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ACMG STATEMENT

A primer on regulation of laboratory-developed testing procedures: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG)

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Introduction

For more than 3 decades, the Centers for Medicare and Medicaid Services (CMS) has been the primary body responsible for regulating clinical laboratory testing of human biospecimens through the Clinical Laboratory Improvement Amendments (CLIA). This regulatory mechanism has allowed clinical laboratories the ability to provide and continuously improve patient care while maintaining high standards that ensure patient safety. Fully understanding the current clinical testing and regulatory processes

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is essential for maintaining patient care and safety and avoiding unnecessary regulatory burdens that would decrease access to clinical testing. Although other documents detailed the technical aspects of clinical testing, this statement is intended to assist policymakers in gaining familiarity with clinical testing services and the CLIA-based regulatory framework that governs the operations of clinical laboratories. The statement also addresses potential areas for modernization of the existing regulatory framework.

What Is a Clinical Testing Laboratory?

Clinical testing laboratories are certified health care facilities that perform testing procedures ordered by health care professionals, the results of which aid clinicians in making decisions about the diagnosis, management, and treatment of patients.[1] Such laboratories can exist within academic/university-based institutions, community hospitals, public or private companies, nonprofit institutions, and government agencies. Clinical laboratories generally have different specialties, such as chemistry, microbiology, hematology, histopathology, or genetics. In a medical genetics setting, the types of procedures performed may include testing for inherited disorders associated with congenital anomalies or disabilities, cancer testing for diagnosis and therapy selection, and prenatal testing, all of which are considered high-complexity tests. Depending on the scope of clinical indications, a wide array of testing methodologies may be utilized, including Sanger sequencing, microarray analysis, enzyme assays, and rapidly evolving technologies, such as next-generation sequencing and tandem mass spectrometry.[2,3]

Depending on the test complexity of a laboratory, there are different requirements that the laboratory must meet to perform testing. In general, clinical tests are categorized according to their degree of complexity: waived or nonwaived, which is further divided into moderate and high complexity. Waived tests are cleared by the US Food and Drug Administration (FDA) for specific uses that have a low risk of erroneous results. The determination of moderate vs high complexity of testing is based on several criteria laid out in the CLIA regulations. Factors used to determine complexity include personnel training and experience required for the testing process, characteristics of the operational steps involved, quality programs and proficiency testing materials, and the minimal interpretation and judgment needed for preanalytic, analytical, and postanalytic processes.[4] High-complexity testing requires more training and experience, and more frequent quality-control evaluations compared with moderate-complexity testing. Notably, any tests newly developed by a laboratory or those that have been modified from the approved manufacturer's instructions default to high complexity.[5]

Multiple types of testing personnel are involved in the daily functioning of clinical laboratories. At a minimum, clinical laboratories have directors and technologists who have fulfilled education and training requirements and obtained appropriate certifications as specified by the CMS (see below for a detailed description of the testing personnel requirements). In genetic testing laboratories, testing personnel may also include genetic counselors (clinically trained personnel who serve as liaisons between the laboratory and ordering clinicians), variant scientists (individuals who identify and classify variants from genomic data), and bioinformaticians (individuals who use computational tools to analyze large genomic sequence data for clinical testing).

Points to consider are as follows:

- Clinical testing laboratories are accredited health care facilities that provide professional testing services, the results of which aid clinicians in making decisions regarding the diagnosis, management, and treatment of patients.
- Clinical laboratories employ trained and certified personnel to perform various laboratory procedures and deliver results to ordering clinicians.

What Is a Laboratory-Developed Test?

Laboratory-developed tests (LDTs), also referred to as laboratory developed procedures or laboratory-developed testing procedures, are medical services developed and used by certified clinical laboratories for patient care. LDTs are validated testing protocols used by laboratory medical professionals to produce interpretive reports describing test results and their clinical significance in a particular patient. This report is then integrated by ordering health care professionals with other clinical information and diagnostic results to inform the diagnosis, prognosis, or treatment strategy for the patients in their care. LDTs are designed, developed, validated, performed, and interpreted by board-certified clinical laboratory professionals. LDTs are often created in response to unmet clinical needs and are instrumental in the early and precise diagnosis, monitoring, and guidance of patient care. It is critical to recognize that LDTs are different from in vitro diagnostic (IVD) tests, which are fully developed and manufactured by an independent commercial entity for limited intended clinical use and are broadly distributed to laboratories to be used only according to the approved package insert. In contrast, LDTs are not manufactured but are testing procedures performed by board-certified laboratory professionals.

Both IVDs and LDTs are commonly used in clinical laboratories. However, most genetic testing services currently available for both cancer and noncancer indications are LDTs. Owing to the rarity of genetic diseases and some cancer subtypes, there are often no IVD test kits available that are appropriate for the clinical specimen type or the intended use required for determining the diagnosis and treatment of these conditions. LDTs developed by

clinical laboratories can fulfill these requirements. Although some cancer tests are marketed as companion diagnostics approved by the FDA, many laboratories using these have, out of necessity, modified the scope of these tests to accommodate off-label applications in response to testing needs within the clinical spectrum of disease (eg, an FDA-approved test for adults being revalidated for pediatric populations). Any modification to an FDA-approved diagnostic test automatically renders it an LDT; such modifications require additional rigorous validation of test performance but are often needed to allow for increased accessibility, lower costs, better scalability, or to otherwise improve the analytical or clinical utility of the test.[6] Further, IVD manufacturers are not involved in actually performing the clinical testing and are therefore not subject to CLIA regulations. The onus for following CLIA regulations and ensuring that test results are accurate and reliable falls on the clinical testing laboratory, regardless of whether it uses an LDT or incorporates FDA-approved IVDs into its procedures.

Points to consider are as follows:

- LDTs are testing procedures that are designed, developed, validated, performed, and interpreted by board-certified professionals in a clinical laboratory.
- The modification of FDA-cleared or FDA-approved IVDs is often necessary to meet clinical needs. Such modifications require complete validation and a change in the classification from IVD to LDT.

What Is the Current Regulatory Oversight for Clinical Testing Laboratories and LDTs?

To perform clinical testing, laboratories must be federally certified by the CMS through the CLIA program. The current CLIA regulations, enacted in 1988, set forth standards for clinical laboratories that perform testing on human biospecimens, resulting in the diagnosis, prevention, and treatment of diseases. The CLIA requirements are divided into 2 categories: moderate-complexity testing and high-complexity testing. The main difference between these 2 complexities is that for high-complexity tests, more specialized training/knowledge is required for personnel, along with more stringent quality-control standards for each testing procedure. Because genetic testing is considered highly complex, the remainder of this statement focuses specifically on the CLIA requirements for high-complexity testing. Where possible, the associated Code of Federal Regulations (CFR) references are listed.[7]

In brief, CLIA defines the responsibilities of various testing personnel roles, such as laboratory directors, clinical consultants, supervisors, and testing personnel (42 CFR 493.1443, 493.1445, 493.1453, 493.1457, 493.1449, 493.1451, 493.1461, 493.1463, 493.1489, and 493.1495) and establishes qualifying requirements, documentation, and certifications for each. Each laboratory test must have an established written protocol (42 CFR 493.1251), and testing personnel must be properly trained before testing (42 CFR 493.1495). Regular competency assessments of the testing personnel are also required to demonstrate continued adherence to standard operating procedures.

Each component and reagent of a laboratory test must also be documented (42 CFR Subpart K). Equipment such as thermocyclers and pipettes must be regularly calibrated (42 CFR 493.1249, 493.1254, and 493.1255). For example, temperature-controlled storage (eg, freezers) is monitored daily to ensure functionality, reagents are qualified and validated before clinical use (42 CFR 493.1252), and each testing batch requires appropriate controls to ensure reliable results (42 CFR 493.1256). Under the CLIA, all clinical tests, including LDTs, must be analytically validated, and laboratories must demonstrate the performance characteristics of each test, including the minimum accuracy, precision, analytical sensitivity and specificity, reportable ranges, and reference intervals (42 CFR 493.1253).

Clinical laboratories are also required to enroll in Department of Health and Human Services (HHS)-approved proficiency testing (PT) programs (42 CFR Subpart H). PT programs are objective assessments of the performance of individual laboratories for specific tests or measurements and are used to monitor and ensure the continuing performance of laboratories (42 CFR 493.1236, 493.801). PT assessment must be completed for all LDTs performed in the laboratory to verify continued test performance. PT assessments generally occur through accredited agencies. PT is performed semi-annually with samples that are anonymized and incorporated into a laboratory's routine workload and thus treated as a routine patient sample from sample receipt to reporting (42 CFR 493.1236). For failed PT outcomes, laboratories must investigate and evaluate the causes of the erroneous results and establish corrective actions (42 CFR 493.803). If the laboratory fails 2 consecutive PT challenges, the laboratory must cease testing.[8]

As part of the CLIA, clinical laboratories must be inspected regularly to maintain their certification. The CMS has authorized 3rd party organizations to perform inspections on its behalf, such as the College of American Pathologists (CAP) and the Commission on Office Laboratory Accreditation. Organizations such as these also further support the clinical testing environment by establishing voluntary accreditation programs that address additional aspects of clinical testing that may be beyond the current scope and authority of the CMS.

Many, if not most, clinical genetics laboratories are accredited by the CAP. During a CAP inspection, depending on the laboratory's specialty (eg, microbiology, cytogenetics, molecular pathology, and biochemical genetics), the inspectors use appropriate CAP-accredited checklists created by experts, including representation from the ACMG, which provides a roadmap and guidelines for clinical testing regulatory compliance. These checklists allow inspectors to examine the laboratory's documentation, assess the evidence of compliance, and determine whether the laboratory is using the best practices for patient care.[9]

Items reviewed during an inspection range from the physical environment of the laboratory to records of instrument checks, competency assessments, PT participation, test development and validation documentation, and more (CAP checklist items GEN.55450, GEN.59980, GEN.60000, GEN.60150, GEN.60250, GEN.61500, GEN.61600, GEN.55500, COM.01300, and MOL.30785). Notably, in addition to demonstrating the analytical validity of LDTs as required by CLIA, CAP requires LDT validation to document clinical validity, which refers to the accuracy with which the test identifies a person with the intended clinical status (MOL.31590).[10]

Beyond the CLIA and CAP, some states may require their own accreditation processes. For example, New York has its own Clinical Laboratory Evaluation Program which sets standards for laboratories that operate in the state.[11] Specifically, New York sets standards and requires direct submission and approval of LDTs performed on New York residents, even if the performing laboratory is not located in New York. California has specific requirements for accrediting testing personnel, including laboratory directors and laboratory staff.[12]

At the time that this statement was drafted, the FDA finalized a rule to regulate LDTs as devices under the Federal Food, Drug, and Cosmetic Act. However, because of legal challenges and pending legislation, there is uncertainty regarding the FDA's final rules. Therefore, this statement does not cover FDA regulations for LDTs.

Points to consider are as follows:

- Clinical laboratories that perform testing on human biospecimens are regulated by the CLIA, which sets standards for testing personnel qualifications, quality assurance, test development and performance, and PT. Some states (eg, New York) may have additional policies and procedures that require compliance.
- Clinical laboratories must undergo regular CLIA inspections, whether by CLIA directly or by an HHS-approved 3rd party, such as CAP.

How Does the Current CLIA Framework Provide Regulatory Oversight of Clinical Laboratories to Protect Patient Safety While Allowing for Innovation to Improve Patient Care?

As described above, the CLIA ensures patient safety by providing regulatory oversight of LDTs, including laboratory environment and personnel, testing components, analytical validation, test development, and PT. Laboratories must satisfy the requirements set by the CLIA to perform clinical testing on human biospecimens and issue results for clinical use. If any components of the LDT are changed, the laboratory must perform additional validation or verification to ensure that the LDT performance remains the same or demonstrates improvement. The extent of validation depends on the scale of change in the LDT. For example, an update in the computational data analysis pipeline may require a validation study to demonstrate the concordance between the existing validated method and the updated pipeline. Before substituting a testing reagent, validation is needed to show the same or improved testing performance as the original reagent.

The CLIA regulatory framework has allowed clinical laboratories to update and improve their clinical tests while maintaining patient safety. Science and medicine are constantly evolving and new scientific data that broaden our understanding of human diseases in ways that can be applied to patient care are continually being published. In medical genetics, the discovery of new genes that cause rare inherited diseases can provide answers to patients and families. Thousands of new associations between genetic changes and disease are continuously documented in the medical literature and accompanying databases (eg, Online Mendelian Inheritance in Man, ClinVar, and ClinGen). The rapidly evolving field of medical genetics requires a flexible regulatory system, such as the CLIA, so that patients can benefit from up-to-date medical testing that reflects the current landscape of medical knowledge. For example, the number of genes included in a condition-specific gene panel test may change with the expanded knowledge of a particular disease spectrum and its genetic causes (eg, a microcephaly gene panel or a hereditary breast and ovarian cancer gene panel). The LDT mechanism enables fast, reliable, and regulated translation of new scientific discoveries into clinical care, allowing patients to benefit from the latest breakthroughs in medical science without sacrificing test quality.

In addition to medicine and our understanding of human diseases, innovations can occur in laboratory technologies and operations. For example, as technologies advance, machinery automation, such as robotic pipetting, has become available, which allows faster and more scalable sample processing, thus delivering results to patients more quickly and usually at lower costs. Automation also reduces the human errors that can occur during manual processes. In recent years, artificial intelligence and machine learning have been incorporated into the components of clinical genetic laboratory processes to help sort and process data. However, the use of these newer technologies is complemented by the validation of the accuracy of the implemented processes and oversight by board-certified clinical laboratory professionals.[13,14] Under CLIA, laboratories can validate such operational improvements and integrate them into the testing protocol in a timely manner, and any future modernization of CLIA regulations must consider the rapid pace of advancement in all areas of medical genetic testing and ensure that new discoveries and technologies can be safely and smoothly translated into clinical care.

In addition to innovation, laboratories must adapt and adjust to new challenges during desperate times. During the COVID-19 pandemic, many reagents and consumables, such as pipette tips and nasal swab collection kits, were affected by supply chain issues and were unavailable to laboratories, thus

delaying the results of clinical testing and negatively affecting patient care. Under the current CLIA regulatory framework, many laboratories have been able to identify and validate alternative reagents to ensure test quality and continued availability. This approach allows laboratories to minimize delays in patient care. Box 1 shows example scenarios demonstrating how the CLIA framework allows clinical laboratories to adapt and address various challenges.

Point to consider are as follows:

- By setting strict regulations to ensure patient care, the CLIA framework allows certified clinical laboratories to innovate and adapt to new challenges, such as a growing body of knowledge, opportunities for operational efficiency, technological improvements, and challenging supply chain issues.

Box 1. Example scenarios that highlight the rigor, innovation, and adaptability of laboratory-developed tests (LDTs) under the current Clinical Laboratory Improvement Amendments (CLIA) regulatory framework.

A laboratory offers a sequencing test to analyze important variants in leukemia and lymphoma. The LDT is validated for use on blood or bone marrow specimens. However, some lymphoma patients do not show abnormalities in the blood or bone marrow but instead have solid malignancies of their lymph nodes. Oncologists want to be able to order this test for these lymphoma patients; therefore, the laboratory validates test performance on solid tumor specimens.

- **The flexibility to respond to clinical needs and validate additional specimen types improves patient access to testing.**

The laboratory offers respiratory chain enzyme activity testing in skeletal muscle, liver, heart, and skin fibroblasts. This test is performed on patients with various neurologic symptoms, excessive fatigue, cardiac issues, renal dysfunction, hearing loss, and hair and skin abnormalities. LDT is often performed after exome sequencing when a variant of uncertain significance is identified in a gene encoding 1 of the 5 respiratory chain enzymes. Biochemical tests can determine whether the respiratory chain enzyme activity is normal. This LDT is currently available in only 2 clinical laboratories in the United States and is not utilized at a sufficient volume to justify in vitro diagnostic (IVD) approval and manufacturing.

- **The ability for the laboratory to maintain this unique, clinically validated testing is crucial for diagnosing and treating patients with this rare condition.**

A rapid aneuploidy test for prenatal samples is validated to use a specific type of glass microscope slide. Owing to supply chain limitations, the laboratory was informed that this type of glass slide would be back-ordered for several months. The laboratory performed validation studies to demonstrate that an alternative glass slide with similar specifications but from a different manufacturer produced consistent test results.

- **The laboratory maintains continuity of care in time-sensitive prenatal testing and is not required to stop testing because of reagent/supply availability.**

A test for diagnosis and management of chronic lymphocytic leukemia (CLL) uses fluorescent probes provided by a commercial supplier. As per the current CLIA regulations, the laboratory verified the performance of each new lot of reagent. A laboratory verified a new batch of fluorescent probes using known positive and negative CLL samples and found that they did not produce reliable results. One probe failed to detect cases that were known to be positive for a chromosome abnormality. The laboratory contacted the supplier, who discovered that the incorrect probe was shipped. The supplier provides a new batch of correct probes and, after appropriate verification, the laboratory continues to offer the test.

- **Because of the rigorous validation and verification procedures already in place involving all reagents, incorrect test results are not reported to patients, despite a reagent mix-up by the supplier.**

An US Food and Drug Administration (FDA)-approved kit for common genetic abnormalities was used in the laboratory. However, the FDA-cleared protocol includes manual washing of slides. The laboratory identified automated machinery that can move slides between wash baths and validated that the use of machinery does not have any impact on the analytical accuracy of the test.

- **The modification of the FDA-cleared kit with additional validation studies enables the laboratory to improve the cost, scalability, and consistency of obtaining passing results (fewer failures due to human error).**

A laboratory test was developed to identify newborns at risk of a recently identified severe congenital anomaly that could be treated if diagnosed before clinical presentation. Because of the new test, the Department of Health and Human Services secretary agreed to add this condition to the recommended newborn screening (NBS) programs nationwide. State and partner clinical laboratories must validate and offer this new LDT to meet the requirements of the updated NBS program.

- **This highlights the adaptability of LDTs as both screening and confirmatory tests in NBS.**

How Can CLIA Regulation be Modernized?

Over the last 3 decades, the CLIA regulatory model has set the professional standards required for clinical testing laboratories. However, since its advent in 1988, the state of clinical testing has evolved and the expertise and methodologies involved have grown in complexity. Unlike cytogenetics (42 CFR 493.1276), the CLIA does not provide specific standards for molecular and biochemical genetic laboratories. In medical genetics, testing has evolved from testing single genes one at a time to parallel sequencing of the entire genome and has also expanded to analyze RNA in addition to DNA. Furthermore, an ever-expanding catalog of biochemical analytes has been detected and measured in biochemical genetics laboratories to diagnose inborn metabolic errors. Data outputs have shifted from radioactively labeled images to gigabytes of sequencing data files or complex data outputs from tandem mass spectrometry. The analysis of genetic and biochemical data has become more dynamic, and data interpretation is customized to patients' individual disease phenotypes. Although the CLIA framework allows the flexibility necessary to keep pace with rapidly evolving technology and medical knowledge, it also needs to be updated to account for the evolution of the clinical testing environment.

Establishment of new CLIA-certified laboratories

Currently, there are general concerns that new laboratories may not have reached the proper operational standards for clinical testing before offering services. Specifically, pop-up laboratories opened during the COVID-19 pandemic to monetize the high demand for testing, but they may not have completed proper validations, implemented a quality management system, or properly documented personnel training before initiating patient testing.

The current CLIA framework allows new high-complexity laboratories to operate before inspection. There is a time lag from obtaining the initial certificate of registration to obtaining the certificate of compliance, which is issued following a successful inspection. This allows new laboratories to perform testing before inspection. Having an inspection by a CLIA or HHS-authorized party, such as the CAP, before the acceptance of clinical patient specimens by a new laboratory would ensure that appropriate standards of quality and care are met. The inspectors examine not only the test validation(s) but also the entire CLIA system and laboratory environment, including testing personnel training, established written standard operating procedures, documentation of competencies, and appropriate quality monitoring systems, all of which ensure patient safety.

Creating a requirement for successful inspection before beginning patient testing in a new CLIA-certified laboratory requires a timely inspection process. The CMS needs to allocate adequate resources to ensure that inspections are conducted within a time frame suitable for all stakeholders.

Risk-based requirement of validation data before test launch

As previously outlined in a position statement by the ACMG, a tier-based framework can help establish appropriate regulatory requirements for the development of new low-, moderate-, and high-risk LDTs.[15] It is important to note that, in this tier-based framework, risks are not only determined by the morbidity or mortality of incorrect results but also by the complexity and novelty of the methodology and the ability for independent verification of results. For lower-risk LDTs, detailed internal validation documenting clinical and analytical test performance may be sufficient. For higher-risk assays, establishing industry-wide minimum performance standards that must be met before the test launch may be a more appropriate approach. Such standards can be created by convening expert panels to establish minimal analytical and clinical acceptability metrics for various test classes. For example, grouping laboratory tests by methodology (eg, next-generation sequencing, fluorescent in situ hybridization, and tandem mass spectrometry) would allow a method-specific approach to reduce the number of standards required.

Demonstration of clinical validity of LDTs

CLIA-certified laboratories must demonstrate the analytical validity of their LDTs, as required by the CFR. We suggest that the CLIA also examine the clinical validity of LDTs. Clinical validity refers to the sensitivity and specificity with which a test identifies individuals with a defined clinical condition within a given population.[16] Clear demonstration of clinical validity of a genetic test is important because it can assist ordering providers in selecting the most appropriate test for their patient's presentation and can indicate the likelihood that a patient has a particular disease, even when testing results are negative. Clinicians can consider relevant follow-up tests or explore alternative diagnoses based on a clear understanding of the clinical sensitivity and specificity of the tests they order. It should be noted that because clinical validity is influenced by the prevalence of the disorder, some genetic disorders are so rare that clinical validity may be difficult to discern.

Although CAP accreditation currently requires a demonstration of clinical validity and thus most laboratories are already demonstrating clinical validity, the incorporation of this requirement into the CLIA regulatory framework will further improve the transparency of LDTs and facilitate appropriate test utilization by ordering clinicians.

Public database of clinical test validation data

Establishing a publicly accessible database to which clinical laboratories must submit key deidentified validation data (such as clinical and analytical sensitivity and specificity metrics) for all clinical tests would promote transparency

and accountability. This data would demonstrate compliance with the CLIA-established minimum standards for the test type. These changes would build on the existing CLIA framework, which focuses on evaluating the clinical testing procedure from all perspectives, including the physical laboratory, testing personnel, training, competency, and proficiency, as described above.

PT mechanism for tests that involve more than 1 laboratory

As the complexity of the testing methodologies increases, different steps of a single validated LDT may be performed by more than 1 clinical laboratory to complement each other's expertise. Because current regulations prohibit sending PT samples to another laboratory for analysis, an alternative PT mechanism is required for LDTs involving more than 1 clinical laboratory (ie, distributive testing models). The CLIA can develop additional PT options to robustly assess these distributive clinical tests, allowing all aspects of the LDT testing process across participating laboratories to comply with the CLIA and other accrediting bodies.

Oversight of marketing claims

Patients, health care professionals, and the community must trust clinical laboratories to provide reliable and actionable genetic testing results. To this end, the regulation of marketing materials used to promote tests to patients and/or health care professionals should be subject to rigorous oversight by appropriate agencies or regulatory bodies. Such an oversight should carefully consider the target audience of marketing materials (patients and clinicians) because the needs of each group may differ. Because CLIA already inspects the analytical performance of assays and can incorporate the assessment of clinical validity, as suggested above, we suggest that CLIA should also examine marketing materials of the corresponding tests during inspection and verify that such materials do not include claims or information that are not supported by the validation data. If issues with marketing materials are identified, such as improper claims about test sensitivity or specificity, the CLIA can notify and coordinate with the Federal Trade Commission for appropriate enforcement, if necessary.

Big-picture regulation—taking into account testing environment(s) for validated tests

Effective regulation must consider the entire process and environment of the test rather than treat each test as a packaged kit that is evaluated outside its context, as is done with IVDs. The CLIA already affords this essential advantage by issuing specifications for the laboratory environment and personnel and assessing these aspects of laboratory medicine in inspections. Promoting CLIA as a regulatory framework from test development through operations recognizes the relationship that already exists between these 2 functions in a laboratory. As validated tests are performed in the laboratory and the scale increases, additional opportunities for test optimization are identified and can be developed, validated, and implemented with bidirectional communication between developers and operational staff, all overseen by board-certified laboratory directors.

Points to consider are as follows:

- CLIA should be modernized to ensure relevance with the increased complexity of clinical testing.
- CLIA inspections should be conducted promptly before new clinical laboratories perform high-complexity testing.
- The establishment of industry-wide minimum performance standards will ensure patient safety in validation studies involving high-risk assays.
- To promote transparency and accountability, a publicly accessible database should be established to which clinical laboratories must submit key validation data, such as clinical and analytical sensitivity and specificity metrics, for all clinical tests.
- CLIA should examine both analytical and clinical validation of LDTs.
- The current PT mechanism can be modernized to support the current clinical testing landscape, in which different steps of a single validated LDT may be performed in more than 1 clinical laboratory.
- A CLIA inspection should examine marketing materials and verify that they do not include claims or information that is not supported by validation data.

Conclusion

Any significant changes to the existing LDT regulatory framework must be tailored to the clinical testing services. Efforts to treat LDTs as manufactured IVD test kits omit numerous aspects of LDT services that affect overall results. Any regulatory changes must be implemented thoughtfully, with ample notice and feedback from laboratories. This includes possible opportunities for existing LDTs to be grandfathered for a period so that laboratories can comply with new regulations in a timely, reasonable, and nondisruptive manner. The goal of regulatory improvements should be to promote the quality and accuracy of testing services without being detrimental to patient care or the availability of such services. Thus, the burden of regulation on laboratories must be balanced by the benefits they provide and the flexibility necessary to meet patient needs.

Conflict of Interest

Marco L. Leung, Raymond C. Caylor, Olivia D'Annibale, TaraChandra Narumanchi, Laura M. Sack, and Sarah T. South received salaries for providing clinical services

relevant to the content of this document in either the laboratory or patient care setting at their listed affiliations. The following workgroup members have additional conflicts of interest: Sarah T. South (Quest Diagnostics [Stock]). All other authors declare no conflicts of interest.

References

1. Bayot ML, Lopes JE, Zubair M, Naidoo P. *Clinical laboratory*. In: *StatPearls*. StatPearls Publishing; 2024. Accessed March 27, 2025. https://www.ncbi.nlm.nih.gov/books/NBK535358/
2. Durmaz AA, Karaca E, Demkow U, Toruner G, Schoumans J, Cogulu O. Evolution of genetic techniques: past, present, and beyond. *BioMed Res Int*. 2015;2015:461524. http://doi.org/10.1155/2015/461524
3. Mardis ER. DNA sequencing technologies: 2006-2016. *Nat Protoc*. 2017;12(2):213-218. http://doi.org/10.1038/nprot.2016.182
4. CLIA categorizations. United States Food and Drug Administration. Accessed September 18, 2024. https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clia-categorizations
5. Test complexities. Clinical Laboratory Improvement Amendments, Centers for Disease Control and Prevention. Accessed September 18, 2024. https://www.cdc.gov/clia/php/test-complexities/
6. Kim AS, Bartley AN, Bridge JA, et al. Comparison of laboratory-developed tests and FDA-approved assays for BRAF, EGFR, and KRAS testing. *JAMA Oncol*. 2018;4(6):838-841. http://doi.org/10.1001/jamaoncol.2017.4021
7. Title 42. Code of Federal Regulations. Accessed July 17, 2024. https://www.ecfr.gov/current/title-42/chapter-IV/subchapter-G/part-493
8. Proficiency testing and PT referral. do's and don't's. Clinical Laboratory Improvement Amendments, Centers for Medicare and Medicaid Services. Accessed July 17, 2024. https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/cliabrochure8.pdf
9. Sidiropoulos N, Daley SK, Briggs M, et al. Most frequently cited accreditation inspection deficiencies for clinical molecular oncology testing laboratories and opportunities for improvement. *Arch Pathol Lab Med*. 2022;146(12):1441-1449. http://doi.org/10.5858/arpa.2021-0448-CP
10. Burke W. Genetic tests: clinical validity and clinical utility. *Curr Protoc Hum Genet*. 2014;81:9.15.1-9.15.8. http://doi.org/10.1002/0471142905.hg0915s81
11. Clinical Laboratory Evaluation Program. New York State, Department of Health, Wadsworth Center. Accessed July 17, 2024. https://www.wadsworth.org/regulatory/clep
12. Laboratory field services. California Department of Publish Health. Accessed July 17, 2024. https://www.cdph.ca.gov/Programs/OSPHLD/LFS/pages/clinicallaboratorypersonnel.aspx
13. Dias R, Torkamani A. Artificial intelligence in clinical and genomic diagnostics. *Genome Med*. 2019;11(1):70. http://doi.org/10.1186/s13073-019-0689-8
14. Quazi S. Artificial intelligence and machine learning in precision and genomic medicine. *Med Oncol*. 2022;39(8):120. http://doi.org/10.1007/s12032-022-01711-1
15. South ST, McClure M, Astbury C, et al. Risk categorization for oversight of laboratory-developed tests for inherited conditions: an updated position statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2020;22(6):983-985. http://doi.org/10.1038/s41436-020-0765-x
16. NCI dictionary of genetics terms. National Cancer Institute. Accessed July 17, 2024. https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/clinical-validity