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What Are *In Vitro* Diagnostic Tests, and How Are They Regulated?

Oversight may not be keeping pace with changes in the diagnostics market

Overview

Health care providers rely on a variety of tools to diagnose conditions and guide treatment decisions. Among the most common and widely used are *in vitro* diagnostics (IVDs), which are clinical tests that analyze samples taken from the human body. Patients may receive—or forgo—medical care based on diagnostic test results, making it critically important that tests are reliable. These tests are regulated by the Food and Drug Administration as medical devices, which means manufacturers must submit studies confirming a test's accuracy and usefulness in diagnosing a particular condition before bringing it to market. However, FDA has historically exempted from this requirement any IVDs that are developed and used within the same laboratory, often referred to as laboratory-developed tests (LDTs).

Though some test developers dispute that FDA has jurisdiction over LDTs—arguing that the tests are more properly seen as procedures that constitute the practice of medicine—the agency maintains that these tests are devices and fall under agency jurisdiction through the Medical Device Amendments of 1976. At the time of that bill's passage, LDTs were used mostly for rare diseases and generally relied on manual (rather than automated or software-based) analysis and interpretation. Because they posed a lower risk, LDTs were exempted from the more stringent regulatory requirements that apply to other IVDs. However, LDTs have become increasingly complex in recent years, driven by advances in technology that have made elaborate analyses like genetic sequencing both quicker and more affordable.

Much like FDA-reviewed IVDs, LDTs are essential to the diagnosis and treatment of many conditions and are an indispensable tool in the practice of precision medicine—a still-emerging but highly promising approach to clinical care that relies heavily on genetic or molecular profiling of patients. But while LDTs have evolved, the FDA continues to exercise relatively little oversight over them.

What are commercial IVDs and how are they regulated?

IVDs[1] are used to analyze human samples such as blood and saliva, either by measuring the concentration of specific substances, or analytes (such as sodium and cholesterol), or by detecting the presence or absence of a particular marker or set of markers, such as a genetic mutation or an immune response to infection.[2] Clinicians regularly use IVDs to diagnose conditions, guide treatment decisions, and even mitigate or prevent future disease (for example, through screening tests that indicate a patient's risk of developing a given condition in the future).

Since the passage of the Medical Device Amendments of 1976, FDA has regulated medical devices, which include products "intended for use in the diagnosis of disease or other conditions."[3] Accordingly, FDA asserts this authority over diagnostic tests and their components (such as reagents, which are used to facilitate a chemical reaction that helps detect or measure another substance). Under the current regulatory regime, IVDs that are developed for the commercial market are subject to FDA regulatory requirements intended to ensure their safety and effectiveness.

IVD regulation is risk-based, with tests falling into one of three regulatory categories. Tests are classified in the lowest tier, Class I, if they pose relatively little risk to patients and the public health if they are inaccurate (such as a cholesterol test). Moderate-risk tests, such as pregnancy tests, are categorized as Class II, while tests in the highest risk tier, Class III, are considered to pose the greatest potential risk if they are inaccurate (such as a genetic test used to select cancer therapies). These categories correspond with increasing levels of regulatory scrutiny, with most tests in Class I—and some in Class II—being exempt from premarket requirements, while most Class II and all Class III tests require some form of premarket review before they can be used with patients.

FDA maintains two primary premarket review pathways for tests. The premarket approval (PMA) pathway is the more stringent of the two, requiring demonstration of safety and effectiveness before the test may be marketed. These are typically Class III tests that pose a high degree of risk, or tests that have no known equivalent on the market. The other pathway, known as the premarket notification or the "510(k)" pathway (for the section of the Food, Drug, and Cosmetic Act that describes it), does not impose the same strict evidence requirements as the PMA. It is intended for tests that can be described as "substantially equivalent" to a product already on the market, but other tests may also qualify if they are low-to-moderate risk and the manufacturer petitions the agency to reclassify it.[4]

To be approved or cleared through either pathway, IVDs must demonstrate safety and effectiveness through analytical and clinical validation, which are key standards in determining a test's accuracy. Analytical validation is focused on ensuring a test is able to correctly and reliably measure a particular analyte, while clinical validation is the process for determining whether the test can accurately identify a particular clinical condition in a given patient.

Glossary

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.

Clinical utility relates to whether the use of a given test is associated with improved patient outcomes, as well as the risks that occur as a result of the testing. Because clinicians may determine their approach to treatment based on the results of a given test, its clinical utility is an important consideration.

What are LDTs and how are they regulated?

The key distinction between FDA-reviewed IVDs and LDTs is where they are made: LDTs are designed and used in a single laboratory, and are sometimes referred to as "in-house" tests.[5] LDTs are developed in facilities ranging from physicians' offices, hospitals, and academic medical centers to large testing companies.[6] Though LDTs may contain the same or similar components as FDA-reviewed tests, they must be developed and used within the same facility. FDA has historically viewed LDTs as posing a lower risk to patients than most commercial testing kits, and has exempted them from nearly all regulatory requirements under the Food, Drug, and Cosmetic Act. As such, the agency does not review these tests to ensure that they are accurate and reliable, and their exact number is unknown. Reporting to FDA is voluntary; there is no single registry of all laboratories that utilize LDTs, so estimates vary widely. While FDA has estimated that 650 laboratories develop these tests,[7] the American Clinical Laboratory Association has said that the majority of the 11,633 laboratories permitted to develop and perform LDTs do so.[8]

In the past, most LDTs were relatively simple screens for single analytes, or tests developed to diagnose rare diseases where the lack of demand had created barriers to commercial IVD development. These tests were developed at a small scale, made with components legally marketed for clinical use, and were typically interpreted by health care professionals working directly with patients.[9]

In recent years, LDTs have been developed for a wider range of conditions, including infectious diseases (such as human papillomavirus, Lyme disease, and whooping cough) and cancers.[10] Increasingly, these tests are marketed nationwide, sometimes by large laboratories or companies, and potentially affect many more people than the local populations who may have used them in the past. LDTs may be made with instruments and components not legally marketed for clinical use, or rely on complex algorithms and software to generate results and clinical interpretations.[11] However, because these tests are developed and used within a single entity, they are still considered to be LDTs, despite in many cases being substantially similar to the commercial IVDs that are approved or cleared by FDA and then sold as prepackaged kits. Though FDA generally waives regulatory requirements for LDTs, the agency has intervened in several cases to ensure patient safety.

It is important to note that an LDT is not necessarily less accurate or reliable than its FDA-reviewed counterpart. Some may perform as well as or even better than tests that have gone through the clearance or approval process, particularly if they are performed in more sophisticated laboratories with highly trained staff, or if they are relatively straightforward to administer and interpret.[12] However, this is not always the case, and once an LDT is on the market it may take a substantial amount of time before problems are identified and corrected.[13] In the meantime, patients receiving the test may undergo improper treatment, or forgo treatment altogether, on the basis of inaccurate results.

The role of the Centers for Medicare & Medicaid Services

Oversight of these LDTs is principally conducted through a lab certification process overseen by the Centers for Medicare & Medicaid Services (CMS).[14] All laboratories performing testing on human specimens are subject to regulation under the Clinical Laboratory Improvement Amendments of 1988 (CLIA),[15] which governs the accreditation, inspection, and certification of all clinical laboratories. For those laboratories administering tests that have not received FDA clearance or approval (such as LDTs), CLIA establishes an additional set of quality standards, with a focus on affirming tests' analytical validity—that is, whether the tests run by the lab detect or measure what they intend to.[16] Analytical validations are conducted as a part of CMS laboratory surveys that occur every two years.[17]

However, the standards for analytical validity under the CLIA process are not the same as those applied during FDA premarket review. CLIA auditors validate tests performed by the lab to ensure that they precisely, accurately, and reliably measure relevant analytes in a given sample. But their assessment is limited to the conditions and patient population of that particular lab so—unlike FDA's review of IVDs—a determination of analytical validity from a CLIA audit cannot be extrapolated to other sites or patient populations.[18] 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.

In addition to providing oversight of labs under CLIA, CMS may also conduct a separate evaluation of particular tests in order to determine whether it will reimburse providers for their use. In making these determinations, CMS principally focuses on assessing a test's clinical utility—that is, whether the use of the test improves patient outcomes (a standard that the FDA does not apply to its decision-making)—rather than its analytical or clinical validity.

Table 1

Current Oversight of Diagnostic Tests[19]

	FDA	CMS
Primary statutory authority	Food, Drug, and Cosmetic Act, as amended by the Medical Device Amendments of 1976 (MDA)	Public Health Services Act, as amended by the Clinical Laboratory Improvement Amendments of 1988 (CLIA)
Oversees	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 validate tests, whether LDT or IVD.
Validation standard(s)	Analytical validity Clinical validity	Analytical validity
How are tests validated?	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"[20]).
When are tests validated?	At various points prior to the legal marketing of that test.	During inspections every two years (may be up to two years after an LDT is first performed).
Adverse event reporting	Mandatory reporting of adverse events by manufacturers, device user facilities (e.g., 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.
Recall authority	Yes	No

* U.S. Food and Drug Administration, "Medical Device Reporting (MDR)," https://www.fda.gov/medicaldevices/safety/reportaproblem/default.htm.

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Is oversight adequate?

In recent years, diagnostics manufacturers, patient organizations, FDA, and members of Congress in both major political parties have urged modernization of federal oversight of LDTs.[21] Calls for reform are likely to increase with continued advances in diagnostic technology, the resulting changes in these tests' clinical use, and their potential to affect thousands of patients.

In response to proposals seeking to increase FDA's oversight of the industry, groups representing the laboratory and clinical pathology fields have developed counterproposals focused on reforming oversight of laboratory processes under CLIA. These groups have historically maintained that any direct federal regulation of LDTs constitutes unwarranted regulation of the practice of medicine.[22] The American Clinical Laboratory Association has also previously petitioned FDA, claiming that LDTs are not medical devices, but instead are services performed by clinical labs—a form of "medical practice" that FDA has no authority to regulate.[23] Those opposed to a greater FDA role also argue that CMS provides adequate oversight, or that targeted updates to CLIA regulations would provide the reforms necessary to accommodate changes in the industry and the use of such tests. Furthermore, they maintain that any additional federal regulation of LDTs would impose an unnecessary burden on test developers, potentially hampering innovation.

Proponents of greater FDA oversight, including the agency itself,[24] have argued that diagnostics should be regulated based on risk, not on where tests are made, and that applying the same requirements to LDTs as apply to other IVDs would help protect patients from harm and create a more level playing field for test developers.[25] Proponents of an updated regulatory system note that the diagnostics market has changed in several important ways in recent decades:

- **Tests are no longer hyperlocal or just for rare diseases.** LDTs are being developed by large, commercial organizations and performed for patients across state lines. These tests have also been developed for a wide range of conditions, and are increasingly being used in precision medicine to diagnose or guide treatment for serious conditions. Faulty or misleading results could now affect a broad range of patients, magnifying the potential for harm.
- **Test results may be inaccurate.** All diagnostic tests carry the risk of providing inaccurate results. However, the CLIA regulatory framework does not require a laboratory to demonstrate an LDT's ability to accurately diagnose or predict the risk of a particular outcome (its clinical validity) before those tests are used on patients.[26] Without this safeguard, the chance that an inaccurate test will be introduced into the market increases, potentially exposing patients to harm. These harms include:
  - False-positive results, which could lead patients to pursue unnecessary treatments and also delay the timely diagnosis of underlying conditions.
  - False-negative results, which can delay or prevent patients from receiving proper treatment, potentially leaving the disease or condition to progress.[27]
- **Tests are not subject to premarket review.** Neither FDA nor CMS reviews the validity of LDTs before they are on the market,[28] nor does any regulator review their labeling or marketing claims to ensure they are supported by sufficient data. This means inaccurate or unreliable tests may be used for years until discovered through CLIA audits or other evaluations performed internally or by other researchers.
- **Adverse events are not reported to regulators.** LDT developers are not compelled to notify FDA of the tests they use, and there is no mechanism for adverse event reporting for LDTs.[29] This makes it challenging for FDA to identify emerging risks to the public health and respond appropriately.

- **Enforcement discretion distorts the diagnostics market.** Basing a test's regulation on where it is produced creates an uneven playing field between LDT developers and other IVD developers. The cost of navigating FDA's approval process limits developers' incentive to conduct the research that could make a test more accurate and clinically meaningful, and instead provides an incentive to simply market tests as LDTs.
- **Lack of transparency.** Without oversight of product labeling, providers may lack the information necessary to adequately interpret a test's results. Providers may also lack knowledge of the test's performance, the basis for manufacturer claims, or even whether the test has been approved or cleared by FDA.

Given the increasing risks associated with widespread use of lab-developed tests, and their importance in modern medical care, regulatory oversight should correspond to a test's risk and complexity.

What Can Happen When Patients Are Exposed to Bad Tests?

Unreliable tests can cause patient harm, as these two examples show. In the case of OvaSure, patients may have undergone irreversible and life-altering surgery based on faulty test results. With Theranos, a group of patients allege that inaccurate test results caused them to delay needed treatments or undergo unnecessary treatments.

OvaSure Screening Test

In June 2008, LabCorp began offering a new test called OvaSure, which was marketed as an LDT that could detect ovarian cancer in high-risk populations—such as women with a family history of the disease—at an early stage. The test had shown promising results in studies published earlier that year. But shortly after it came to market, medical research groups began to raise concerns about its reliability, arguing that both the original developer—a cancer researcher based at Yale—and LabCorp had overstated the potential benefits of the test and downplayed uncertainty about its validity.[30]

Subsequent evaluations found that the test developer had miscalculated the degree to which a positive test result was predictive of cancer. In fact, only 1 of every 15 positive results was accurate, potentially leading to unnecessary and invasive surgery to remove the ovaries.[31] Four months after the test's introduction on the market, FDA sent a warning letter to LabCorp, outlining its concerns about the test's lack of clinical validation and stating that, because LabCorp did not originally develop the test or manufacture its components, it was actually an IVD under FDA's jurisdiction, not an LDT as LabCorp had claimed.[32] LabCorp stopped offering the test the following month. However, because it was offered as an LDT, the company did not report any adverse events associated with its use, so the scale of its impact on patients is not fully known.

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Theranos

In 2012, the diagnostics start-up Theranos opened a CLIA-certified laboratory in Newark, California, conducting blood-based tests for a range of conditions.[33] Though the company claimed to have developed new "microfluidics" technology that would allow for a broad range of testing using only a few drops of blood drawn from the finger, it was later revealed that the company's own technology was faulty and inaccurate, and that in many cases the company was instead diluting patient samples to enable it to run tests on modified conventional lab equipment that had been developed by other manufacturers.[34] Because Theranos marketed itself as a testing service authorized to perform LDTs (a CLIA lab), its tests were not subject to premarket FDA review, and it was able to run patient samples on them for two years. The company is also alleged to have deliberately misled CLIA inspectors who visited its facility in 2013, though even that inspection cited infractions that Theranos claimed to have resolved.[35]

In July 2015, Theranos was granted FDA clearance for one of the hundreds of tests it claimed to perform: a simple viral screen for herpes simplex-1. Such tests need only detect the presence or absence of a virus, and are relatively straightforward to perform compared to tests that rely on quantitative analysis of patient samples. In the same month, the agency also granted Theranos a waiver that would allow the company to perform that test outside of its own laboratory. However, during subsequent FDA inspections conducted in August and September 2015, the agency identified several regulatory violations and issued a warning letter to the company, stating that the proprietary tubes used to collect samples were misclassified as low-risk devices (and because they had not been cleared by FDA, could not be shipped across state lines), and that the record-keeping at Theranos's labs was deficient in ways that violated federal regulation.[36] One month later, the Wall Street Journal published the first in a series of articles raising questions about Theranos and its technology.[37]

CMS issued its own warning in January 2016 and revoked the lab's certificate later that year. It subsequently invalidated all of the test results Theranos provided to patients, which likely totaled in the hundreds of thousands.[38] However, many patients were put at risk before CMS was able to take these actions. One patient whose blood sample was sent to Theranos received results indicating dangerously elevated levels of multiple analytes, which led to a battery of more invasive tests, including a CT scan and multiple MRIs. Only after incurring a substantial medical bill did she learn that the Theranos test results were inaccurate.[39] Other patients with similar experiences have alleged that they delayed treatment or underwent unnecessary treatment as a result of Theranos testing, and have joined a class-action lawsuit seeking compensation for the costs of unnecessary or misguided treatment.[40]

Considerations for reform

Policymakers and other stakeholders have debated for years over how best to regulate lab-developed tests. It can be challenging to develop and implement a regulatory framework that appropriately balances protecting patient safety and enabling innovative tests to come to the market without undue delays. The following principles can help to guide reform and ensure that these twin aims are met:

- Tests should be regulated based on their characteristics, not based on where they are conducted. This will ensure that all tests are held to the same standards for quality and reliability. Additionally, a common path to market for all diagnostics will help to promote a level playing field, which encourages test developers to invest in the research that not only provides assurance to tests' validity, but also drives innovation in the market, translating to new and better tests for the patients who need them.
- Regulators should be able to ensure—and providers and patients should be able to trust—that all tests on the market have been adequately assessed for analytical and clinical validity. These are key standards that should be applied to all diagnostic tests.
- In order to make appropriate decisions about tests under their purview, regulators need both access to all necessary information and the required scientific expertise to properly evaluate a given test. This would include granting the relevant regulatory agencies the authority to request the full slate of evidence supporting a test's validity, where necessary. It would also require that test developers report adverse events when they occur.
- However, the level of regulatory oversight should be tailored to the risk associated with the test. If an inaccurate test result is unlikely to have serious or long-lasting implications for a patient, then the balance of the review process should favor broader patient access and a quicker path to market. High-risk tests, by contrast, should receive a correspondingly greater level of regulatory scrutiny before they are approved for use.
- Regulators must also have the ability to take action when any test poses a risk to public health—including removing the test from use, if necessary. This enforcement authority should be clearly defined and adequately funded, with no significant jurisdictional overlap across the relevant oversight agencies.

Conclusion

Providers and patients rely on clinical tests to inform their treatment decisions. But while technology has advanced and the way providers use diagnostic tests has evolved, the oversight framework has remained largely unchanged. IVDs and LDTs often serve the same role in clinical practice, but are subject to far different levels of oversight. This creates distortions in the diagnostics market, prevents regulators from having a comprehensive understanding of the tests used in clinical practice, and puts patients at increased risk of making consequential and perhaps irreversible medical decisions on the basis of inaccurate test results.

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