CLIA Regulations Assessment Workgroup: April 1, 2022, Meeting Summary

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At what point in the total testing process should CLIA regulations begin to apply and where does CLIA coverage of the process end?

Comments on where CLIA should start in the TTP

- The landscape is changing, laboratories are assisting clinicians in test selection, and algorithms are built in to facilitate test selection with artificial intelligence (AI) playing role in the future.
- Several workgroup members agreed that CLIA regulations should begin to apply at the time of request of a review or assistance with test selection while others agreed CLIA should start when a specimen arrives in the laboratory for testing.
- Laboratories should be responsible for the stewardship of test selection including the oversight of that laboratory's testing menu and the information regarding the test that's being performed. The regulations should ensure that the test menu reflects the specimen types that have been validated by the laboratory.
- If a laboratory operates its own specimen collecting stations, then those would be covered under the overseeing laboratory’s CLIA certificate.
- There may be some opportunity for expansion of CLIA around the pre-analytic assessment of specimen conditions and acceptability.

Comments on where CLIA should end in the TTP

- It would be difficult for CLIA regulations to cover clinical interpretation and follow-up
- The ability to conduct remote telepathology and control how data is handled once it leaves the laboratory makes it difficult to determine where CLIA regulations should end.
- The testing process goes through reporting including the data interpretation process even when performed remotely.
- CLIA should regulate the interpretation of bioinformatic data and variant calling.

Are there definitions included in the CLIA regulations that should be modified or added?

The CLIA Standards and Certification: Laboratory Requirements (42 CFR 493) regulations define a test system as "the instructions and all of the instrumentation, equipment, reagents, and supplies needed to perform an assay or examination and generate test results."

- The definition should be modified to include the algorithm or software algorithm used to generate a test result.
- Definition of test system will need to include components that will have an overall impact on what the physician will use to make the clinical decision.
- When data leaves a laboratory to be analyzed and interpreted at another site, that process should be considered part of the test system.
- Consider adding the term "materials" to the definition of a test system and include a definition of materials in the CLIA regulations.

The term “materials” is included in several sections of the CLIA Standards and Certification: Laboratory Requirements (42 CFR 493) law and regulations, but a definition is not provided.

- Revisit the April 2019 CLIAC Nontraditional Testing Workflow Models Workgroup Recommendation that “HHS issue proposed regulations that reflect that the word “materials” in the CLIA-88 definition of a clinical laboratory shall include all data derived from a patient specimen, including images, genetic and protein sequence(s), –omics data, and other data.”
- Consider extending the definition of the term “materials” to be broad to encompass many things, even including a software company that processes, handles, analyzes, and interprets patient laboratory data.

The term “specimen” is not defined in the CLIA Standards and Certification: Laboratory Requirements (42 CFR 493) regulations.

- Data analysis and sequencing analysis and image analysis are all integral parts of the laboratory process and there may be a need to define these as specimens without impeding current workflows and efficiencies that have been built up over time.

The definition of a “laboratory” or “clinical laboratory” in the CLIA law

- The term ‘‘laboratory’’ or ‘‘clinical laboratory’’ means a facility for the biological, microbiological, serological, chemical, immuno-hematological, hematological, biophysical, cytological, pathological, or other examination of 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.” The term is also included in other sections of the law without a definition provided. Clinical Laboratory Improvement Amendments (42 USC 263a).
  - The definition of a laboratory in the CLIA law includes the statement “…materials derived from the human body…” The term “derived” can be used to apply to images and data because they are derivations from the materials from the human body.

Other Discussions

Remote Analysis

There is a need to redefine what a laboratory is and if there's an allowance for there to be extensions of laboratories that would encompass those remote analysis sites. The analysis of laboratory data can be performed in almost any setting so there is a need to determine when the CLIA certificate can be extended to remote data analysis. A suggestion would be that if an employee of a laboratory is working out of their home or at another remote location, then that data analysis and interpretation would be covered through an extension of the home laboratory's CLIA certificate. Under a distributive model where laboratory A does the wet lab work and laboratory B does the interpretation, those two sites should have separate and distinct CLIA certificates.

At-Home Specimen Collection

- The COVID-19 pandemic brought at-home specimen collection to the forefront. The workgroup agreed that laboratory testing quality begins at the time of specimen collection, but it would be very difficult to inspect the front-end process of specimen collection including at-home or remote, packaging, transportation, patient information validation, etc. There should be more stringent requirements for stability studies both with the vendor and as a confirmation in the laboratory to address the specimen shipment issues.
  - Vendors should perform studies (stability, transportation, etc.) on at-home collected specimens and provide that information as part of the FDA approval process. These studies should include specimen stability.
  - FDA should consider requiring a human adequacy control for detection in a specimen and for at-home collection and testing.
  - Specimen collection devices should have internal controls to ensure that sufficient specimen was collected and monitor the integrity of the specimen during transportation to the testing laboratory.

VPN and Encryption Standards

- Acceptable VPN and encryption standards based on current standards should be defined in regulatory standards.
  - HIPAA already requires any protected health information (PHI), which includes genetic information, which is defined as PHI under the HIPAA Omnibus Rule, to adhere to requirements under the HIPAA Final Security Rule.

Use of Non-CLIA Laboratories or Companies

- It is becoming very rare for data from clinical testing to only be maintained in the laboratory. For instance, almost all high-throughput next generation sequencing (NGS) is processed in the cloud using tools provided by non-CLIA laboratories or companies. The current distributive testing model still does not accommodate software tools in the cloud.
  - Sites that perform informatic analysis on laboratory data should be certified under CLIA. This may require a new type of CLIA laboratory designation beyond Certificate of Compliance or Accreditation.
  - Sites that perform variant interpretation with “variant scientists” are not currently required to be CLIA-certified resulting in a non-regulated practice by an external entity that may increase patient risk.
  - The process to generate a list of variants requires a significant degree of expertise and it is a large component of the test analysis. Not only could a company hide variants from view so that the interpreter has no way of knowing that that variant existed, but they could also generate false positives with inaccurate variant allele fractions if they're not maintaining a list of their artifacts or their consistent false positives. So, even if they may not be interpreting the significance of those variants, it's still very much a huge part of that test.

Use of Non-CLIA Laboratories or Companies

- The laboratory is responsible for validating the accuracy of the entire process, whether they outsource a piece to an independent bioinformatic entity or use a bioinformatic tool on site.
- The vast majority of CLIA Laboratory Directors do not have sufficient knowledge, training, and experience to review laboratory reports involving variant interpretation using NGS technologies. Thus, there is a need for a distributive model to allow for interpretation at sites that should be regulated.
- Professional certification may need to be required for laboratory professionals who sign out reports that include clinical variant interpretations.
- There is a need for a new class of personnel for the post-analytic analysis of laboratory data or results to accommodate other areas of practice such as NGS, drug screen toxicology, etc. Currently, there is no option to identify these types of laboratory personnel or for companies performing these types of services to obtain a CLIA certificate.