IVDs, LDTs, FDA and CLIA

UNDERSTANDING THE ALPHABET SOUP OF LABORATORY ASSAYS

Learning Objectives

Understand the difference between the CLIA and FDA regulations

Understand when an assay is an investigational device and subject to FDA regulations

Understand when CLIA applies

Learn about the process of obtaining CLIA certification.

Regulatory Frameworks

FDA

- *Regulates manufacturers and devices* under the Federal Food, Drug, and Cosmetic Act (FFDCA) to ensure that devices, including those intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, are reasonably safe and effective for their intended use.
- Assesses analytic validity and clinical validity as part of evaluation of safety and efficacy.

CLIA

- Clinical Laboratory Improvement Amendments, under CMS
- *Regulates laboratories* to ensure accurate and reliable test results when laboratories perform testing on patient specimens.

HHS vs FDA

Common Rule (HHS)

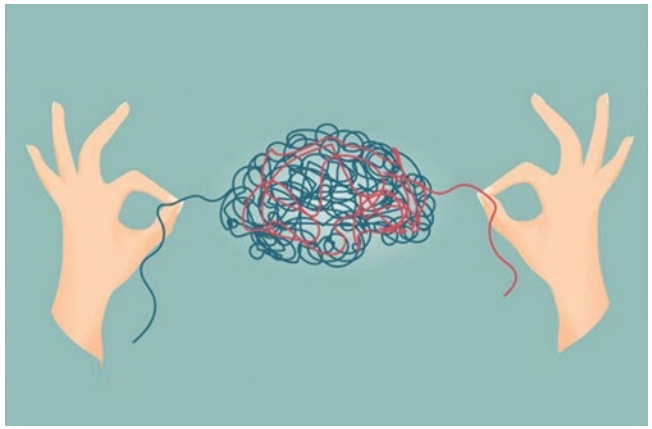
- ***Research***-A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.
- ***Human subject*** means a living individual about whom an investigator (whether professional or student) conducting research:
  - (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
  - (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

FDA regulations

- ***Investigation*** means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.
- ***Subject*** means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.

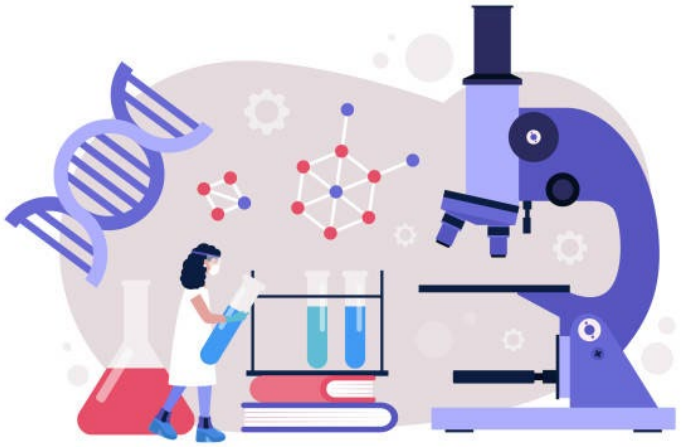
So what?

Some studies might be considered “not human subjects research” under the Common Rule and therefore not require IRB review under those regs, BUT still be considered a clinical investigation under FDA regulations, and therefore will require IRB review and potentially study risk determinations under 21 CFR 812



What is an IVD?

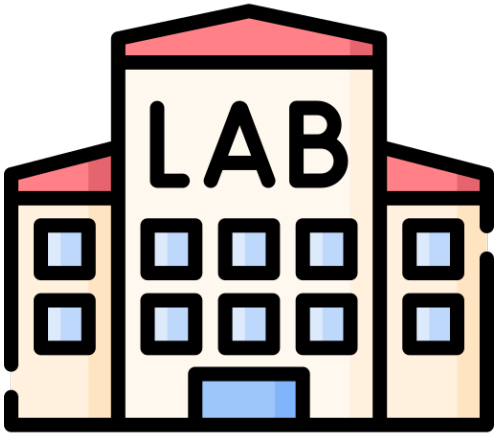
In vitro diagnostics (IVD) are tests done on samples such as blood or tissue that have been taken from the human body. In vitro diagnostics can detect diseases or other conditions, and can be used to monitor a person's overall health to help cure, treat, or prevent diseases.



https://www.fda.gov/medical-devices/products-and-medical-procedures/in-vitro-diagnostics

LDTS are IVDs

Laboratory Developed Tests (LDTs) are in vitro diagnostic products (IVDs) that are intended for clinical use and are designed, manufactured, and used within a single clinical laboratory which meets certain laboratory requirements. Specifically, such laboratory must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and meet the regulatory requirements under CLIA to perform high complexity testing.



https://www.fda.gov/medical-devices/in-vitro-diagnostics/laboratory-developed-tests

What is a medical device?

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- *(A) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,*
- *(B) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or*
- *(C) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o)*

IVDs are medical devices

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

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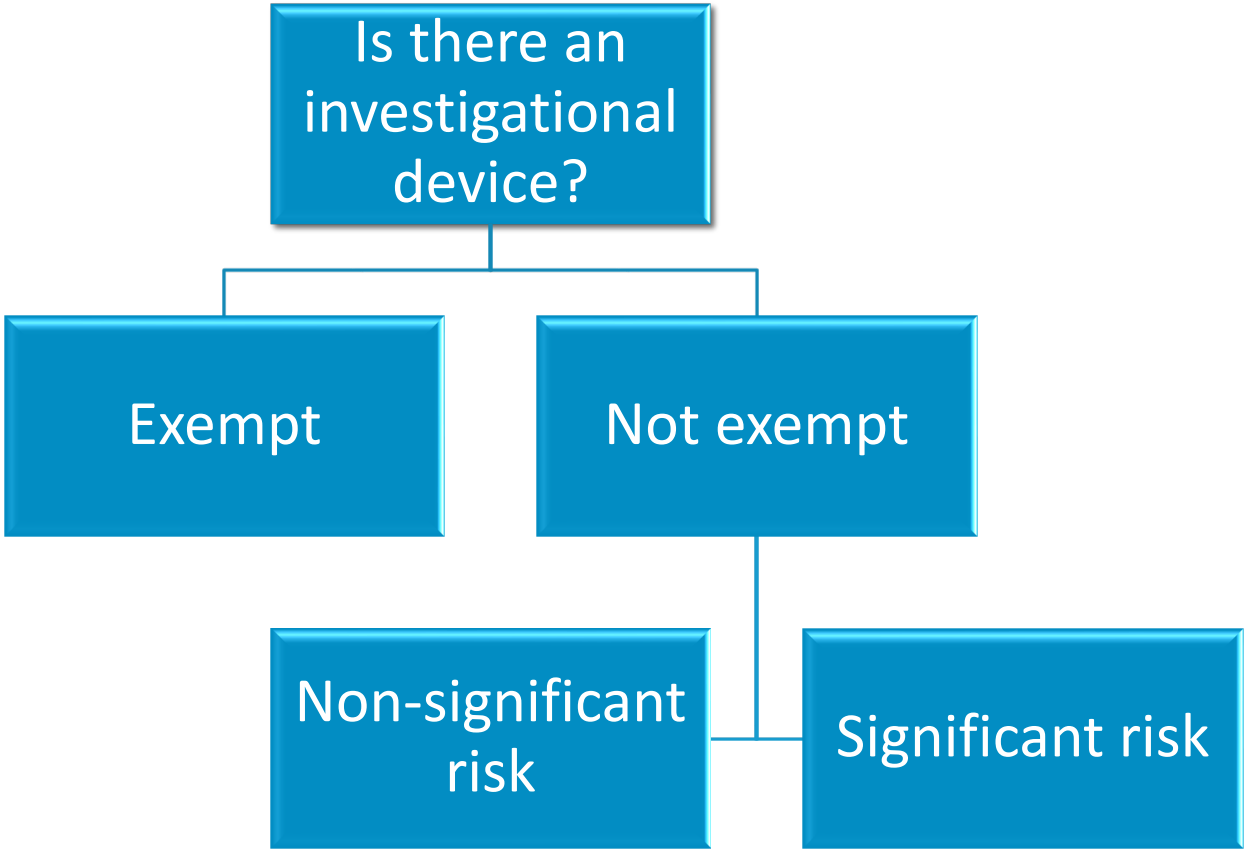
FDA and IVDs (including LDTs) in research



FDA and IVDs (including LDTs) in research

Is there an investigational device?

Investigation with one or more subjects to determine the safety and efficacy of the device.

Device is the "object of the investigation"

FDA considers biospecimens to be human subjects ***even if not identifiable.***

Examples:

- Study of a new blood test to diagnose disease XYX.
- Assay result used for eligibility or assignment to a particular arm of the trial.

FDA and IVDs (including LDTs) in research

Exempt

Used within its approved labeling, or

A diagnostic device, if the sponsor complies with applicable requirements in § 809.10(c) and if the testing:

- (i) Is noninvasive,
- (ii) Does not require an invasive sampling procedure that presents significant risk,
- (iii) Does not by design or intention introduce energy into a subject, and
- (iv) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

Exempt from the requirement for an IDE, not from IRB review

LDTs don't have a label, as they are not FDA approved or cleared.

21 CFR 812.2(c)

FDA and IVDs (including LDTs) in research

Significant Risk

Significant risk device means an investigational device that:

- (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- (2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- (3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Subject to full IDE requirements

21 CFR 812.3(m)

FDA and IVDs (including LDTs) in research

Non-Significant Risk

Everything else

Subject to abbreviated IDE requirements (21 CFR 812.2(b))

IRB review

Describe the device and its use in the protocol.

Sponsor/investigator makes initial risk determination, provides justification in the protocol.

IRB reviews and agrees or disagrees with sponsor determination.

FDA always wins.

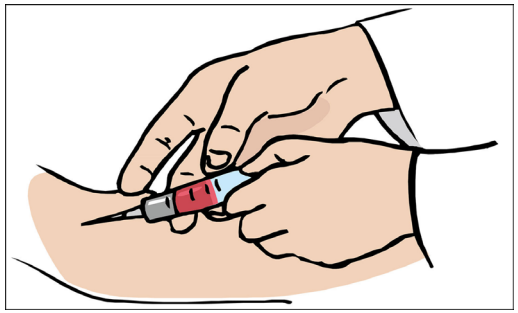
Risk determination is for a study, not a device.

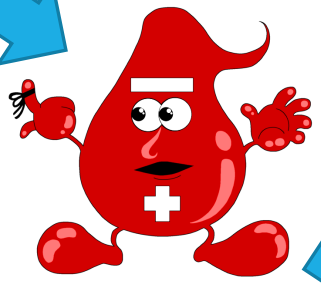
- New study, new device determination.

Using lab assay results

RESEARCH

CLINICAL PRACTICE



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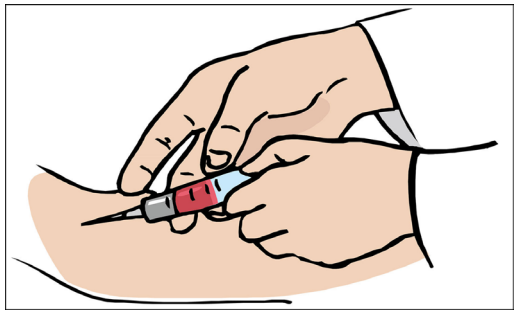
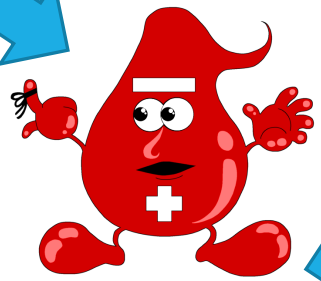
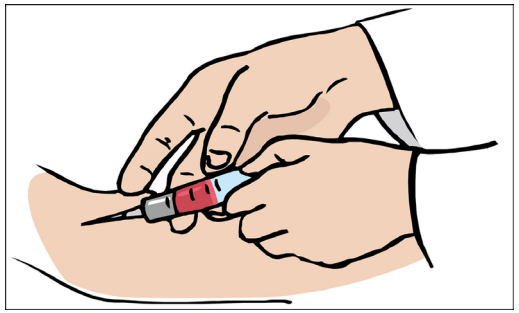
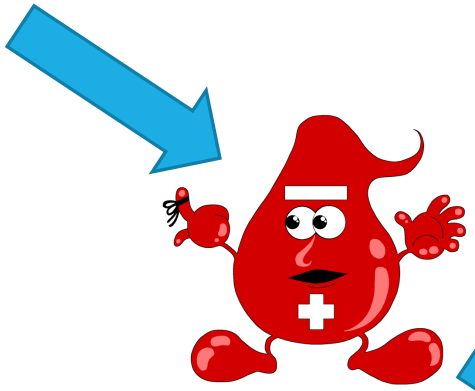




Clinical Laboratory Improvement Amendments



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When does CLIA apply?

CLIA applies to **all laboratories** that examine "materials derived from the human body for the purpose of providing information for the *diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings."* (*see* 42 U.S.C. § 263a(a)).

CLIA requires **all** facilities that perform even one test, including waived tests, on "materials derived from the human body for the purposes of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings" to obtain a CLIA certificate and meet CLIA regulatory requirements.

When does CLIA not apply?

b) ***Exception.*** These rules do not apply to components or functions of—

- (1) Any facility or component of a facility that only performs testing for forensic purposes;
- (2) 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; or
- (3) Laboratories certified by the Substance Abuse and Mental Health Services Administration (SAMHSA), in which drug testing is performed which meets SAMHSA guidelines and regulations. However, all other testing conducted by a SAMHSA-certified laboratory is subject to this rule.

(c) ***Federal laboratories.*** Laboratories under the jurisdiction of an agency of the Federal Government are subject to the rules of this part, except that the Secretary may modify the application of such requirements as appropriate

42 C.F.R. § 493.3(b)(2)

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42 C.F.R. § 493.3(b)(2)

The research exception

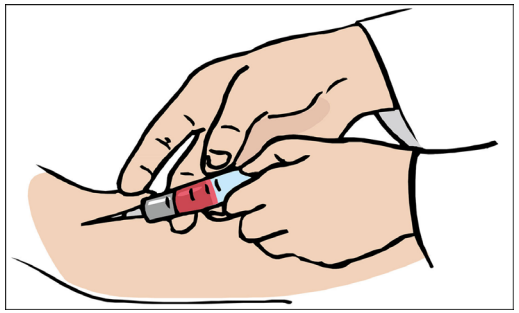
What types of research testing are subject to CLIA?

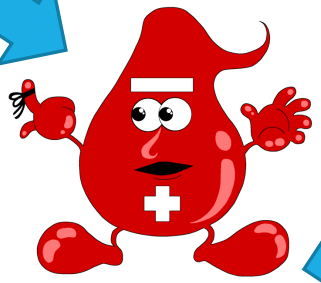
In most cases, research testing where patient-specific results are reported from the laboratory, and those results will be or could be used "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings" are presumed to be subject to CLIA absent evidence to the contrary

Only those labs that do not report patient specific results are exempt

- e.g. 10 out of 30 participants are positive for gene X = *excepted*
- Mr Smith is positive for gene A = *not excepted*, if the result will be or could be used for the purposes of providing information for the diagnosis or treatment of any disease, or for the assessment of the health of human beings.

IRB approval of the protocol is irrelevant.



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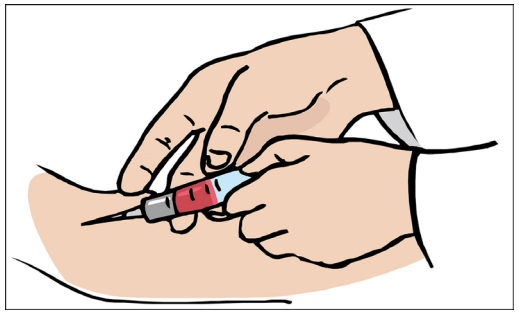

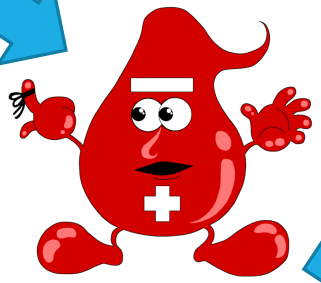


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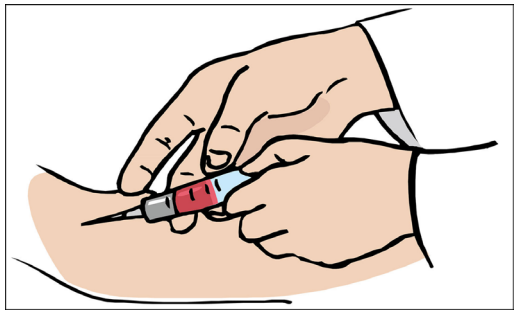
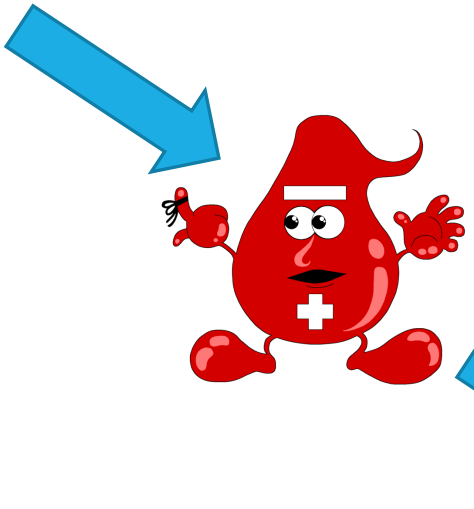
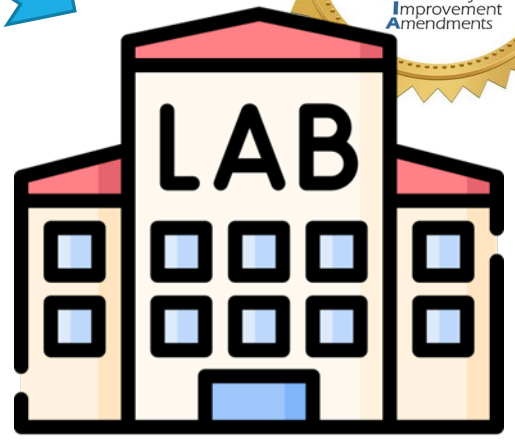
CENTERS FOR MEDICARE & MEDICAID SERVICES
CLINICAL LABORATORY IMPROVEMENT AMENDMENTS
CERTIFICATE OF COMPLIANCE
LABORATORY NAME AND ADDRESS
MOSAIC DIAGNOSTICS, LLC
9221 QUIVIRA ROAD
OVERLAND PARK, KS 66215
CLIA ID NUMBER
17D0919498
EFFECTIVE DATE
12/02/2022
LABORATORY DIRECTOR
ANGELA R PURVIS Ph.D.
EXPIRATION DATE
12/01/2024
CMS






RUSH!


CLIA
Certified
Clinical
Laboratory
Improvement
Amendments
LAB

The short answer to the CLIA question

CLIA applies when: (1) patient-specific results are reported from the laboratory to another entity; AND (2) the results are made available "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings.

Role of the IRB

When protocol specifies research results will be returned to participants or their health care providers, IRB will ask about CLIA.

When done “clinically” for individual patients and not part of protocol, no visibility. IRB will not/cannot police.

Example 1

Dr Smith studies autoimmune disease. As part of their research, they have developed an assay that can detect many different auto-antibodies in the patient's serum. Some of these are well characterized and known to be clinically important. Others are novel and the clinical significance is uncertain. One of the aims of the research is to develop this test as a diagnostic assay. The laboratory is a research laboratory and is not CLIA certified or compliant.

Question 1: Is the auto-antibody assay a medical device?

Yes. This meets the definition of a device

- *An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals,*

Question 2: Is the device an investigational device

- Yes, as one of the aims of the research is to develop the test as diagnostic assay.

Example 1 continued

Dr Smith wishes to provide the results of the clinically validated autoantibodies to the patient's medical providers, as their may be important treatment implications for their disease. His lab is not CLIA certified.

Can he provide the results to the participant or their physician?

No. Dr Smith's lab is not CLIA certified, therefore he cannot report these results. These results are patient specific results that are being made available for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings. Therefore, they must come from a CLIA lab.

Example 1 continued

Dr Smith is upset with this interpretation/application of the CLIA regulations and believes it is not in the participant's best interest. What can they do?

Dr Smith should determine if the tests are available in CLIA compliant labs. If so, Dr Smith should send a confirmatory sample to a CLIA lab, which can then provide the test result to the participant and/or their clinical provider.

Alternatively, Dr Smith could seek CLIA certification for their lab.

Example 2

Dr J is an expert in disease XYZ.

As part of a natural history protocol that does not include any therapy (investigational or otherwise), Dr J's lab has characterized the immune profile of patients, including the measurement of serum cytokine levels using a research assay. Along with other data, he believes that disease activity correlates well with activation of a specific cytokine signal transduction pathway.

Dr J is now caring for a patient, Mr D, that is sick with disease XYZ. Mr D has not responded to usual therapies.

Based only on his extensive knowledge of the disease, Dr J treats Mr D with a targeted inhibitor (FDA approved drug) that acts on the signal transduction pathway he has identified as active in xyz disease. He does not measure serum cytokine levels on this individual patient.

CLIA certification is NOT required for the lab performing the research cytokine assay.

Example 3

Dr J is the PI of a natural history study of disease XYZ.

As part of a natural history protocol that does not include any therapy (investigational or otherwise), Dr J's lab has characterized the immune profile of patients, including the measurement of serum cytokine levels using a research assay. Along with other data, he believes that disease activity correlates well with activation of a specific cytokine signal transduction pathway.

Dr J is now caring for a patient, Mr D, that is sick with disease XYZ. Mr D has not responded to usual therapies.

Dr J collects a sample of blood from Mr D and takes it to his research lab, where he runs the research cytokine assay. The results show highly elevated cytokine levels. Based on this result, he decides to treat Mr D with a targeted inhibitor (FDA approved drug) that acts on that pathway.

CLIA certification IS required for the lab performing the assay on Mr D, as a patient specific result is being used *"for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings"*

Resources

CLIA LDT FAQs

CLIA research exception

CMS site: https://www.cms.gov/medicare/quality/clinical-laboratory-improvement-amendments

Clinical Laboratory Improvement Amendments (CLIA-88)
THE LAW - Section 353 of Public Health Service Act
(42 USC 263a)

As Dr. Green cited, CLIA-88 includes federal standards applicable to all U.S. facilities or sites that test human specimens for health assessment or to diagnose, prevent, or treat disease.

In the early 1960's, several clinical cytopathology laboratories had high error rates which was attributed to staff being overworked and lack of regulations. *Consider variances in labs nationwide.*

CLIA began development in 1967, and Congress pass CLIA-88 in order to develop comprehensive quality standard to ensure accuracy, reliability and timeliness of patient results regardless of where the testing was performed in the United States.

CLIA-88: The Regulations

Final CLIA regulations were published in 1992, which established regulations based on the complexity of testing performed.

Categories by test complexity:

- Waived tests
- Moderate complexity, including PPM procedures
- High complexity test

Each laboratory must either be CLIA-exempt or possess one of the following CLIA certificates, as defined in §493.2

Certificate of Registration or Registration Certificate

- Approved for testing pending inspection by a CLIA-approved entity
- Applies for certification, meets CLIA standards

Certificate of Waiver

- Simple, cleared by FDA for home use, no reasonable risk
- Minimal scientific and technical knowledge required to test

Certificate of Provider Performed Microscopy (PPM) procedures

- E.g., KOH, Wet Prep, Fern Test, Urine Sediment, Nasal Smears, Fecal Leukocyte
- Physician, Dentist, or Midlevel Practitioner

Certificate of Compliance

- May be moderate or high complexity
- Inspected by a State Agency or Federal CLIA-approved inspector

Certificate of Accreditation (DLM, LP, Transfusion Medicine)

- CMS may deem a laboratory to meet all applicable CLIA program requirements through accreditation by a private nonprofit accreditation program (that is, grant deemed status), or may exempt from CLIA program requirements all State licensed or approved laboratories in a State that has a State licensure program established by law, if the following conditions are met

CLIA Requirements Overview

Personnel Qualification and Responsibilities (e.g. Medical Director, Testing Personnel)

Training and Competency

Proficiency Testing

Preanalytic, Analytic and Postanalytic Systems

- Preanalytic: test requisitions, specimen collection and submission
- Analytic: test systems, reagents, materials, procedure manual, equipment maintenance, verification and validation of methodologies
- Postanalytic: test report elements

Continuous Quality Assessment Systems

- Monitor quality control, quality indictors (e.g. TAT, errors)
- Address errors with investigations (RCA), corrective actions with system errors

Elaborate on Training and Competency

To ensure testing personnel are trained and competent to perform specified testing in the laboratory , accomplished by:

1. Direct observations of routine patient test performance
2. Monitoring the recording and reporting of test results including critical results
3. Review of intermediate test results or worksheets, proficiency testing results, quality control records, and preventive maintenance records
4. Direct observation of performance of instrument maintenance and function checks
5. Proficiency or blind sample test results
6. Evaluation of problem-solving skills including written tests, instrument troubleshooting, or sample handling issues