POSITION STATEMENT

Modernization of CLIA: LDTs

August 2024

Introduction

Clinical laboratories are regulated by the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA). ADLM believes that CLIA has accomplished many of the objectives set forth by Congress. Under a uniform regulatory structure, there are mechanisms to assure test performance, standards for personnel qualifications, and mandated onsite inspections. In recent years, several stakeholders have urged the 'modernization' of CLIA, particularly as it pertains to the development and use of laboratory developed tests (LDTs).

Background

Concerns about CLIA Oversight of LDTs

In 1988, Congress passed CLIA to establish uniform regulation of laboratory testing, including mechanisms for assuring test performance and quality. The resulting regulations, which have been in effect since 1994, have remained largely unchanged since then. For the past two decades there have been increasing calls for enhanced federal oversight of LDTs from the in vitro diagnostics (IVD) industry, government advisory committees, consumer groups, and members of Congress. LDTs are currently regulated by CMS and its deemed accrediting bodies under CLIA and by the New York State Department of Health, which has its own LDT regulations.

Current CLIA Requirements

The Food and Drug Administration (FDA) defines an LDT as an "in vitro diagnostic test that is manufactured and used within a single laboratory" (1). CMS accepts this definition (2). In addition, the agency considers any modification to an FDA cleared or approved assay as the creation of a new test and therefore an LDT. All LDTs are classified as high complexity tests, the most stringent category of testing under CLIA. Laboratories performing such testing must comply with rigorous quality control (QC), proficiency testing (PT), and personnel requirements and must demonstrate the test's analytical validity. Although CLIA does not require clinical laboratories to establish clinical validity[1], the major private sector accrediting organizations to which many laboratories conducting LDTs subscribe, such as the College of American Pathologists (CAP) and the Joint Commission, do require that laboratories document clinical validation.[2]

ADLM POSITION:

The Association for Diagnostics & Laboratory Medicine (ADLM) recommends that CLIA remain the primary mechanism for overseeing clinical laboratories. The Association supports modernizing the laboratory standard to ensure that it continues to meet the changing needs of the healthcare community. Revisions to the regulations should particularly address the laboratory inspection process, quality control recommendations, proficiency testing requirements, and the definition of what constitutes an LDT.

Proposed Changes to LDT Oversight

The FDA asserts that the Medical Device Amendments of 1976 have always given it the statutory authority to regulate LDTs, claiming further that it has used its "enforcement discretion" to defer LDT oversight to CMS under CLIA (1). Some have called into question the FDA's claim of statutory authority (3). The FDA argues that recent scientific and

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technological advances have caused the agency to change its opinion and that it now feels compelled to regulate LDTs, particularly tests that use multiple test panels and proprietary algorithms to assess the risk or prognosis of a disease (1). In May 2024, the FDA issued a final rule addressing perceived regulatory gaps in LDT oversight. The agency is requiring that laboratories performing LDTs comply with FDA pre-market review, post-market surveillance, and clinical validity requirements similar to those imposed on manufacturers. These requirements would be in addition to the high complexity standards CMS already enforces under CLIA.

Stakeholder Response

ADLM and many other stakeholders in the healthcare community have expressed concerns about the potential impact of the FDA rule on innovation and patient access to testing as well as the duplicative aspects of the new standard. The American Hospital Association suggests FDA oversight would "disrupt medical innovation" and urges the agency to defer to CMS and CLIA for overseeing LDTs performed in a hospital (4). Similarly, the American Medical Association asserts that FDA regulation of LDTs "will undoubtedly cause significant upheaval to the laboratory community with detrimental results for patients" (5). ADLM argues that the rule will create a dual regulatory structure that overlaps with the CMS registration, quality, inspection, and use fee requirements (6). In addition, others have raised concerns about whether the agency has the regulatory bandwidth to take on this new responsibility (7).

Considerations

Definition of a Laboratory-developed Test

Much of the discussion pertaining to laboratory developed tests focuses on how the tests should be regulated rather than what constitutes an LDT. It is clear that a new test developed and used in one laboratory without FDA clearance or approval is an LDT. However, there is considerable uncertainty around when a modification to an approved or cleared test warrants the label of LDT. By current regulatory definitions, any such modification would warrant the label of LDT. ADLM believes that a modification to an FDA cleared or approved assay, which does not change the assay itself, should not be considered an LDT if the laboratory demonstrates that the modification does not adversely affect the analytical performance of the assay. A more refined definition of LDTs may assist regulators and the laboratory community in assessing those tests that need additional oversight and those that do not. Regulators and Congress should work together to better define LDTs before moving forward with additional regulations.

- Operational changes to an FDA cleared or approved test that do not alter the manufacturer's clinical claim and/or test interpretation; and
- A test ordered and used off-label by a physician, which was performed by the laboratory according to manufacturer specifications or with modifications that did not alter the claims about the intended use. This use of the test falls under the practice of medicine.

Clinical Validity

Government, medical and professional societies, and consumer organizations are advocating that clinical laboratories demonstrate the clinical validity of LDTs prior to introducing these tests. The FDA states that labs performing LDTs do not clinically validate them (1). This claim is not entirely correct. More than 8,000 laboratories are accredited by CAP or the TJC (both deemed accrediting organizations under CLIA), both of which require clinical validation of any claim relating to the use of LDTs for patient care (8).

The New York State Department of Health similarly requires that all laboratories licensed to perform testing for their residents provide evidence of clinical validity for each registered LDT. Such evidence can take a variety of forms, including published studies in the peer-reviewed literature and the use of clinical guidelines. Expanding clinical validity to all LDTs under CLIA appears to be a viable regulatory option that would achieve the goal of ensuring clinical validity without the prohibitive administrative burden of dual oversight by FDA and CMS.

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Third Party Review

If CLIA is modified to require clinical validation of LDTs, CMS will need a mechanism for implementing this new requirement. There are several options available to the agency. CMS could hire and train the additional staff to review the laboratory validation data, utilize the existing processes already in place at CAP, TJC and New York State, and/or contract with third parties to conduct the reviews. The agency does not need to select only one method but could choose to pursue a combination of options.

Ensuring the Quality of LTDs

Some stakeholders have expressed concern that the current CLIA QC standards for LDTs are insufficient. Several options have been suggested to address this concern. One pathway is to update the CMS Interpretative Guidelines for CLIA to provide testing facilities with additional guidance on design controls, such as risk mitigation, clinical evaluation, and establishing test reliability. Another approach is for CMS and its accrediting organizations to ensure that CLIA inspection teams include member experts with the requisite expertise to evaluate laboratories performing LDTs and that high complexity laboratory directors document their ability to oversee the LDTs they perform. While board certification is sufficient in most cases, newer, more specialized technologies (e.g., next-generation sequencing, mass spectrometry, and flow cytometry) require additional credentials to demonstrate competency. These efforts are not mutually exclusive and, if adopted, could address concerns regarding LDT oversight within the existing regulations.

Proficiency Testing

CLIA laboratories must participate in PT or develop an alternate means for evaluating analytical performance. PT is not available for many LDTs and there is currently no formal mechanism in place for adding or deleting new tests to the CLIA list of regulated analytes. Updating the PT process could enhance all laboratory testing, including LDTs. Additional guidance also could be helpful regarding how to develop alternative PT methods.

Positions

- ADLM recommends CLIA remain the primary mechanism of regulating LDTs.
- CLIA should be updated to require laboratories to demonstrate that LDTs are clinically valid for use in medical decisions.
- ADLM encourages CMS to credential third-party organizations to review a laboratory's clinical validation data for LDTs.
- Additional guidance from CMS to laboratories performing LDTs is recommended to help ensure that the results produced consistently meet clinical needs and expectations.
- ADLM urges CMS and its deemed accrediting organizations to ensure that CLIA inspection teams include individuals with specialized method expertise to evaluate LDTs.
- CMS should update CLIA PT requirements to allow for the addition or deletion of required analytes subject to PT and to reevaluate the number of challenges and scoring criteria.
- ADLM urges policymakers to define LDTs as 'new' or significantly modified tests for which the modification alters the clinical claims.

References

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4. American Hospital Association comments to the FDA regarding its October 3, 2014 draft guidance on LDT oversight. February 2, 2015. http://www.aha.org/advocacy-issues/letter/2015/150202-cl-fda2011d0360.pdf
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questions pertaining to the 21st Century Cures legislation. January 5, 2014.
6. Centers for Medicare and Medicaid Services. CLIA Statistical Tables/Graphs, Number of CLIA Certificate of Accreditation Laboratories by Accreditation Organization. July 2018. https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/statacrd.pdf

1. Analytical validity is the ability of the laboratory to establish the technical performance of an assay.
2. Clinical validation is a process to demonstrate that a laboratory test is fit for its intended purpose in assisting physicians with medical decisions regarding their patients.

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