulation.pdf); Association of American Medical Colleges, "Policy Priorities to Improve Our Nation's Health From America's Medical Schools and Teaching Hospitals" (2016), <https://www.aamc.org/system/files/c/2/472838-policy-priorities-improve-nations-health.pdf>.
- 15 S. Kaplan, "FDA Puts Off Closing Lab-Test 'Loophole,' Leaving Decision to Congress and Trump," *STAT*, <https://www.statnews.com/2016/11/18/fda-lab-test-loophole/>; U.S. Food and Drug Administration, "Discussion Paper on Laboratory Developed Tests (LDTs)" (2017), <https://www.fda.gov/media/102367/download>.
- 16 Verifying Accurate Leading-Edge IVCT Development Act of 2020, S. 3404, U.S. Senate—116th Congress 2nd Session (2020), <https://www.congress.gov/bill/116th-congress/senate-bill/3404/text>.
- 17 L. Richardson, "Clinical Lab Tests Need Stronger FDA Oversight to Improve Patient Safety," *The Pew Charitable Trusts*, Jan. 11, 2021,

<https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/01/clinical-lab-tests-need-stronger-fda-oversight-to-improve-patient-safety>.

- 18 M. Molteni, "How Much Prenatal Genetic Information Do You Actually Want?" *Wired*, March 27, 2019, <https://www.wired.com/story/how-we-reproduce-testing/>.
- 19 Society for Maternal Fetal Medicine, "SMFM Statement: Maternal Serum Cell-Free DNA Screening in Low Risk Women," accessed July 27, 2021, <https://www.smfm.org/publications/157-smfm-statement-maternal-serum-cell-free-dna-screening-in-low-risk-women>; R. Farrell et al., "Online Direct-to-Consumer Messages About Non-Invasive Prenatal Genetic Testing," *Reproductive Biomedicine & Society Online* 10, no. 1 (2016): 88-97, <https://doi.org/10.1016/j.rbms.2016.02.002>.
- 20 U.S. Food and Drug Administration, "Lists of Direct-to-Consumer Tests With Marketing Authorization," last modified Dec. 20, 2019, <https://www.fda.gov/medical-devices/in-vitro-diagnostics/direct-consumer-tests#list>.
- 21 A. Regalado, "More Than 26 Million People Have Taken an at-Home Ancestry Test," *MIT Technology Review*, Feb. 11, 2019, <https://www.technologyreview.com/s/612880/more-than-26-million-people-have-taken-an-at-home-ancestry-test/>.
- 22 S. Tandy-Connor et al., "False-Positive Results Released by Direct-to-Consumer Genetic Tests Highlight the Importance of Clinical Confirmation Testing for Appropriate Patient Care," *Genetics in Medicine* 20 (2018): 1515-21, [https://www.nature.com/articles/gim201838?mc\\_cid=b693215d3b&mc\\_eid=08a1c14744](https://www.nature.com/articles/gim201838?mc_cid=b693215d3b&mc_eid=08a1c14744); A.D. Bowser, "Direct-to-Consumer Genetic Testing Fraught With Validity Concerns," *MDedge*, April 16, 2019, <https://www.mdedge.com/internalmedicine/article/199003/business-medicine/direct-consumer-genetic-testing-fraught-validity>.
- 23 Tandy-Connor et al., "False-Positive Results Released."
- 24 A. Towse and L.P. Garrison Jr., "Economic Incentives for Evidence Generation: Promoting an Efficient Path to Personalized Medicine," *Value Health* 16, no. 6 (2013), <https://doi.org/10.1016/j.jval.2013.06.003>.
- 25 J. Shuren, "Jeffrey Shuren, M.D., J.D., Director of the FDA's Center for Devices and Radiological Health and Janet Woodcock, M.D., Director of the FDA's Center for Drug Evaluation and Research on Agency's Warning to Consumers About Genetic Tests That Claim to Predict Patients' Responses to Specific Medications," news release, Nov. 1, 2018, <https://www.fda.gov/news-events/press-announcements/jeffrey-shuren-md-jd-director-fdas-center-devices-and-radiological-health-and-janet-woodcock-md>.
- 26 A. Stenzinger et al., "Tumor Mutational Burden Standardization Initiatives: Recommendations for Consistent Tumor Mutational Burden Assessment in Clinical Samples to Guide Immunotherapy Treatment Decisions," *Genes, Chromosomes & Cancer* 58, no. 8 (2019): 578-88, <https://pubmed.ncbi.nlm.nih.gov/30664300/>.
- 27 U.S. Food and Drug Administration, "In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff" (2014), <https://www.fda.gov/media/81309/download>.
- 28 U.S. Department of Health and Human Services, "Determination That a Public Health Emergency Exists," last modified Jan. 31, 2020, <https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx>.
- 29 U.S. Food and Drug Administration, "Emergency Use Authorizations for Medical Devices," last modified March 1, 2021, <https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations-medical-devices>; U.S. Food and Drug Administration, "Coronavirus Disease 2019 (COVID-19) Emergency Use Authorizations for Medical Devices," last modified June 30, 2021, <https://www.fda.gov/medical-devices/emergency-use-authorizations-medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices>.
- 30 U.S. Food and Drug Administration, "Policy for Coronavirus Disease-2019 Tests During the Public Health Emergency (Revised): Immediately in Effect Guidance for Clinical Laboratories, Commercial Manufacturers, and Food and Drug Administration Staff" (2020), <https://www.fda.gov/media/135659/download>.
- 31 U.S. Food and Drug Administration, "Risk of False Results With the Curative SARS-CoV-2 Test for COVID-19: FDA Safety Communication," Jan. 4, 2021, <https://www.fda.gov/medical-devices/safety-communications/risk-false-results-curative-sars-cov-2-test-covid-19-fda-safety-communication>.
- 32 U.S. Food and Drug Administration, "Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chembio Antibody Test," news release, June 16, 2020, <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chembio-antibody-test>.
- 33 D. Lim and Z. Brennan, "Trump Administration Limits FDA Review of Some Coronavirus Tests," *Politico*, Aug. 19, 2020, <https://www.politico.com/news/2020/08/19/trump-fda-review-coronavirus-tests-398924>; U.S. Department of Health and Human Services, "Rescission of Guidances and Other Informal Issuances Concerning Premarket Review of Laboratory Developed Tests," last modified Jan. 21, 2021, <https://web.archive.org/web/20210121202702/https://www.hhs.gov/coronavirus/testing/recission-guidances-informal-issuances-premarket-review-lab-tests/index.html>. HHS subsequently removed the original policy announcement but has not retracted the policy.
- 34 R. Charrow, general counsel, letter to Stephen Hahn, commissioner of food and drugs, "Federal Authority to Regulate Laboratory Developed Tests," June 22, 2020, <https://www.politico.com/f/?id=00000174-e9b2-d951-a77f-f9fe04fa0000>; D. Diamond and D. Lim,

- "Memo Details HHS Push to Upend FDA's Testing Oversight," Politico, Oct. 2, 2020, <https://www.politico.com/news/2020/10/02/hhs-memo-fda-testing-oversight-425139>.
- 35 Centers for Medicare & Medicaid Services, "Laboratories by Type of Facility (Exempt and Non-Exempt)" (March 2020), <https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/factype.pdf>; Centers for Disease Control and Prevention, "Waived Tests," Jan. 25, 2021, <https://www.cdc.gov/labquality/waived-tests.html>.
  - 36 Centers for Medicare & Medicaid Services, "Laboratories by Type of Facility (Exempt and Non-Exempt)."
  - 37 BCG analysis of the Quality Improvement and Evaluation System (QIES) database.
  - 38 U.S. Department of Health and Human Services et al., "Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories."
  - 39 J.M. Adams and A.R. Talati, "NDI Guidance: The Waiting Game," Regulatory Affairs Professionals Society, Oct. 30, 2017, <https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/10/ndi-guidance-the-waiting-game>.
  - 40 P.H. Gilligan and M.B. Miller, "Will Regulatory and Financial Considerations Dampen Innovation in the Clinical Microbiology Laboratory?," *American Society for Microbiology* (Feb. 2, 2016), <https://mbio.asm.org/content/7/1/e02178-15>.
  - 41 B.W. Buchan and N.A. Ledebor, "Emerging Technologies for the Clinical Microbiology Laboratory," *American Society for Microbiology Journals* (2014), <https://cmr.asm.org/content/27/4/783>; S.H. Katsanis and N. Katsanis, "Molecular Genetic Testing and the Future of Clinical Genomics," *Nature Reviews Genetics* 14, no. 6 (2013): 415-26, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4461364/>; B.L. Wickes and N.P. Wiederhold, "Molecular Diagnostics in Medical Mycology," *Nature Communications* 9 (2018), <https://doi.org/10.1038/s41467-018-07556-5>.
  - 42 Kalorama Information, "The Worldwide Market for In Vitro Diagnostic Tests, 12th Edition" (Aug. 2, 2019), <https://kaloramainformation.com/product/the-world-market-for-in-vitro-diagnostic-tests-12th-edition/>.
  - 43 Towse and Garrison, "Economic Incentives."
  - 44 A.S. Kim et al., "Comparison of Laboratory-Developed Tests and FDA-Approved Assays for BRAF, EGFR, and KRAS Testing," *JAMA Oncology* 4, no. 6 (2018): 838-41, <https://jamanetwork.com/journals/jamaoncology/fullarticle/2665746>; M.M. Park et al., "ER and PR Immunohistochemistry and HER2 FISH Versus Oncotype Dx: Implications for Breast Cancer Treatment," *The Breast Journal* 1 (2014): 37-45, <https://doi.org/10.1111/tbj.12223>.
  - 45 Stenzinger et al., "Tumor Mutational Burden Standardization Initiatives."
  - 46 National Down Syndrome Society, "Noninvasive Prenatal Tests (NIPTs)," accessed April 30, 2021, <https://www.ndss.org/programs/ndss-legislative-agenda/healthcare-research/noninvasive-prenatal-tests-nipts/>; Molteni, "How Much Prenatal Genetic Information Do You Actually Want?"
  - 47 V.A. Miller, "FDA Regulation of Laboratory-Developed Tests," *Clinical Advances in Hematology & Oncology* 14, no. 5 (2016), <https://www.hematologyandoncology.net/archives/may-2016/fda-regulation-of-laboratory-developed-tests/>.
  - 48 Food and Drug Administration Notification and Medical Device Reporting for Laboratory Developed Tests.
  - 49 K. Phillips et al., "Genetic Test Availability and Spending: Where Are We Now? Where Are We Going?" *Health Affairs (Millwood)* 37, no. 5 (2018): 710-16, <https://pubmed.ncbi.nlm.nih.gov/29733704/>.
  - 50 Z. Brennan and D. Lim, "FDA Pushed Through Scores of Inaccurate Antibody Tests Without Agency Review," Politico, April 27, 2020, <https://www.politico.com/news/2020/04/27/reliable-antibody-tests-coronavirus-207589>; D. Lim, "FDA Reverses Policy That Let Over 100 Antibody Tests on Market Without Review," Politico, May 4, 2020, <https://www.politico.com/news/2020/05/04/fda-enacts-stricter-rules-for-antibody-tests-after-congressional-investigation-233867>.
  - 51 J. Shuren and T. Stenzel, "COVID-19 Molecular Diagnostic Testing—Lessons Learned," *The New England Journal of Medicine* 383, no. e97 (2020), <https://www.nejm.org/doi/full/10.1056/NEJMp2023830>.
  - 52 Gottlieb, "Blueprint for Breakthroughs—Charting the Course for Precision Medicine."
  - 53 BCG analysis of CLIA data (accessed via QIES database); [https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/CLIA\\_Laboratory\\_Demographic\\_Information](https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/CLIA_Laboratory_Demographic_Information); Centers for Medicare & Medicaid Services, "Laboratories by Type of Facility (Exempt and Non-Exempt)" (March 2020), <https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/factype.pdf>; In-scope labs are categorized as 1) holding an active CLIA certificate of compliance, accreditation, or registration (able to conduct moderate- and high-complexity tests), 2) fall within CLIA categories of 14: hospitals, 15: independent reference labs, 24: public health labs. Academic medical centers based on American Hospital Association data on teaching/research institutions. Large reference labs based on identifying Quest and LabCorp labs by name within CLIA data.
  - 54 U.S. Department of Health and Human Services et al., "Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories—Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)."
  - 55 Ibid.

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