

POSITION STATEMENT

Oversight of Laboratory Developed Tests

October 2020

Introduction

Laboratory developed tests (LDTs) are “diagnostic tests that are developed, validated and performed by individual laboratories... These assays are developed for in-house use and are not commercially distributed to other laboratories” (1). Clinical laboratories develop LDTs to assist in patient care, particularly for patients with medical conditions for which a commercial test does not exist or when an existing test does not meet changing clinical needs. LDTs are currently regulated by Centers for Medicare and Medicaid Services (CMS) as high-complexity tests—the most stringent standards—under Clinical Laboratory Improvement Amendments (CLIA).

In recent years, the Food and Drug Administration (FDA) has asserted that LDTs are medical devices subject to agency review. While the agency has deferred to CMS oversight in the past, the FDA argues that the dramatic increase in the number of and complexity of LDTs, particularly in the field of genetic testing, necessitates that some LDTs be cleared or approved by the agency to ensure their safe and effective use in patient care.

Background

FDA Involvement

Since the 1990s, there has been an ongoing discussion between the FDA and stakeholders regarding the appropriate level of regulation for LDTs. The FDA asserts that the Medical Device Amendments Act of 1976 authorizes it to regulate LDTs as medical devices, but has, until now, used its “enforcement discretion” to not regulate LDTs. According to the FDA, the number and complexity of LDTs has increased dramatically in recent years putting patients at risk, thus warranting agency attention (2).

In 2010, the FDA stated that all LDTs should be subject to agency oversight. In 2014, the agency published draft guidance that would have regulated many laboratories like medical

AACC POSITION:

Laboratory developed tests (LDTs) provide timely, accurate, quality testing for many conditions for which no commercial test exists or when an existing test does not meet current clinical needs. The regulation of LDTs should remain under CLIA and its deemed accreditation bodies, except for high risk tests that should be subject to both FDA and CMS oversight.

device manufacturers (2). AACC and many other laboratory and physician organizations opposed this one-size-fits-all approach to regulating LDTs. In November 2016, the FDA announced that it would postpone work on the guidance and work with Congress and stakeholders to find a solution.

In 2020, Representatives Larry Bucshon (R-IN) and Diana DeGette (D-CO), and Senators Richard Burr (R-NC) and Michael Bennett (D-CO), introduced the Verifying Accurate Leading-edge IVCT Development (VALID) Act, which would give the FDA expanded authority over LDTs. Subsequently, Senator Rand Paul (R-KY) introduced the Verified Innovative Testing in American Laboratories

(VITAL) Act, which would codify the existing CLIA regulations as the appropriate mechanism for regulating LDTs. AACC has endorsed VITAL.

In September 2020, HHS announced that future FDA LDT policy recommendations will need to go through the formal rulemaking process (3).

Existing Public and Private Sector Oversight of LDTs

Currently LDTs are regulated by CMS under CLIA, which subjects LDTs to strict personnel, quality control, and proficiency testing standards. In addition, CLIA laboratories must document the analytic validity of LDTs and make that information available to inspectors. Many laboratories conducting LDTs are subject to state and private sector oversight as well. For example, New York State requires laboratories document analytic and clinical validity prior to introducing a test. Similarly, the College of American Pathologists requires that testing facilities demonstrate the analytic validity of LDTs and document clinical validation. AACC supports retaining the current regulatory model by CMS as the primary means for regulating LDTs.

Medical Laboratory Director Responsibilities for LDTs

All LDTs are classified as high complexity tests under CLIA. This means an MD or a PhD with specific board-certification is responsible for approving all new tests, including ensuring proper validation, overseeing test performance, and, when requested, providing interpretative assistance to the ordering physician. The medical laboratory director (MLD) who fails to meet these responsibilities is subject to potential sanctions at the federal and local level. AACC believes the vast majority of LDTs can be safely performed without FDA oversight under the supervision of MLDs who have obtained appropriate training and board certification (4).

Test Innovation

The development of LDTs plays a critical role in providing new innovative technologies that offer hope and assistance to many patients. Under the current regulatory structure, the clinical laboratory community has been quick to respond to changing clinical and service needs, such as the need for more sensitive and specific therapeutic drug monitoring tests (5) and when commercial tests are not available, removed from the market or no longer supported, such as fetal lung maturity status (6). Similarly, clinical laboratories rapidly addressed world health crises, such as HIV and SARS, by developing accurate tests for diagnosing and confirming these conditions (7).

New regulatory barriers, unless carefully developed and targeted, could hinder or prevent laboratories from developing LDTs in response to immediate health care needs.

Considerations

LDTs are critical to providing adequate patient care as well as advancing the field of laboratory medicine. They assist clinicians each day in diagnosing and treating patients with cancer, infectious diseases, and genetic disorders, among many other conditions. To eliminate or significantly limit access to these tests would negatively impact patient care and possibly impede advances in health care. However, AACC agrees there are legitimate reasons to review the existing LDT regulatory model and provide additional scientific scrutiny and regulatory oversight for certain laboratory tests. AACC believes FDA and CMS should jointly oversee high risk laboratory tests. Most LDTs are sufficiently regulated through the existing CLIA certification and laboratory accreditation processes and do not require additional FDA oversight. Any regulatory changes, however, must be consistent, understandable and attainable.

Definition of an LDT

LDTs have been defined as those in vitro diagnostic tests that are developed and used by a laboratory in a healthcare setting. The vast majority of LDTs are either not commercially available or have been developed in response to an unmet need. LDTs additionally include any FDA-cleared or approved test whose manufacturer's instructions have been modified. LDTs are analytically and clinically validated by the laboratory before being used to generate laboratory results for diagnosing or treating a patient. Currently, these tests are not subject to FDA clearance or approval but are regulated under CLIA.

Regulatory Model

The FDA suggested establishing a risk-based classification approach for determining the level of oversight for LDTs. AACC agrees with this approach. We believe the categories within this scheme should be broadly categorized as high, moderate, and low. We recommend that professional laboratory associations, such as AACC, work in collaboration with the FDA and CMS and other stakeholders in determining the criteria for categorizing tests as high, moderate, and low risk. Some distinguishing criteria associated with these categories might include:

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- ▶ High risk LDT: analytically and clinically validated test that could lead to patient harm if there is a testing error since the result is the primary means for diagnosing or treating the patient. High risk tests should be subject to joint FDA and CMS oversight. The two agencies should coordinate their efforts to eliminate duplicative oversight functions.
- ▶ Moderate risk LDT: analytically and clinically validated test, but is unlikely to harm a patient if the test result is inaccurate since the result is used in conjunction with other clinical information.
- ▶ Low risk LDT: analytically and clinically validated test, but does not result in patient harm due to a testing error, because the result is only one of many factors used to diagnose and treat the patient.

AACC believes that moderate and low risk LDTs should remain solely under CMS utilizing the existing CLIA regulations. These tests are provided by hospitals and independent clinical laboratories that are certified or accredited as high complexity testing facilities.

Clinical Validity

Clinical laboratories utilizing LDTs should demonstrate the analytical and clinical validity of the test prior to its use.

Government and private sector regulatory bodies should allow laboratories to establish clinical validity through a variety of means, including the use of existing literature review, providing an assessment of patient benefit, or documenting that the test has become “standard of care” (e.g., existing tests already on the market that are being utilized by other laboratories and clinical protocols exist). However, clinical validation of the assay can be challenging given that some rare conditions may present few true positive patient samples and other technological limitations. Laboratories using high risk LDTs should meet joint FDA and CMS requirements, whereas laboratories employing moderate to low risk LDTs should meet CLIA high complexity requirements

under CMS and private accreditation agencies like CAP and Joint Commission.

Reporting Testing Errors

Clinical laboratories work diligently to provide quality laboratory tests. When a laboratory identifies a testing error it should report that mistake to the appropriate oversight body. Adverse events involving high risk tests should be reported to the FDA and CMS or the appropriate accrediting organization. Errors involving low to moderate risk tests should be documented and reported by the laboratory to CMS and/or relevant accrediting bodies. Additional guidance should be provided on what constitutes an error or adverse event.

The specific actions needed from the various stakeholders to develop and use LDTs appropriately to attain better patient care are outlined below:

Congress

- ▶ Congress should review and provide input to FDA, CMS, and other relevant government agencies regarding regulatory policies affecting LDTs. Lawmakers should ensure that these tests are safe, accurate, harmonized and provide useful information, while ensuring that any regulatory actions balance the need for federal oversight with patient access to LDTs.

Public and Private Sector Oversight Organizations

- ▶ Public and private sector oversight organizations should regularly review and update regulations pertaining to LDTs. Any regulatory changes must take into consideration its potential impact on test innovation and patient access to these valuable, often life-saving, tests.
- ▶ Oversight organizations must work with clinical laboratories to ensure that adequate quality assurance processes can be implemented to ensure reliable test results.

Clinical Laboratories

- ▶ Clinical laboratories play a vital role in developing LDTs important to patient care. Laboratories fill a gap not addressed by the marketplace by developing tests for rare conditions, public health emergencies, and the distinct needs in laboratory medicine. This role should continue.
- ▶ Laboratories are responsible for validating the performance of an LDT prior to implementation in order to meet CLIA and accreditation requirements.

In addition the clinical laboratory must establish sufficient quality assurance processes to ensure robust test results, including proficiency testing utilizing externally analyzed quality assurance specimens.

In Vitro Diagnostics Manufacturers

- ▶ IVD Manufacturers should continue to work with clinical laboratories to identify areas of need and to make test kits that are vital to patient care. The partnership between the IVD manufactures and clinical laboratories is critical to providing safe, accurate and timely patient testing.

Clinicians

- ▶ The vast majority of LDTs are high quality, accurate tests. Clinicians should be able to continue to use such tests to diagnose, monitor and treat their patients.

Medical Laboratory Directors

- ▶ MLDs are highly educated and trained individuals, who are responsible for overall laboratory operations, including the introduction of new tests, such as LDTs. These individuals should continue to play a central role in the development, use and interpretation of these tests.
- ▶ Laboratory directors must assure the analytical and clinical validity of any LDTs developed in their institution.

Patients

- ▶ Patients need to be educated by the laboratory community (e.g., Laboratory Tests Online) on the important and valuable role that LDTs perform in the health care system, such as assisting clinical diagnosis and monitoring of patients.
- ▶ Consumers, working in conjunction with patient advocacy organizations, need to support legislative and regulatory efforts that support the use of new LDT tests designed to improve patient care and outcomes.

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