

The CLIA Framework

What is CLIA?

The **Clinical Laboratory Improvement Amendments Act of 1988 (CLIA)** was enacted to help improve the quality of laboratory practices.

Compliance with CLIA provides the legal bar needed to release information “for the *diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings.*”¹ Laboratories are exempt from CLIA requirements if they are “research laboratories that test human specimens but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients.”² This means that whether a laboratory needs to comply with CLIA depends on the kinds of results they report to participants. Laboratories that report individual-level results to research participants may fall within CLIA even if they do not charge for the testing or qualify test results with statements that testing was done on a research basis.³

CLIA is administered by the Centers for Medicare & Medicaid Services (CMS).

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What laboratories must do to comply with CLIA depends on the [nature and complexity of the tests](#) they perform. The FDA is responsible for determining the complexity level of various tests.

- **Laboratories that perform “waived” tests:** Laboratories that only perform test systems that are simple laboratory examinations and procedures that pose no reasonable risk of harm if performed incorrectly may qualify for a certificate of waiver.⁴ These laboratories must follow the manufacturers’ instructions for performing the test and meet certain additional requirements such as permitting announced and unannounced HHS inspections.
- **Laboratories that perform moderate and high complexity tests:** These laboratories must be issued a Certificate of Compliance by CMS or a Certificate of Accreditation by an [approved accreditation organization](#).
- **Laboratories that perform specific specialty and subspecialty testing areas:** CLIA has additional requirements for specific testing areas. These include bacteriology; mycobacteriology; mycology; parasitology; virology; syphilis serology; general immunology; routine chemistry; urinalysis; endocrinology; toxicology; hematology; immunohematology; histopathology; oral pathology; cytology; clinical cytogenetics; radiobioassay; and histocompatibility.

Most molecular genetic tests are classified as moderate or high complexity. There is no specific category for genetic testing, which means laboratories have to meet basic criteria for high complexity tests but no additional requirements.

¹ 42 U.S.C. 263a.

² 42 CFR 493.3(2).

³ David H. Ledbetter and W. Andrew Faucett, “Issues in Genetic Testing for Ultra-Rare Diseases: Background and Introduction,” *Genetics in Medicine* 10, no. 5 (May 2008): 309–313, doi:10.1097/GIM.0b013e3181729d99.

⁴ 42 CFR 493.15.

Proficiency Testing (PT) Programs

CLIA requires laboratories to take ongoing measures to verify the accuracy of tests and procedures. The “gold standard” for doing this is through proficiency testing (PT) programs.

What is PT?

PT involves an approved PT program sending unknown samples to a laboratory, which must test them in the same manner as the laboratory tests patient specimens. The laboratory then reports its sample results back to their PT program, which grades them. Finally, laboratories must review and evaluate their PT results.

Which Laboratories Must Undertake PT?

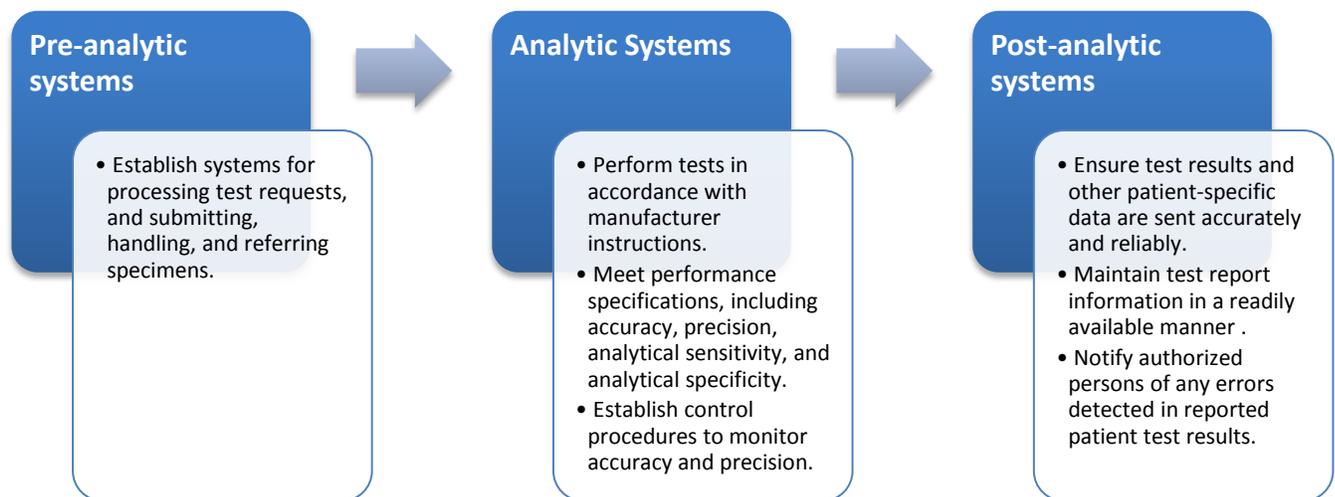
Every laboratory seeking certification in one or more specialty testing areas must enroll in an approved PT program for each such specialty.

Laboratories that perform moderate- or high-complexity tests that do not fall within a specialty testing area (including molecular genetic tests) have the option of evaluating their own testing programs at least twice annually. They can do this through voluntary proficiency testing programs or exchanging samples with other laboratories.⁵

Currently, formal PT programs are only available for a few genetic tests. Developing PT programs has proved difficult for rare genetic conditions and those for which testing is performed in only one or a few laboratories.⁶

Establishing Quality Systems for Testing Programs

CLIA requires laboratories to establish quality systems for their testing processes and general laboratory systems.⁷



⁵ 42 CFR 493.801(2)(ii).

⁶ Bin Chen et al., *Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions*, Morbidity and Mortality Weekly Report (Atlanta GA: Coordinating Center for Infectious Diseases, June 12, 2009).

⁷ 42 CFR 493.1200.

Additional Requirements

Laboratories that perform *unmodified FDA-cleared or approved* test systems must demonstrate that they can obtain performance specifications comparable to those established by the manufacturer.

For *modified FDA-cleared or approved test systems or test systems not subject to FDA clearance or approval*, a performing laboratory must establish performance specifications for accuracy, precision, analytical sensitivity, analytical specificity, reportable range of test results, reference intervals (normal values), and other performance characteristics required for test performance.

[Good Laboratory Practices For Molecular Genetic Testing](#), published by the CDC, proposes additional steps for establishing performance specifications in the molecular genetics context. These include:

- Conducting a review of available scientific studies and pertinent references
- Defining appropriate patient populations for which the test should be performed
- Selecting the appropriate test methodology for the disease/condition being evaluated
- Establishing analytic performance specifications and determining quality control procedures
- Ensuring that test results and their implications can be interpreted for an individual patient or family and that the limitations of the test are defined and reported⁸

Personnel Requirements

CLIA requires laboratories performing moderate- and high-complexity tests to have particular expertise available.

- **Laboratory director:** Laboratory directors are responsible for the overall operation and administration of the laboratory. The laboratory director must ensure that consultation is available to the laboratory's clients on matters relating to the quality of the test results reported and their interpretation regarding specific patient conditions. CLIA sets out specific qualification requirements for laboratory directors, depending on the complexity of tests a laboratory performs.
- **Technical consultant/technical supervisor:** For laboratories performing moderate-complexity testing, one or more persons must be qualified to provide *technical consultation* for each of the specialties and subspecialties for which the laboratory is accredited. For high-complexity testing, laboratories must have a *technical supervisor* for each such specialty and subspecialty. These persons are responsible for ensuring appropriate test methodology, verifying test procedures, and establishing quality control programs.
- **Clinical consultant:** Laboratories performing moderate- and high-complexity testing must employ a clinical consultant, who is qualified to consult with and render opinions to laboratory clients regarding the diagnosis, treatment and management of patient care.
- **General supervisor:** For high-complexity testing, laboratories also must employ one or more general supervisors to provide day-to-day supervision of testing personnel and reporting of test results. Specific qualifications apply depending on the specialty and sub-specialty testing performed by the laboratory.

⁸ Chen et al., *Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions*.

Inspection and Enforcement

CLIA-certified laboratories must permit CMS or CMS agents to inspect the laboratory to assess its compliance with CLIA requirements.⁹

The Act also sets out enforcement mechanisms, including cancelling a laboratory's approval to receive Medicare payments and limiting Medicaid payments.¹⁰ Civil monetary penalties may be imposed on laboratories in amounts up to \$10,000 per day of non-compliance or per violation. If CMS has reason to believe that continuation of laboratory activities would constitute a significant hazard to the public health, it may bring suit in a U.S. district court.¹¹

CLIA Operationalization under State Laws

A State-licensed laboratory may be exempt from CLIA requirements if it is in a state that has laws that CMS has determined are as stringent as or more stringent than the federal CLIA regulations.¹² As of December 2013, only New York and Washington have satisfied these criteria.

The New York [Clinical Laboratory Evaluation Program](#) (CLEP) requirements apply to all laboratories that conduct clinical testing on specimens originating in New York State (including out-of-State facilities that accept such specimens). The Program Guide specifies that research testing is considered clinical if it generates a patient-identified result, including "results used to make clinical decisions for patient management under an IRB-approved research protocol or clinical trial."¹³

Granting a NY laboratory testing permit requires certification of a director or assistant director for each specialty testing category, a satisfactory on-site inspection, successful performance in proficiency testing or alternate requirements for each permit category, and departmental review and approval of any in-house developed or non-FDA approved tests.¹⁴

In contrast to CLIA, the NY Department of Health has implemented specific genetic testing standards, which laboratories seeking a [genetic testing permit](#) must satisfy. These require, for example, that laboratories obtain the subject's informed consent, or the consent of a legally authorized decision maker. Laboratories also must include in their reports a statement of and an interpretation of its findings, the test's technical limitations, suggestions for additional testing, recommendations for referral to a genetic counsellor (if applicable), the test methodology, and a list of all variants examined in the assay.

Washington is the other CLIA-exempt State.¹⁵ Laboratories that undertake clinical testing in the State must obtain a license for the tests to be performed. Laboratories that have been accredited, certified, or licensed by an organization or agency approved by the department consistent with federal law and regulations shall receive a license.

⁹ 42 CFR 493.1773.

¹⁰ 42 CFR 493.1808-9.

¹¹ 42 CFR 493.1846.

¹² 42 C.F.R. § 493.551.

¹³ New York State Department of Health, "Clinical Laboratory Evaluation Program Guide," October 2013, 4, <http://www.wadsworth.org/labcert/clep/ProgramGuide/CLEPGUIDE2013.pdf>.

¹⁴ Ibid.

¹⁵ The relevant laws are set out at Title 246, Chapter 246-338.