CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE (CLIAC)
CLIA REGULATIONS ASSESSMENT WORKGROUP

MEETING SUMMARY REPORT

April 1, 2022 Meeting

1. **At what point in the total testing process should CLIA regulations begin to apply, and where does CLIA coverage of the process end?**
   - How should the CLIA requirements be revised to clarify the laboratory's role and responsibilities for providing consultation for test selection, especially considering emerging technologies?
   - How should the CLIA requirements be revised to clarify the laboratory's role and responsibilities with respect to result interpretation and reporting, especially considering emerging technologies?

   Workgroup Discussion and Comments
   - Any new CLIA requirements should be crafted in such a way as to anticipate technology advancement and changing healthcare environments.
   - Comments on where CLIA should start in the total testing process (TTP):
     - The landscape is changing, laboratories are assisting clinicians in test selection, and algorithms are built to facilitate test selection with artificial intelligence (AI) playing a role in the future.
     - Several workgroup members agreed that CLIA regulations should begin to apply at the time of request for a review or assistance with test selection. In contrast, others agreed that 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 being performed. The regulations should ensure that the test menu reflects the specimen types that the laboratory has validated.
     - If a laboratory operates its own specimen collecting stations, 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, even when performed remotely.
     - CLIA should regulate the interpretation of bioinformatics data and variant calling.

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

   Workgroup Discussion and Comments
   - 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 a test system will need to include components that will impact 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, sequencing, 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: "As used in this section, 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.

3. Other Workgroup Discussions

- There is a need to redefine what a laboratory is and if there's an allowance for 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 interprets, those two sites should have separate and distinct CLIA certificates.
- 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. Still, 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 at-home collection devices and testing systems.
    - Specimen collection devices should have internal controls to ensure sufficient specimen was collected and monitor the specimen's integrity during transportation to the testing laboratory.
- Acceptable VPN and encryption standards based on current standards should be defined in regulatory standards.
    - HIPAA already requires any protected health information (PHI), including genetic information, defined as PHI under the HIPAA Omnibus Rule, to adhere to requirements under the HIPAA Final Security Rule.
- It is becoming rare for data from clinical testing only to 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 of generating a list of variants requires a significant degree of expertise and 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 interpret the significance of those variants, it's still a part of that test.
    - 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 be needed 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. There is no option to identify these types of laboratory personnel or companies performing these services to obtain a CLIA certificate.

May 6, 2022 Meeting

1. **Summary of the previous workgroup meeting (April 1, 2022)**
   Workgroup Discussion and Comments
   - A member commented that another possibility would be an additional specialty to accommodate the post-analytic analysis of laboratory data or results to accommodate other practice areas such as NGS, drug screen toxicology, etc. By adding an additional specialty, you can keep the existing CLIA certificate structure with oversight under a Certificate of Compliance or Certificate of Accreditation without creating a new certificate type.
   - Another member commented on the CLIA regulations' difficulty in covering clinical interpretation and follow-up and suggested additional discussion to define clinical interpretation properly. There is variant interpretation, and then there is result interpretation, and both should be considered separately.
   - Workgroup members noted that laboratory directors might not have sufficient knowledge, training, and experience to review laboratory reports involving variant interpretation using NGS technologies or other emerging technologies.
   - Sites performing informatics and data interpretation should be regulated under CLIA.

2. **Does using robotics in the laboratory impact the quality of testing?**
   - How does CLIA apply to the use of these technologies?
   - What requirements should be added or revised in CLIA to ensure testing quality when robotics is part of the total testing process?

   Workgroup Discussion and Comments
   - Robotics has been a part of the general chemistry laboratory for almost a decade. Using robotics has been shown to improve quality by standardizing repetitive operations.
   - The use of robotics should fall under CLIA because laboratory personnel ensures that the robotic equipment performs as expected through validation and establishment of performance characteristics.
   - Liquid handlers have become a regular part of laboratory operations for SARS-CoV-2 testing and should be covered under CLIA.
   - Robotics is an advanced way to perform specimen movement, handling, extraction, and processing, and all of those processes are currently regulated under CLIA.
   - Laboratories have different types of robotic equipment, from liquid handling to all-encompassing and producing results, such as the Clear Labs instrument that performs DNA extraction, library prep, sequencing, and analysis.

3. **How do technologies that utilize artificial intelligence play a role in the total testing process?**
   - How does CLIA apply to the use of these technologies?
   - What requirements should be added or revised in CLIA to ensure testing quality when artificial intelligence is part of the total testing process?

   Workgroup Discussion and Comments
   - A definition of artificial intelligence (AI) may be needed to determine CLIA applicability.
   - It is essential to understand some of the basics of artificial intelligence to help inform decisions. AI can be developed in different ways. One can develop and train a model, test it, validate it, and then test it, and that model stays static in its use. Another way is to develop a model that incorporates new data and trains itself again in an iterative process. One of those models is consistent with current CLIA regulations, and the other one is not unless you want to undergo continuous revalidation.

- Members agreed that a presentation on the basics of AI would be beneficial to set the stage for discussions. It is also essential to understand how AI differs from a bioinformatics pipeline and where the risks exist.
- Members also agreed that a presentation on the current practice of variant interpretation would be beneficial to continue the discussion on where CLIA regulations should end.

4. If analytical work or data analysis is performed by a contractor, a private company, or a different institution, how should the CLIA regulations apply to the contractor, private company, or other institution?

Workgroup Discussion and Comments

- In most cases, facilities that do not have a molecular pathologist, geneticist, or bioinformatician in-house will send out their bioinformatic pipelines to a different institution.
- 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.
- The workgroup concurs with the following CLIAC recommendations:
  - November 2019: CLIAC recommends that the CLIA Program consider that when laboratory professionals are providing patient care through the selection, interpretation, and reporting of patient results by accessing data remotely in a secure environment, they shall be deemed as performing those services at the primary site that houses the CLIA Certificate.
  - April 2022: Laboratory practice over the last two years has demonstrated the success of remote analysis and interpretation of digital data securely. CLIAC augments its 2019 recommendation that CMS and the U.S. Department of Health and Human Services permanently codify that a laboratory's CLIA certificate covers employees of that laboratory who are performing data analysis and interpretation of digital information under the quality oversight from a primary site when working remotely under the home laboratory's CLIA certificate.

5. Data as a Specimen

- How does "data" fit into the total testing process as a specimen, especially when handed off to other entities for processing, analysis, or interpretation?
- If data were considered a specimen, what parts of CLIA would need to be updated, including additional terminology to be defined?
- If data were to be considered a specimen, which types of data analysis (or "activity involving such data" from the CLIAC recommendation) should be considered a "test system" or otherwise regulated under CLIA?
- Does the determination of whether data analysis is a separate "test system" depend on whether the entity conducting the analysis differs from the laboratory that performed the testing that generated the data?
- Which activity involving data (provided that the activity is related to the diagnosis, prevention, or treatment of disease or impairment of, or the assessment of, the health of human beings) would need to be performed under a CLIA certificate?

Workgroup Discussion and Comments

- One member commented on outside data coming to a laboratory, such as at-home COVID-19 or glucometer results, and if that is regulated under CLIA and when it should be included in the medical record. It is hard to determine the authenticity and quality of these results for inclusion in the laboratory report.

- A member added that the Office of the National Coordinator for Health IT (ONC) is a venue to discuss at-home testing results and inclusion in the electronic health record (EHR). Including patient-generated results in an EHR is happening, but there is an appropriate way to label those results.
- A member noted that if data is considered a specimen, then sites that perform informatic analysis on laboratory data would fall under CLIA.
- Members agreed that the CLIA definition of a laboratory includes the terminology "materials derived from the human body" and that "derived" could apply to images and data because they are a derivation of material from the human body. It would be beneficial to have examples of the types of data currently transferred in laboratory testing.
- The workgroup members concurred with the April 2019 recommendations:
    - Any site that performs an activity that involves such data (provided that the activity is related to the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of, the health of human beings) shall be considered a "laboratory," if that site is not an extension of an existing CLIA-certified laboratory."
    - 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.
    - The CLIA Program considers that when laboratory professionals provide patient care through the selection, interpretation, and reporting of patient results by accessing data remotely in a secure environment, they shall be deemed as performing those services at the primary site that houses the CLIA Certificate.
- Several members commented on the need for proficiency testing (PT) to extend beyond the laboratory to assess the total testing process, especially with data transfer for analysis at another facility. The members agreed with the April 2019 CLIAC recommendation that HHS develop guidance to allow distributive PT models, including analytes currently subject to CLIA-required PT, to assure quality across the whole testing cycle.
- There is a need to redefine what a laboratory is and if there's an allowance for 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.

June 3, 2022 Meeting

1. **Summary of the previous workgroup meeting (May 6, 2022)**
   Workgroup Discussion and Comments
   - The workgroup chairs provided an overview of the current workgroup agreements.
   - One member commented on the need to demonstrate testing proficiency before offering the test to the public.
   - The workgroup chairs provided an overview of the workgroup agreement process and presentation to CLIAC for deliberation.

2. **Testing Process Review – Artificial Intelligence (AI) Presentation and Discussion (Presentation provided by Dr. Alexis Carter)**
   - How do technologies that utilize artificial intelligence play a role in the total testing process?
     - How does CLIA apply to the use of these technologies?
     - What requirements should be added or revised in CLIA to ensure the quality of testing when artificial intelligence is part of the total testing process?

   Workgroup Discussion and Comments
   - There are certain principles on how to develop your AI model correctly and then verify performance. There may be a need for laboratories to have guidelines to assist in troubleshooting when the algorithm produces spurious data or when problems are detected with vendor-developed AI algorithms.
   - There is a need for CLIA to have definitions around personnel, such as a data scientist who looks at and helps mitigate issues with these algorithms.
   - AI performance algorithms can change over time due to shifts in population, shifts over time in the health of the general population or race, and ethnicity variations over time. In applying the current CLIA framework, there should be a verification process at the algorithm launch. There should also be a way to identify a shift and drift over time to determine when a reverification frequency on the patient population of that institution is needed.
   - For laboratory-developed machine learning algorithms, CLIA regulations should focus on how the algorithm was developed with defined criteria around how it was designed and the population used to create it. Also, proficiency testing (PT) is needed for that algorithm to prove that it achieves the correct answer.
   - Some checklists are available that provide a list of requirements for developing a machine learning algorithm, but many focus on using accurate data at the onset. It is essential to clearly define the population and train the algorithm using good, quality data representative of the population.
   - Both laboratory-developed and FDA-cleared algorithms should be monitored, and discrepancies should be reported to the manufacturer and investigated in the laboratory. In some cases, the algorithm is retrained, and a new version is developed based on the provided updated training and data.
   - There is a need for guidance on validating algorithms to assure quality for static and adaptive algorithms.
   - Static algorithms should be used for laboratory testing. If the algorithm needs to be updated, re-verification and re-validation are required to ensure patient safety, similar to the practice used for bioinformatic pipelines.
   - CLIA could define QC and PT requirements for continuously improving algorithms.

3. **Total Testing Process Review and Data as a Specimen – The Practice of Variant Interpretation/Classification Presentation and Discussion (Presentation provided by Dr. Birgit Funke)**
   - How should the CLIA requirements be revised to clarify the laboratory's role and responsibilities with respect to result interpretation and reporting, especially considering emerging technologies?
   - Which activity involving data (provided that the activity is related to the diagnosis, prevention, or treatment of disease or impairment of, or the assessment of, the health of human beings) would need to be performed under a CLIA certificate?

Workgroup Discussion and Comments

- The personnel performing variant classification in laboratories include MD pathologists, PhD geneticists, and genetic counselors with additional training in laboratory genetics. The personnel performing variant classification should have documented expertise in human genetics and the ability to understand the published evidence.
- There are specific requirements needed for the variant scientists that work in the oncology setting, and there is a need for specific expertise depending on the genetics area. These requirements may not need to be as stringent for infectious disease testing, where personnel shortages are a challenge.
- New professional roles have emerged since the CLIA regulations were implemented, and there is a need to define these roles and their associated training and competency. The workgroup should define these roles and discuss educational, training, and competency requirements for testing personnel such as bioinformaticians and variant scientists.
- The CAP provides a molecular checklist with requirements beyond the CLIA requirements. These checklists could be helpful to use as a starting point for workgroup discussions.
- The current personnel requirements for high-complexity Technical Supervisors for transfusion medicine, histocompatibility, and anatomic pathology are more stringent. The workgroup could use those requirements as a guide to personnel discussions.
- The workgroup should look at the broad laboratory environment to determine the need to revise the current CLIA requirements.
- CLIA should regulate all steps of the testing process for variant classification that represent objective data gathering and application of rules. Laboratories must document their policies and procedures for the discipline of variant classification.

August 5, 2022 Meeting

1. **Summary of the previous workgroup meeting (June 3, 2022)**
   Workgroup Discussion and Comments
   - The workgroup chairs provided a summary from the June 3, 2022 meeting and an overview of the current workgroup agreements.
   - It is important to consider if the CLIA personnel requirements need to be modified to include data as a specimen as related to the transmittal and receiving of data. When a pathologist uses the data to make a clinical decision, that falls into the practice of medicine.

2. **Digital Pathology**
   - What changes should be made to current CLIA requirements to ensure the quality of digital pathology (e.g., microbiology, molecular, histopathology, cytology) or any testing process that involves a digital image when parts of the process may be performed in the same laboratory or in separate facilities or locations?
     - How should a laboratory validate a whole slide digital imaging system for diagnostic purposes before it is placed in clinical service? This includes the process, concordance rate, and the number of cases for review.
     - What should CLIA require for digital images to ensure proper specimen identification and integrity?
     - What should CLIA require for quality control of digital images and the digital pathology process?
     - Are current CLIA requirements for record retention applicable to digital images, or how should they be modified?
     - Should information retrieved during the conversion of the slide to a digital image be saved as data? Is it part of the total testing process?
     - What should CLIA require for personnel and competency assessments for staff performing digital pathology, including pathologist competency and staff (e.g., image technician, cytotechnologist, histotechnologist, physician assistants, information technology personnel, and/or consultants)?
     - Who should be responsible for each distinct part of the remote analysis process?
     - Does a laboratory's CLIA certificate cover the pathologist when using a VPN to review and report cases remotely?
   - How does a laboratory ensure patient confidentiality and the accurate electronic transfer and submission of patient data from one testing location to another protected under CLIA regulations?
   - How should the current CLIA requirements be revised to ensure information technology (IT) security and encryption, especially when test interpretation is performed off-site?
   - What are the advantages and disadvantages of allowing the remote review of histopathology slides, as permitted during the COVID-19 public health emergency?
     - How should CLIA be revised to ensure the quality, reliability, accuracy, and timeliness of test results if these CLIA flexibilities were permanently incorporated into the regulations?
     - What specialties and subspecialties, in addition to cytology have the potential for remote analysis and should be considered if this flexibility was made permanent?

   Workgroup Discussion and Comments
   - CAP published the following:
     - Validating whole slide imaging for diagnostic purposes in pathology: guideline from the College of American Pathologists Pathology and Laboratory Quality Center in 2013.
     - Validating Whole Slide Imaging Systems for Diagnostic Purposes in Pathology: Guideline Update From the College of American Pathologists in Collaboration With the American Society for Clinical Pathology and the Association for Pathology Informatics in 2022.

- There should be clear, separate verification, validation, and training requirements. Many times, laboratories will group these three together when working with a vendor to onboard a test system.
- Laboratories should have a quality assurance (QA) program to monitor the entire workflow.
- Quality control (QC) applies to some areas of digital pathology. For example, in quantitative image analysis using algorithms, there is an assumption that the algorithm is always correct. By requiring QC steps, the laboratory can identify problem areas. The overall QA program would dictate which QC is required for each application.
- Part of a QC check also ensures that the images are scanned with appropriate resolution, quality, and color. Vendors do not offer tools for this QC step when using a whole slide scanner.
- One challenge with whole slide imaging is when there is a small piece of detached cancer on a slide outside of the image detection algorithm, and it does not get scanned. The vendors do not offer technology to identify those areas with an alert or for the laboratories to know the right image to look at, the macro image, thumbnail, etc.
- When developing requirements for digital pathology, there needs to be an understanding that laboratories will have difficulty meeting the requirements if there are no processes or the technology is unavailable from vendors.
- Pathology assistants should be included in the personnel and competency discussions.
- CLIA cytology control regulations at §493.1274(c)(3) state that for each patient with a current HSIL, adenocarcinoma, or other malignant neoplasms, a laboratory review of all normal or negative gynecologic specimens received within the previous five years, if available in the laboratory (either on-site or in storage). If significant discrepancies are found that will affect current patient care, the laboratory must notify the patient's physician and issue an amended report. Digital imaging with AI complicates this requirement. For instance, are the slides scanned again, and is the AI algorithm re-run? What if it analyzes completely different cells? Or do you leave the original AI scan of the case and utilize a different cytologist to look at the results of the previous AI algorithm? Is the control for the cytologist or the AI system?
- Possible solutions to ensure quality include modular proficiency testing to monitor the AI pathway.
- Many digital pathology systems, including FDA-approved systems, are not compliant with HIPAA Final Security regulations, putting laboratories in a difficult position if the system is not compliant with federal regulations.
- Laboratories should have a policy/procedure to ensure specimen integrity throughout the analytical process.
- The bioinformatics pipeline validation guideline for patient identification requires four different identifiers for the specimen, the run, and the patient. More prescriptive CLIA requirements would force vendors to comply with the requirements from the laboratories. Any time a device is going to be storing data on a specimen, whether that's the pipeline, digital image, etc., the device needs to be able to store some unique identifier about the scan or the run, in the case of NGS or the assay. Because a single sample could be analyzed multiple times. There should be an identifier for the actual specimen and then something for the patient.
- CAP specifies that digital images for diagnosis must be retained for ten years if original glass slides are unavailable. There is no retention requirement for images of glass slide preparations when the source slides remain readable for the required retention period. See CAP's Anatomic Pathology Checklist, ANP.12500-Record, and Material Retention - Surgical Pathology.
- Storing digital images is an extensive part of the laboratory process and may require a large portion of the budget devoted to data storage.
- One member added that frozen slides must be retained when storing images for telepathology. Another member noted that many frozen sections are being done using robotic microscopy, and

nothing is saved. There may need to be different requirements for whole slide imaging versus live images and the specimen type.

- Some retention factors were addressed in the American Telemedicine Association clinical guidelines for telepathology publication.
- A suggestion was made that a laboratory should have a retention policy that defines the length of time and what they store. This allows CLIA to be broad and enables the laboratories to have the flexibility to design their retention policy.
- There may be a need to address image technicians as a CLIA personnel category.
- The National Society for Histotechnology, in collaboration with the Digital Pathology Association, developed the Digital Pathology Certificate Program. It is an online, self-paced certificate program to increase competency and improve knowledge in whole slide imaging and digital pathology to meet the educational needs of the growing community of individuals involved with and utilizing this technology.
- CLIA should have personnel and competency assessment requirements for staff performing digital pathology. Competency assessment needs to cover familiarity with the technology and the use of the new technology. CAP's Anatomic Pathology Checklist, ANP.10010-Professional Competency, states that the laboratory director ensures the professional competency of pathologists who provide interpretive services to the anatomic pathology laboratory. The mechanism for competency assessment must be pertinent to the type of interpretive services provided (e.g., general anatomic, neuropathology, renal pathology, forensic pathology). There must be a written policy for assessing professional competency at defined intervals, criteria for the assessment, and records of the assessment must demonstrate review by the laboratory director.
- If a laboratory uses a VPN to a site, the main laboratory's CLIA certificate is responsible for the quality, analysis, and QA/QC of the entire remote analytical process.
- The CLIA regulations should include references to the HIPAA final security rule or the HIPAA regulations. This requirement could go a long way to helping laboratories tell vendors that their systems need to be compliant. There are issues with digital imaging systems that are outdated and no longer supported by Microsoft. The vendors are not responsible for being data entry points for ransomware or malware. Also, the internal security team will turn off systems without notice if they are determined to pose a risk. This could be critical if the system is being used for patient testing.
- The HIPAA Security Rule establishes national standards to protect individuals' electronic personal health information that is created, received, used, or maintained by a covered entity. The Security Rule requires appropriate administrative, physical and technical safeguards to ensure the confidentiality, integrity, and security of electronically protected health information. Any data transfer must adhere to the HIPAA Security Rule, and bioinformatic companies must have a CLIA certificate and adhere to the HIPAA Security Rule.
- A list of references for HIPAA:
    - Privacy and security of patient data in the pathology laboratory
    - Considerations for Genomic Data Privacy and Security when Working in the Cloud
    - Guidance on HIPAA & Cloud Computing
- The medical director is responsible for ensuring that pathologists are privileged to practice at the site where you send tests. The Medical Director of the site you practice under is ultimately responsible even when referring the specimen.

October 7, 2022 Meeting

The workgroup reviewed the current list of workgroup agreements and refined them in preparation for the November 9-10, 2022 workgroup report and CLIAC discussion.

Workgroup Agreements (Ongoing List)

- Sites performing informatics and data interpretation should be regulated under CLIA.
- 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.
- The CLIA definition of a laboratory includes the terminology "materials derived from the human body," and that "derived" could apply to images and data because they are a derivation of material from the human body. It would be beneficial to have examples of the types of data currently transferred in laboratory testing.
- If a laboratory employee works out of their home or at another remote location performing duties such as data analysis and interpretation associated with that laboratory, then that would be covered through an extension of that laboratory's CLIA certificate.
- Under a distributive model where a laboratory performs the wet laboratory work, and another separate entity performs the data analysis and/or interpretation, those two sites should have separate and distinct CLIA certificates, and proficiency testing should be required for both locations.
- The COVID-19 pandemic brought at-home specimen collection to the forefront. The workgroup agreed that laboratory testing quality begins during specimen collection. Still, 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 at-home collection and testing.
    - Specimen collection devices should have internal controls to ensure sufficient specimen was collected and monitor the specimen's integrity during transportation to the testing laboratory.
    - Laboratories that choose to use a home collection device that has not been cleared for use by the FDA will need to submit that device for FDA review and approval.
    - Laboratories must have policies in place to accept and reject specimens collected outside of their laboratory, including home-collected specimens. If the laboratory chooses to test a specimen that falls outside of the collection device's manufacturer's instructions, then the laboratory will need to provide performance studies to validate that modification.
- Workgroup members agree that CLIA should broadly define new personnel roles, such as the personnel performing activities such as bioinformatic data analysis, variant classification, variant analysis for patient care, etc. (variant scientists).
- There is a need to consider an additional specialty to accommodate the post-analytic analysis of laboratory data or results to accommodate other practice areas such as NGS, drug screen toxicology, etc. By adding an additional specialty, you can keep the existing CLIA certificate structure with oversight under a Certificate of Compliance or Certificate of Accreditation without creating a new certificate type.
- The use of robotics should fall under CLIA because laboratory personnel must ensure that the robotic equipment performs as expected through validation and establishment of performance characteristics.

- The workgroup concurs with the following CLIAC recommendations:
  - April 2019: Any site that performs an activity that involves such data (provided that the activity is related to the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of, the health of human beings) shall be considered a "laboratory," if that site is not an extension of an existing CLIA-certified laboratory."
  - April 2019: 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.
  - April 2019: HHS develop guidance to allow distributive proficiency testing (PT) models, including analytes that are currently subject to CLIA-required PT, to assure quality across the whole testing cycle.
  - November 2019: CLIAC recommends that the CLIA Program consider that when laboratory professionals are providing patient care through the selection, interpretation, and reporting of patient results by accessing data remotely in a secure environment, they shall be deemed as performing those services at the primary site that houses the CLIA Certificate.
  - April 2022: Laboratory practice over the last two years has demonstrated the success of remote analysis and interpretation of digital data securely. CLIAC augments its 2019 recommendation that CMS and the U.S. Department of Health and Human Services permanently codify that a laboratory's CLIA certificate covers employees of that laboratory who are performing data analysis and interpretation of digital information under the quality oversight from a primary site when working remotely under the home laboratory's CLIA certificate.
- For any digital data, laboratories should have a policy/procedure to ensure specimen integrity throughout the analytical process.
- Any device storing data should require an identification number for the image, a patient identifier, and an institutional identifier.
- Laboratories must implement software and devices compliant with the applicable components of the HIPAA Final Security Rule. In addition, laboratories must ensure that implemented devices do not pose a significant risk to the safety and security of the patient data that the laboratory stores, manages, creates, or analyzes.
- CLIA should require training and competency assessments for staff such as pathology assistants, image technicians, cytotechnologists, and histotechnologists performing digital pathology.
- A laboratory's CLIA certificate covers the qualified laboratory personnel when using a VPN to review and report cases remotely.
- If an entity is manipulating information, performing data analysis, etc., received from a clinical laboratory and returning it to the laboratory for inclusion in the patient report or for patient care, that entity needs to have the appropriate CLIA certificate. Under that CLIA certificate, they are subject to the same patient confidentiality and requirements as the referring laboratory.
- The CLIA regulations should be revised to allow remote analysis for any CLIA specialty or subspecialty.

November 4, 2022 Meeting

The workgroup continued to review the current list of workgroup agreements and refined them in preparation for the November 9-10, 2022 workgroup report and CLIAC discussion.

December 2, 2022 Meeting

The workgroup reviewed the November 9-10, 2022 CLIAC recommendations related to the CLIA Regulations Assessment Workgroup report and presentation.

- Several members commented on privacy issues as related to the CLIA requirement for inclusion of the name and address of the laboratory where the test is performed on the final report. Members suggested that for remote locations such as home offices that perform analysis, that a laboratory code be allowed as part of the main laboratory address.
- Members commented on the need for security regulations when accessing laboratory networks from remote locations and suggested the inclusion of compliance with existing HIPAA regulations in the CLIA regulations.
- The workgroup members discussed the process of reviewing Subpart K – Quality System for Nonwaived Testing and were encouraged to share comments on potential revisions to Subpart K before the next workgroup meeting.

February 3, 2023 Meeting

The workgroup members began reviewing Subpart K – Quality System for Nonwaived Testing.

- Members commented on the need to include clinical validity specifications in the CLIA regulations. Several members commented on laboratory developed tests (LDTs) and the need for specificity on clinical validity requirements. One member noted that many laboratory surveyors do not have the laboratory expertise to determine the clinical validity of an assay, and it would be a heavy burden on surveyors to make a determination of clinical validity. One member suggested the inclusion of a statement in the CLIA regulations that state you must have a process to determine the clinical validity of any LDT.
- The CLIA regulations cover the establishment of performance specifications for the services that laboratories provide to ensure accurate and reliable results. The CLIA Interpretive Guidelines for Laboratories include guidelines and instructions for the listed regulatory requirements and encompass all types of laboratory facilities. The CMS CLIA brochures help explain the CLIA regulation requirements.
- The CDC, CMS, and FDA ex officios and subject matter experts state that clinical validity discussions are out of scope for this workgroup.
- A member suggested using CAP requirements as a starting point to determine the general concepts that should be included in the CLIA regulations, such as analytic requirements for qualitative tests.

March 3, 2023 Meeting

The workgroup members continued to review Subpart K – Quality System for Nonwaived Testing.

- The CLIA program agencies (CDC, CMS, and FDA) have provided the following statement related to the scope of the CLIA Regulations Assessment Workgroup: According to 42 CFR 493.2001, the Clinical Laboratory Improvement Advisory Committee (CLIAC) will review and make recommendations related to quality systems standards or other issues at the request of HHS. With respect to laboratory developed tests or methods developed in-house, CMS, FDA, and CDC have not requested a discussion or review of the existing CLIA regulations related to governing the development of these tests or methods, including the inclusion of performance specifications, clinical correlation, or clinical validity. Therefore, this topic is not open for discussion by CLIAC.
- The workgroup discussed and made several workgroup agreements related to Subpart K – Quality System for Nonwaived Testing of the CLIA regulations. Appendix 1 contains the current CLIA Subpart K regulations with workgroup agreements noted as edits or comments.
- The workgroup CMS ex officio clarified that the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient does not fall under the authority of the CLIA regulations.
- Members discussed the issue of variant classification that is performed by laboratories and the need for regulatory oversight of this process. One member stated that laboratories are performing variant classification and including that information on their laboratory reports. Therefore, it should be regulated to ensure accuracy. Several members agreed that variant classification is evolving regulatory oversight should be a priority for future discussions. A member provided the information included in Appendix 2 that could be used to support future discussions.

- A member commented that § 493.1253 Standard: Establishment and verification of performance specifications does not address qualitative tests such as NGS. The member suggested that one way to promote harmonization of analytical performance terminology and metrics would be to include professional organization guidelines such as the Clinical and Laboratory Standards Institute (CLSI) Harmonized Terminology Database in the CMS State Operations Manual (SOM).

April 7, 2023 Meeting

The workgroup members discussed and finalized the workgroup agreements for the April 2023 CLIAC meeting presentation.

Appendix 1

CLIA Regulatory Assessment Workgroup: CLIA Subpart K – Quality Systems for Nonwaived Testing Workgroup Agreement

Subpart K - Quality System for Nonwaived Testing

Source: 68 FR 3703, Jan. 24, 2003, unless otherwise noted.

§ 493.1200 Introduction.

(a) Each laboratory that performs nonwaived testing must establish and maintain written policies and procedures that implement and monitor a quality system for all phases of the total testing process (that is, preanalytic, analytic, and postanalytic) as well as general laboratory systems.

(b) The laboratory's quality systems must include a quality assessment component that ensures continuous improvement of the laboratory's performance and services through ongoing monitoring that identifies, evaluates ~~and~~, resolves, and limits the likelihood of the recurrence of problems.

(c) The various components of the laboratory's quality system are used to meet the requirements in this part and must be appropriate for the specialties and subspecialties of testing the laboratory performs, services it offers, and clients it serves.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

§ 493.1201 Condition: Bacteriology.

If the laboratory provides services in the subspecialty of Bacteriology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1261, and §§ 493.1281 through 493.1299.

§ 493.1202 Condition: Mycobacteriology.

If the laboratory provides services in the subspecialty of Mycobacteriology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1262, and §§ 493.1281 through 493.1299.

§ 493.1203 Condition: Mycology.

If the laboratory provides services in the subspecialty of Mycology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1263, and §§ 493.1281 through 493.1299.

§ 493.1204 Condition: Parasitology.

Commented [WG1]: CLIA Subpart K - Quality System for Nonwaived Testing should be updated to reflect past CLIAC recommendations related to remote and distributive testing from April 2022 and November 2022.

Commented [WG2]: The definitions in the CLIA regulations or CMS State Operations Manual (SOM) should be updated to include terms used throughout this section, such as those related to the establishment of performance specifications for qualitative and quantitative tests, including accuracy, precision, analytical sensitivity, and analytical specificity. Information in the SOM should include published professional organization guidelines, as applicable.

Commented [CRAWG3]: Subpart K - Quality System for Nonwaived Testing, Analytic Systems should be generalized to address quantitative and qualitative test modalities.

Commented [WG4]: The regulations on quality assessment at § 493.1200(b) should be clarified to address the recurrence of problems, "The laboratory's quality systems must include a quality assessment component that ensures continuous improvement of the laboratory's performance and services through ongoing monitoring that identifies, evaluates, resolves, and limits the likelihood of the recurrence of problems."

If the laboratory provides services in the subspecialty of Parasitology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1264, and §§ 493.1281 through 493.1299.

§ 493.1205 Condition: Virology.

If the laboratory provides services in the subspecialty of Virology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1265, and §§ 493.1281 through 493.1299.

§ 493.1207 Condition: Syphilis serology.

If the laboratory provides services in the subspecialty of Syphilis serology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 493.1281 through 493.1299.

§ 493.1208 Condition: General immunology.

If the laboratory provides services in the subspecialty of General immunology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 493.1281 through 493.1299.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

§ 493.1210 Condition: Routine chemistry.

If the laboratory provides services in the subspecialty of Routine chemistry, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1267, and §§ 493.1281 through 493.1299.

§ 493.1211 Condition: Urinalysis.

If the laboratory provides services in the subspecialty of Urinalysis, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 493.1281 through 493.1299.

§ 493.1212 Condition: Endocrinology.

If the laboratory provides services in the subspecialty of Endocrinology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 493.1281 through 493.1299.

§ 493.1213 Condition: Toxicology.

If the laboratory provides services in the subspecialty of Toxicology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 493.1281 through 493.1299.

§ 493.1215 Condition: Hematology.

If the laboratory provides services in the specialty of Hematology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1269, and §§ 493.1281 through 493.1299.

§ 493.1217 Condition: Immunohematology.

If the laboratory provides services in the specialty of Immunohematology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1271, and §§ 493.1281 through 493.1299.

§ 493.1219 Condition: Histopathology.

If the laboratory provides services in the subspecialty of Histopathology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1273, and §§ 493.1281 through 493.1299.

§ 493.1220 Condition: Oral pathology.

If the laboratory provides services in the subspecialty of Oral pathology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 493.1281 through 493.1299.

§ 493.1221 Condition: Cytology.

If the laboratory provides services in the subspecialty of Cytology, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1274, and §§ 493.1281 through 493.1299.

§ 493.1225 Condition: Clinical cytogenetics.

If the laboratory provides services in the specialty of Clinical cytogenetics, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1276, and §§ 493.1281 through 493.1299.

§ 493.1226 Condition: Radiobioassay.

If the laboratory provides services in the specialty of Radiobioassay, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, and §§ 493.1281 through 493.1299.

§ 493.1227 Condition: Histocompatibility.

If the laboratory provides services in the specialty of Histocompatibility, the laboratory must meet the requirements specified in §§ 493.1230 through 493.1256, § 493.1278, and §§ 493.1281 through 493.1299.

General Laboratory Systems

§ 493.1230 Condition: General laboratory systems.

Commented [WG5]: A new standard is needed in Subpart K - Quality System for Nonwaived Testing under General Laboratory Systems related to electronic data analysis to encompass all types of electronic data that can be manipulated to generate a final laboratory test result.

Each laboratory that performs nonwaived testing must meet the applicable general laboratory systems requirements in §§ 493.1231 through 493.1236, unless HHS approves a procedure, specified in Appendix C of the State Operations Manual (CMS Pub. 7), that provides equivalent quality testing. The laboratory must monitor and evaluate the overall quality of the general laboratory systems and correct identified problems as specified in § 493.1239 for each specialty and subspecialty of testing performed.

§ 493.1231 Standard: Confidentiality of patient information.

The laboratory must ensure confidentiality of patient information throughout all phases of the total testing process that are under the laboratory's control. The laboratory must follow documented policies and procedures to ensure patient confidentially during transfer of data to external referral laboratories, remote testing locations, or other entities. This must include cloud-based computing such as the storage of confidential data, as appropriate. The laboratory must comply with other Federal laws, including but not limited to the HIPAA Final Security Rule.

§ 493.1232 Standard: Specimen identification and integrity.

The laboratory must establish and follow written policies and procedures that ensure positive identification and ~~optimum~~ optimal integrity of a patient's specimen from the time of collection or receipt of the specimen through completion of testing and reporting of results. The laboratory must follow documented policies and procedures for specimen acceptance and rejection.

§ 493.1233 Standard: Complaint investigations.

The laboratory must have a system in place to ensure that it documents all complaints and problems reported to the laboratory. The laboratory must conduct investigations of complaints, when appropriate.

§ 493.1234 Standard: Communications.

The laboratory must have a system in place to identify and document problems that occur as a result of a breakdown in communication between the laboratory and an authorized person who orders or receives test results.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

§ 493.1235 Standard: Personnel competency assessment policies.

As specified in the personnel requirements in subpart M, the laboratory must establish and follow written policies and procedures to assess employee and, if applicable, consultant competency.

§ 493.1236 Standard: Evaluation of proficiency testing performance.

(a) The laboratory must review and evaluate the results obtained on proficiency testing performed as specified in subpart H of this part.

(b) The laboratory must verify the accuracy of the following:

Commented [WG6]: Additional information relating to the confidentiality of patient information should be included in § 493.1231 that the laboratory must follow documented policies and procedures to ensure patient confidentially during data transfer to external referral laboratories, remote testing locations, or other entities. This must include cloud-based computing, such as storing confidential data, as appropriate. The laboratory must comply with other Federal laws, including but not limited to the HIPAA Final Security Rule.

Commented [WG7]: The specimen identification and integrity regulations under § 493.1232 should be clarified to include a requirement that the laboratory must follow documented policies and procedures for specimen acceptance and rejection to address home collection.

(1) Any analyte or subspecialty without analytes listed in subpart I of this part that is not evaluated or scored by a CMS-approved proficiency testing program.

(2) Any analyte, specialty or subspecialty assigned a proficiency testing score that does not reflect laboratory test performance (that is, when the proficiency testing program does not obtain the agreement required for scoring as specified in subpart I of this part, or the laboratory receives a zero score for nonparticipation, or late return of results).

(c) At least twice annually, the laboratory must verify the accuracy of the following:

(1) Any test or procedure it performs that is not included in subpart I of this part.

(2) Any test or procedure listed in subpart I of this part for which compatible proficiency testing samples are not offered by a CMS-approved proficiency testing program.

(d) All proficiency testing evaluation and verification activities must be documented.

§ 493.1239 Standard: General laboratory systems quality assessment.

(a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and, when indicated, correct problems identified in the general laboratory systems requirements specified at §§ 493.1231 through 493.1236.

(b) The general laboratory systems quality assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of general laboratory systems quality assessment reviews with appropriate staff.

(c) The laboratory must document all general laboratory systems quality assessment activities.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

Preanalytic Systems

§ 493.1240 Condition: Preanalytic systems.

Each laboratory that performs nonwaived testing must meet the applicable preanalytic system(s) requirements in §§ 493.1241 and 493.1242, unless HHS approves a procedure, specified in Appendix C of the State Operations Manual (CMS Pub. 7), that provides equivalent quality testing. The laboratory must monitor and evaluate the overall quality of the preanalytic systems and correct identified problems as specified in § 493.1249 for each specialty and subspecialty of testing performed.

§ 493.1241 Standard: Test request.

(a) The laboratory must have a written or electronic request for patient testing from an authorized person.

(b) The laboratory may accept oral requests for laboratory tests if it solicits a written or electronic authorization within 30 days of the oral request and maintains the authorization or documentation of its efforts to obtain the authorization.

(c) The laboratory must ensure the test requisition solicits the following information:

(1) The name and address or other suitable identifiers of the authorized person requesting the test and, if appropriate, the individual responsible for using the test results, or the name and address of the laboratory submitting the specimen, including, as applicable, a contact person to enable the reporting of imminently life threatening laboratory results or ~~panic or alert values~~a critical or clinically impactful value.

(2) ~~The patient's name or unique patient identifier.~~At least two unique patient-specific identifiers.

(3) The sex and age or date of birth of the patient.

(4) The test(s) to be performed.

(5) The source of the specimen, when appropriate.

(6) The date and, if appropriate, time of specimen collection.

(7) For Pap smears, the patient's last menstrual period, and indication of whether the patient had a previous abnormal report, treatment, or biopsy.

(8) Any additional information relevant and necessary for a specific test to ensure accurate and timely testing and reporting of results, including interpretation, if applicable.

(d) The patient's chart or medical record may be used as the test requisition or authorization but must be available to the laboratory at the time of testing and available to CMS or a CMS agent upon request.

(e) If the laboratory transcribes or enters test requisition or authorization information into a record system or a laboratory information system, the laboratory must ensure the information is transcribed or entered accurately.

§ 493.1242 Standard: Specimen submission, handling, and referral.

(a) The laboratory must establish and follow written policies and procedures for each of the following, if applicable:

(1) Patient preparation.

(2) Specimen collection.

(3) Specimen labeling, including ~~patient name or~~ at least two unique patient-specific identifiers and, when appropriate, specimen source.

Commented [WG8]: The use of "panic or alert values" should be replaced with "a critical or clinically impactful value" at §§ 493.1241(c)(1), 493.1251(b)(11), 493.1251(b)(13), and 493.1291(g).

Commented [CRAWG9]: The specimen labeling requirement at § 493.1241(c)(2) and § 493.1242(a)(3) should be updated to remove "patient name or unique patient identifier…" and include "at least two unique patient-specific identifiers."

Commented [WG10]: The specimen labeling requirement at § 493.1241(c)(2) and § 493.1242(a)(3) should be updated to remove "patient name or unique patient identifier…" and include "at least two unique patient-specific identifiers."

(4) Specimen storage and preservation.

(5) Conditions for specimen transportation.

(6) Specimen processing.

(7) Specimen acceptability and rejection.

(8) Specimen referral.

(b) The laboratory must document the date and time it receives a specimen.

(c) The laboratory must refer a specimen for testing only to a CLIA-certified laboratory or a laboratory meeting equivalent requirements as determined by CMS.

(d) If the laboratory accepts a referral specimen, written instructions must be available to the laboratory's clients and must include, as appropriate, the information specified in paragraphs (a)(1) through (a)(7) of this section.

§ 493.1249 Standard: Preanalytic systems quality assessment.

(a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and when indicated, correct problems identified in the preanalytic systems specified at §§ 493.1241 through 493.1242.

(b) The preanalytic systems quality assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of preanalytic systems quality assessment reviews with appropriate staff.

(c) The laboratory must document all preanalytic systems quality assessment activities.

[68 FR 3703, Jan. 24, 2003; 68 FR 3703, Aug. 22, 2003]

Analytic Systems

§ 493.1250 Condition: Analytic systems.

Each laboratory that performs nonwaived testing must meet the applicable analytic systems requirements in §§ 493.1251 through 493.1283, unless HHS approves a procedure, specified in Appendix C of the State Operations Manual (CMS Pub. 7), that provides equivalent quality testing. The laboratory must monitor and evaluate the overall quality of the analytic systems and correct identified problems as specified in § 493.1289 for each specialty and subspecialty of testing performed.

§ 493.1251 Standard: Procedure manual.

(a) A written procedure manual for all tests, assays, and examinations performed by the laboratory must be available to, and followed by, laboratory personnel. ~~Textbooks~~ Other

Commented [WG11]: The procedure manual requirement § 493.1251(a) should be updated to remove the reference to "Textbooks" and replace it with "Other materials reflecting current practice." This change should also be made at § 493.1253(b)(2) to include "other material reflecting current practice."

materials reflecting current practice may supplement but not replace the laboratory's written procedures for testing or examining specimens.

(b) The procedure manual must include the following when applicable to the test procedure:

(1) Requirements for patient preparation; specimen collection, labeling, storage, preservation, transportation, processing, and referral; and criteria for specimen acceptability and rejection as described in § 493.1242.

(2) Microscopic examination, including the detection of inadequately prepared slides.

(3) Step-by-step performance of the procedure, including test calculations, data collection and analysis, and interpretation of results.

(4) Preparation of slides, solutions, calibrators, controls, reagents, stains, and other materials used in testing.

(5) Calibration and calibration verification procedures.

(6) The reportable range for quantitative test results for the test system as established or verified in § 493.1253.

The reportable qualitative test result for the test system as established or verified in § 493.1253.

(7) Control procedures.

(8) Corrective action to take when calibration or control results fail to meet the laboratory's criteria for acceptability.

(9) Limitations in the test methodology, including interfering substances.

(10) Reference intervals ~~(normal values).~~ or expected result(s).

(11) Imminently life-threatening test results, or ~~panic or alert values~~a critical or clinically impactful value.

(12) Pertinent literature references.

(13) The laboratory's system for entering results in the patient record and reporting patient results including, when appropriate, the protocol for reporting imminently life-threatening results, or ~~panic, or alert values~~a critical or clinically impactful value.

(14) Description of the course of action to take if a test system becomes inoperable.

(c) Manufacturer's test system instructions or operator manuals may be used, when applicable, to meet the requirements of paragraphs (b)(1) through (b)(12) of this section. Any of the items under paragraphs (b)(1) through (b)(12) of this section not provided by the manufacturer must be provided by the laboratory.

Commented [WG12]: Additional information is needed under the procedure manual requirements under § 493.1251(b) to include information related to data analysis. For example, § 493.1251(b)(3) should include data collection and analysis. Examples can be added to the SOM.

Commented [WG13]: The regulations related to the reportable range at § 493.1251(b)(6) should be clarified to address both qualitative and quantitative test results. For example, § 493.1251(b)(6) should include "The reportable range for qualitative test results…" Also, § 493.1251(b) should be updated to include a new requirement for the reportable qualitative test result for the test system as established or verified in § 493.1253.

Commented [WG14]: The CLIA regulations should be updated to include a definition of interfering substances as mentioned in § 493.1251(b)(9). Examples related to homologous genome regions can be added to the SOM.

Commented [WG15]: The use of "normal values" should be replaced with "expected result(s)" at §§ 493.1251(b)(10), 493.1253(b)(1)(ii), 493.1253(b)(2)(vi), 493.1282(b)(iii), and 493.1291(d). The term "reference intervals" does not equal "normal values" for genetic and other qualitative tests.

Commented [WG16]: The use of "panic or alert values" should be replaced with "a critical or clinically impactful value" at §§ 493.1241(c)(1), 493.1251(b)(11), 493.1251(b)(13), and 493.1291(g).

Commented [WG17]: The use of "panic or alert values" should be replaced with "a critical or clinically impactful value" at §§ 493.1241(c)(1), 493.1251(b)(11), 493.1251(b)(13), and 493.1291(g).

(d) Procedures and changes in procedures must be approved, signed, and dated by the current laboratory director before use.

(e) The laboratory must maintain a copy of each procedure with the dates of initial use and discontinuance as described in § 493.1105(a)(2).

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

§ 493.1252 Standard: Test systems, equipment, instruments, reagents, materials, and supplies.

Commented [WG18]: The CLIA regulations under § 493.1252 should be updated to include new technologies, data exchange, analysis, and remote/distributive work requirements. The November 2022 CLIAC recommendation to modify the definition of a "test system" to include "…software algorithms, data exchange and analysis procedures, and other components needed to perform an assay or examination and generate test results and report" should be incorporated into this section.

(a) Test systems must be selected by the laboratory. The testing must be performed following the manufacturer's instructions and in a manner that provides test results within the laboratory's stated performance specifications for each test system as determined under § 493.1253.

(b) The laboratory must define criteria for those conditions that are essential for proper storage of reagents and specimens, accurate and reliable test system operation, and test result reporting. The criteria must be consistent with the manufacturer's instructions, if provided. These conditions must be monitored and documented and, if applicable, include the following:

(1) Water quality.

(2) Temperature.

(3) Humidity.

(4) Protection of equipment and instruments from fluctuations and interruptions in electrical current that adversely affect patient test results and test reports.

(c) Reagents, solutions, culture media, control materials, calibration materials, and other supplies, as appropriate, must be labeled to indicate the following:

(1) Identity and when significant, titer, strength or concentration.

(2) Storage requirements.

(3) Preparation and expiration dates.

(4) Other pertinent information required for proper use.

(d) Reagents, solutions, culture media, control materials, calibration materials, and other supplies must not be used when they have exceeded their expiration date, have deteriorated, or are of substandard quality.

(e) Components of reagent kits of different lot numbers must not be interchanged unless otherwise specified by the manufacturer.

§ 493.1253 Standard: Establishment and verification of performance specifications.

(a) ***Applicability.*** Laboratories are not required to verify or establish performance specifications for any test system used by the laboratory before April 24, 2003.

(b)

(1) ***Verification of performance specifications.*** Each laboratory that introduces an unmodified, FDA-cleared or approved test system must do the following before reporting patient test results:

(i) Demonstrate that it can obtain performance specifications comparable to those established by the manufacturer for the following performance characteristics:

(A) Accuracy.

(B) Precision.

(C) Reportable range of test results for the test system.

(ii) Verify that the manufacturer's reference intervals ~~(normal values)~~or expected result(s) are appropriate for the laboratory's patient population.

(2) ***Establishment of performance specifications.*** Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house or laboratory developed tests and standardized methods such as text book procedures, or other materials reflecting current practice), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable:

(i) Accuracy.

(ii) Precision.

(iii) Analytical sensitivity.

(iv) Analytical specificity to include interfering substances.

(v) Reportable range of test results for the test system.

(vi) Reference intervals ~~(normal values).~~or expected result(s).

(vii) Any other performance characteristic required for test performance.

(3) ***Determination of calibration and control procedures.*** The laboratory must determine the test system's calibration procedures and control procedures based upon the performance specifications verified or established under paragraph (b)(1) or (b)(2) of this section.

(c) ***Documentation.*** The laboratory must document all activities specified in this section.

Commented [WG19]: The use of "normal values" should be replaced with "expected result(s)" at §§ 493.1251(b)(10), 493.1253(b)(1)(ii), 493.1253(b)(2)(vi), 493.1282(b)(iii), and 493.1291(d). The term "reference intervals" does not equal "normal values" for genetic and other qualitative tests.

Commented [WG20]: The regulations related to test systems not subject to FDA clearance or approval at § 493.1253(b)(2) should be updated to include laboratory developed test terminology in addition to "in-house" methods.

Commented [WG21]: The procedure manual requirement § 493.1251(a) should be updated to remove the reference to "Textbooks" and replace it with "Other materials reflecting current practice." This change should also be made at § 493.1253(b)(2) to include "other material reflecting current practice."

Commented [WG22]: The CLIA regulations and SOM should be updated to include harmonized definitions for the terms used in § 493.1253(b)(i-vii) so they apply to qualitative and quantitative tests.

Commented [WG23]: The use of "normal values" should be replaced with "expected result(s)" at §§ 493.1251(b)(10), 493.1253(b)(1)(ii), 493.1253(b)(2)(vi), 493.1282(b)(iii), and 493.1291(d). The term "reference intervals" does not equal "normal values" for genetic and other qualitative tests.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

§ 493.1254 Standard: Maintenance and function checks.

(a) ***Unmodified manufacturer's equipment, instruments, or test systems.*** The laboratory must perform and document the following:

(1) Maintenance as defined by the manufacturer and with at least the frequency specified by the manufacturer.

(2) Function checks as defined by the manufacturer and with at least the frequency specified by the manufacturer. Function checks must be within the manufacturer's established limits before patient testing is conducted.

(b) ***Equipment, instruments, or test systems developed in-house, commercially available and modified by the laboratory, or maintenance and function check protocols are not provided by the manufacturer.*** The laboratory must do the following:

(1)

(i) Establish a maintenance protocol that ensures equipment, instrument, and test system performance that is necessary for accurate and reliable test results and test result reporting.

(ii) Perform and document the maintenance activities specified in paragraph (b)(1)(i) of this section.

(2)

(i) Define a function check protocol that ensures equipment, instrument, and test system performance that is necessary for accurate and reliable test results and test result reporting.

(ii) Perform and document the function checks, including background or baseline checks, specified in paragraph (b)(2)(i) of this section. Function checks must be within the laboratory's established limits before patient testing is conducted.

§ 493.1255 Standard: Calibration and calibration verification procedures.

Calibration and calibration verification procedures are required to substantiate the continued accuracy of the test system throughout the laboratory's reportable range of test results for the test system. Unless otherwise specified in this subpart, for each applicable test system the laboratory must do the following:

(a) Perform and document calibration procedures -

(1) Following the manufacturer's test system instructions, using calibration materials provided or specified, and with at least the frequency recommended by the manufacturer;

(2) Using the criteria verified or established by the laboratory as specified in § 493.1253(b)(3) -

(i) Using calibration materials appropriate for the test system and, if possible, traceable to a reference method or reference material of known value; and

(ii) Including the number, type, and concentration of calibration materials, as well as acceptable limits for and the frequency of calibration; and

(3) Whenever calibration verification fails to meet the laboratory's acceptable limits for calibration verification.

(b) Perform and document calibration verification procedures -

(1) Following the manufacturer's calibration verification instructions;

(2) Using the criteria verified or established by the laboratory under § 493.1253(b)(3) -

(i) Including the number, type, and concentration of the materials, as well as acceptable limits for calibration verification; and

(ii) Including, as applicable to the test system, at least a minimal ~~(or zero)~~ value, a mid-point value, and a maximum value near the upper limit of the range to verify the laboratory's reportable range of test results for the test system; and

(3) At least once every 6 months and whenever any of the following occur:

(i) A complete change of reagents for a procedure is introduced, unless the laboratory can demonstrate that changing reagent lot numbers does not affect the range used to report patient test results, and control values are not adversely affected by reagent lot number changes.

(ii) There is major preventive maintenance or replacement of critical parts that may influence test performance.

(iii) Control materials reflect an unusual trend or shift, or are outside of the laboratory's acceptable limits, and other means of assessing and correcting unacceptable control values fail to identify and correct the problem.

(iv) The laboratory's established schedule for verifying the reportable range for patient test results requires more frequent calibration verification.

§ 493.1256 Standard: Control procedures.

(a) For each test system, the laboratory is responsible for having control procedures that monitor the accuracy and precision of the complete analytic process.

Commented [WG24]: The SOM should be updated to include more guidance related to calibration verification procedures under § 493.1255(b). This should include clarification between the analytical measurement range and the reportable range.

Commented [WG25]: •The requirement for including at least a minimal (or zero) value, a mid-point value, and a maximum value near the upper limit of the range to verify the laboratory's reportable range of test results for the test system at § 493.1255(b)(2)(ii) is problematic for qualitative assays. The regulations should be clarified for qualitative assays, or the current regulations should be modified to include "as applicable to the test system." Also, many test systems do not have a "zero" value. The regulations should be updated to remove the reference to a "zero" value.

Commented [WG26]: The SOM should be updated to include more guidance on control procedures for multiplex cartridges related to § 493.1256.

(b) The laboratory must establish the number, type, and frequency of testing control materials using, if applicable, the performance specifications verified or established by the laboratory as specified in § 493.1253(b)(3).

(c) The control procedures must -

(1) Detect immediate errors that occur due to test system failure, adverse environmental conditions, and operator performance.

(2) Monitor over time the accuracy and precision of test performance that may be influenced by changes in test system performance and environmental conditions, and variance in operator performance.

(d) Unless CMS approves a procedure, specified in Appendix C of the State Operations Manual (CMS Pub. 7), that provides equivalent quality testing, the laboratory must -

(1) Perform control procedures as defined in this section unless otherwise specified in the additional specialty and subspecialty requirements at §§ 493.1261 through 493.1278.

(2) For each test system, perform control procedures using the number and frequency specified by the manufacturer or established by the laboratory when they meet or exceed the requirements in paragraph (d)(3) of this section.

(3) At least once each day patient specimens are assayed or examined perform the following for -

(i) Each quantitative procedure, include two control materials of different concentrations;

(ii) Each qualitative procedure, include a negative and positive control material;

(iii) Test procedures producing graded or titered results, include a negative control material and a control material with graded or titered reactivity, respectively;

(iv) Each test system that has an extraction phase, include two control materials, including one that is capable of detecting errors in the extraction process; and

(v) Each molecular amplification procedure, include two control materials and, if reaction inhibition is a significant source of false negative results, a control material capable of detecting the inhibition.

(4) For thin layer chromatography -

(i) Spot each plate or card, as applicable, with a calibrator containing all known substances or drug groups, as appropriate, which are identified by thin layer chromatography and reported by the laboratory; and

(ii) Include at least one control material on each plate or card, as applicable, which must be processed through each step of patient testing, including extraction processes.

Commented [WG27]: The CLIA regulations for control procedures under § 493.1256(d)(3)(i) should be updated to reflect tests such as next generation sequencing where two levels of quality control at different concentrations are not helpful.

Commented [WG28]: The specification for thin layer chromatography under § 493.1256(d)(4) should be removed from the CLIA regulations and included in the SOM.

(5) For each electrophoretic procedure include, concurrent with patient specimens, at least one control material containing the substances being identified or measured.

(6) Perform control material testing as specified in this paragraph before resuming patient testing when a complete change of reagents is introduced; major preventive maintenance is performed; or any critical part that may influence test performance is replaced.

(7) Over time, rotate control material testing among all operators who perform the test.

(8) Test control materials in the same manner as patient specimens.

(9) When using calibration material as a control material, use calibration material from a different lot number than that used to establish a cut-off value or to calibrate the test system.

(10) Establish or verify the criteria for acceptability of all control materials.

(i) When control materials providing quantitative results are used, statistical parameters (for example, mean and standard deviation) for each batch and lot number of control materials must be defined and available.

(ii) The laboratory may use the stated value of a commercially assayed control material provided the stated value is for the methodology and instrumentation employed by the laboratory and is verified by the laboratory.

(iii) Statistical parameters for unassayed control materials must be established over time by the laboratory through concurrent testing of control materials having previously determined statistical parameters.

(e) For reagent, media, and supply checks, the laboratory must do the following:

(1) Check each batch (prepared in-house), lot number (commercially prepared) and shipment of reagents, disks, stains, antisera, (except those specifically referenced in § 493.1261(a)(3)) and identification systems (systems using two or more substrates or two or more reagents, or a combination) when prepared or opened for positive and negative reactivity, as well as graded reactivity, if applicable.

(2) Each day of use (unless otherwise specified in this subpart), test staining materials for intended reactivity to ensure predictable staining characteristics. Control materials for both positive and negative reactivity must be included, as appropriate.

(3) Check fluorescent and immunohistochemical stains for positive and negative reactivity each time of use.

(4) Before, or concurrent with the initial use -

(i) Check each batch of media for sterility if sterility is required for testing;

(ii) Check each batch of media for its ability to support growth and, as appropriate, select or inhibit specific organisms or produce a biochemical response; and

(iii) Document the physical characteristics of the media when compromised and report any deterioration in the media to the manufacturer.

(5) Follow the manufacturer's specifications for using reagents, media, and supplies and be responsible for results.

(f) Results of control materials must meet the laboratory's and, as applicable, the manufacturer's test system criteria for acceptability before reporting patient test results.

(g) The laboratory must document all control procedures performed.

(h) If control materials are not available, the laboratory must have an alternative mechanism to detect immediate errors and monitor test system performance over time. The performance of alternative control procedures must be documented.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

§ 493.1261 Standard: Bacteriology.

(a) The laboratory must check the following for positive and negative reactivity using control organisms:

(1) Each day of use for beta-lactamase methods other than Cefinase™.

(2) Each week of use for Gram stains.

(3) When each batch (prepared in-house), lot number (commercially prepared), and shipment of antisera is prepared or opened, and once every 6 months thereafter.

(b) For antimicrobial susceptibility tests, the laboratory must check each batch of media and each lot number and shipment of antimicrobial agent(s) before, or concurrent with, initial use, using approved control organisms.

(1) Each day tests are performed, the laboratory must use the appropriate control organism(s) to check the procedure.

(2) The laboratory's zone sizes or minimum inhibitory concentration for control organisms must be within established limits before reporting patient results.

(c) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1262 Standard: Mycobacteriology.

(a) Each day of use, the laboratory must check all reagents or test procedures used for mycobacteria identification with at least one acid-fast organism that produces a positive reaction and an acid-fast organism that produces a negative reaction.

Commented [WG29]: The specialty and subspecialty sections starting § 493.1261 through § 493.1278 should be updated to address obsolete regulations and update the regulations to incorporate changes in technology.

- •Generalized statements should be developed for each specialty and subspecialty section to account for new test technologies and the need for remote test analysis and reporting of test results.
- •A crosswalk should be performed in these sections with the general considerations section.
- • The SOM should include information specific to each specialty or subspecialty.
- •Proposed changes to histocompatibility (§ 493.1278)are included in the Clinical Laboratory Improvement Amendments of 1988 (CLIA) Fees; Histocompatibility, Personnel, and Alternative Sanctions for Certificate of Waiver Laboratories. Additional discussion related to histocompatibility is out of scope.

(b) For antimycobacterial susceptibility tests, the laboratory must check each batch of media and each lot number and shipment of antimycobacterial agent(s) before, or concurrent with, initial use, using an appropriate control organism(s).

(1) The laboratory must establish limits for acceptable control results.

(2) Each week tests are performed, the laboratory must use the appropriate control organism(s) to check the procedure.

(3) The results for the control organism(s) must be within established limits before reporting patient results.

(c) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1263 Standard: Mycology.

(a) The laboratory must check each batch (prepared in-house), lot number (commercially prepared), and shipment of lactophenol cotton blue when prepared or opened for intended reactivity with a control organism(s).

(b) For antifungal susceptibility tests, the laboratory must check each batch of media and each lot number and shipment of antifungal agent(s) before, or concurrent with, initial use, using an appropriate control organism(s).

(1) The laboratory must establish limits for acceptable control results.

(2) Each day tests are performed, the laboratory must use the appropriate control organism(s) to check the procedure.

(3) The results for the control organism(s) must be within established limits before reporting patient results.

(c) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1264 Standard: Parasitology.

(a) The laboratory must have available a reference collection of slides or photographs and, if available, gross specimens for identification of parasites and use these references in the laboratory for appropriate comparison with diagnostic specimens.

(b) The laboratory must calibrate and use the calibrated ocular micrometer for determining the size of ova and parasites, if size is a critical parameter.

(c) Each month of use, the laboratory must check permanent stains using a fecal sample control material that will demonstrate staining characteristics.

(d) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1265 Standard: Virology.

(a) When using cell culture to isolate or identify viruses, the laboratory must simultaneously incubate a cell substrate control or uninoculated cells as a negative control material.

(b) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1267 Standard: Routine chemistry.

For blood gas analyses, the laboratory must perform the following:

(a) Calibrate or verify calibration according to the manufacturer's specifications and with at least the frequency recommended by the manufacturer.

(b) Test one sample of control material each 8 hours of testing using a combination of control materials that include both low and high values on each day of testing.

(c) Test one sample of control material each time specimens are tested unless automated instrumentation internally verifies calibration at least every 30 minutes.

(d) Document all control procedures performed, as specified in this section.

§ 493.1269 Standard: Hematology.

(a) For manual cell counts performed using a hemocytometer -

(1) One control material must be tested each 8 hours of operation; and

(2) Patient specimens and control materials must be tested in duplicate.

(b) For all nonmanual coagulation test systems, the laboratory must include two levels of control material each 8 hours of operation and each time a reagent is changed.

(c) For manual coagulation tests -

(1) Each individual performing tests must test two levels of control materials before testing patient samples and each time a reagent is changed; and

(2) Patient specimens and control materials must be tested in duplicate.

(d) The laboratory must document all control procedures performed, as specified in this section.

§ 493.1271 Standard: Immunohematology.

(a) ***Patient testing.***

(1) The laboratory must perform ABO grouping, D(Rho) typing, unexpected antibody detection, antibody identification, and compatibility testing by following the manufacturer's instructions, if provided, and as applicable, 21 CFR 606.151(a) through (e).

(2) The laboratory must determine ABO group by concurrently testing unknown red cells with, at a minimum, anti-A and anti-B grouping reagents. For confirmation of ABO group, the unknown serum must be tested with known A1 and B red cells.

(3) The laboratory must determine the D(Rho) type by testing unknown red cells with anti-D (anti-Rho) blood typing reagent.

(b) ***Immunohematological testing and distribution of blood and blood products.*** Blood and blood product testing and distribution must comply with 21 CFR 606.100(b)(12); 606.160(b)(3)(ii) and (b)(3)(v); 610.40; 640.5(a), (b), (c), and (e); and 640.11(b).

(c) ***Blood and blood products storage.*** Blood and blood products must be stored under appropriate conditions that include an adequate temperature alarm system that is regularly ~~inspected~~tested.

Commented [WG30]: The regulations related to immunohematology at § 493.1271(c) should be updated to change "inspected" to "tested." Also, the CLIA regulations at § 493.1271(c)(2) should be updated to "Alarm system testing must be documented."

(1) An audible alarm system must monitor proper blood and blood product storage temperature over a 24-hour period.

(2) ~~Inspections~~ Alarm system testing~~of the alarm system~~ must be documented.

(d) ***Retention of samples of transfused blood.*** According to the laboratory's established procedures, samples of each unit of transfused blood must be retained for further testing in the event of transfusion reactions. The laboratory must promptly dispose of blood not retained for further testing that has passed its expiration date.

(e) ***Investigation of transfusion reactions.***

(1) According to its established procedures, the laboratory that performs compatibility testing, or issues blood or blood products, must promptly investigate all transfusion reactions occurring in facilities for which it has investigational responsibility and make recommendations to the medical staff regarding improvements in transfusion procedures.

(2) The laboratory must document, as applicable, that all necessary remedial actions are taken to prevent recurrences of transfusion reactions and that all policies and procedures are reviewed to assure they are adequate to ensure the safety of individuals being transfused.

(f) ***Documentation.*** The laboratory must document all control procedures performed, as specified in this section.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

§ 493.1273 Standard: Histopathology.

(a) As specified in § 493.1256(e)(3), fluorescent and immunohistochemical stains must be checked for positive and negative reactivity each time of use. For all other differential or special stains, a control slide of known reactivity must be stained with each patient slide or group of patient slides. Reaction(s) of the control slide with each special stain must be documented.

(b) The laboratory must retain stained slides, specimen blocks, and tissue remnants as specified in § 493.1105. The remnants of tissue specimens must be maintained in a manner that ensures proper preservation of the tissue specimens until the portions submitted for microscopic examination have been examined and a diagnosis made by an individual qualified under § 493.1449(b), (l), or (m).

(c) An individual who has successfully completed a training program in neuromuscular pathology approved by HHS may examine and provide reports for neuromuscular pathology.

(d) Tissue pathology reports must be signed by an individual qualified as specified in paragraph (b) or, as appropriate, paragraph (c) of this section. If a computer report is generated with an electronic signature, it must be authorized by the individual who performed the examination and made the diagnosis.

(e) The laboratory must use acceptable terminology of a recognized system of disease nomenclature in reporting results.

(f) The laboratory must document all control procedures performed, as specified in this section.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

§ 493.1274 Standard: Cytology.

Commented [WG31]: The regulations related to cytology at § 493.1274 should be clarified to account for the use of immunocytochemical slides in workload recording.

(a) ***Cytology slide examination site.*** All cytology slide preparations must be evaluated on the premises of a laboratory certified to conduct testing in the subspecialty of cytology.

(b) ***Staining.*** The laboratory must have available and follow written policies and procedures for each of the following, if applicable:

(1) All gynecologic slide preparations must be stained using a Papanicolaou or modified Papanicolaou staining method.

(2) Effective measures to prevent cross-contamination between gynecologic and nongynecologic specimens during the staining process must be used.

(3) Nongynecologic specimens that have a high potential for cross-contamination must be stained separately from other nongynecologic specimens, and the stains must be filtered or changed following staining.

(c) ***Control procedures.*** The laboratory must establish and follow written policies and procedures for a program designed to detect errors in the performance of cytologic examinations and the reporting of results. The program must include the following:

(1) A review of slides from at least 10 percent of the gynecologic cases interpreted by individuals qualified under § 493.1469 or § 493.1483, to be negative for epithelial cell abnormalities and other malignant neoplasms (as defined in paragraph (e)(1) of this section).

(i) The review must be performed by an individual who meets one of the following qualifications:

(A) A technical supervisor qualified under § 493.1449(b) or (k).

(B) A cytology general supervisor qualified under § 493.1469.

(C) A cytotechnologist qualified under § 493.1483 who has the experience specified in § 493.1469(b)(2).

(ii) Cases must be randomly selected from the total caseload and include negatives and those from patients or groups of patients that are identified as having a higher than average probability of developing cervical cancer based on available patient information.

(iii) The review of those cases selected must be completed before reporting patient results.

(2) Laboratory comparison of clinical information, when available, with cytology reports and comparison of all gynecologic cytology reports with a diagnosis of high-grade squamous intraepithelial lesion (HSIL), adenocarcinoma, or other malignant neoplasms with the histopathology report, if available in the laboratory (either on-site or in storage), and determination of the causes of any discrepancies.

(3) For each patient with a current HSIL, adenocarcinoma, or other malignant neoplasm, laboratory review of all normal or negative gynecologic specimens received within the previous 5 years, if available in the laboratory (either on-site or in storage). If significant discrepancies are found that will affect current patient care, the laboratory must notify the patient's physician and issue an amended report.

(4) Records of initial examinations and all rescreening results must be documented.

(5) An annual statistical laboratory evaluation of the number of -

Commented [WG32]: The regulations related to the requirement for an annual statistical laboratory evaluation for cytology at § 493.1274(c)(5) should be removed.

(i) Cytology cases examined;

(ii) Specimens processed by specimen type;

(iii) Patient cases reported by diagnosis (including the number reported as unsatisfactory for diagnostic interpretation);

(iv) Gynecologic cases with a diagnosis of HSIL, adenocarcinoma, or other malignant neoplasm for which histology results were available for comparison;

(v) Gynecologic cases where cytology and histology are discrepant; and

(vi) Gynecologic cases where any rescreen of a normal or negative specimen results in reclassification as low-grade squamous intraepithelial lesion (LSIL), HSIL, adenocarcinoma, or other malignant neoplasms.

(6) An evaluation of the case reviews of each individual examining slides against the laboratory's overall statistical values, documentation of any discrepancies, including reasons for the deviation and, if appropriate, corrective actions taken.

(d) ***Workload limits.*** The laboratory must establish and follow written policies and procedures that ensure the following:

(1) The technical supervisor establishes a maximum workload limit for each individual who performs primary screening.

(i) The workload limit is based on the individual's performance using evaluations of the following:

(A) Review of 10 percent of the cases interpreted as negative for the conditions defined in paragraph (e)(1) of this section.

(B) Comparison of the individual's interpretation with the technical supervisor's confirmation of patient smears specified in paragraphs (e)(1) and (e)(3) of this section.

(ii) Each individual's workload limit is reassessed at least every 6 months and adjusted when necessary.

(2) The maximum number of slides examined by an individual in each 24-hour period does not exceed 100 slides (one patient specimen per slide; gynecologic, nongynecologic, or both) irrespective of the site or laboratory. This limit represents an absolute maximum number of slides and must not be employed as an individual's performance target. In addition -

(i) The maximum number of 100 slides is examined in no less than an 8-hour workday;

(ii) For the purposes of establishing workload limits for individuals examining slides in less than an 8-hour workday (includes full-time employees with duties other than slide examination and part-time employees), a period of 8 hours is used to prorate the number of slides that may be examined. The formula -

$$\frac{\text{Number of hours examining slides} \times 100}{8}$$

is used to determine maximum slide volume to be examined;

(iii) Nongynecologic slide preparations made using liquid-based slide preparatory techniques that result in cell dispersion over one-half or less of the total available slide may be counted as one-half slide; and

(iv) Technical supervisors who perform primary screening are not required to include tissue pathology slides and previously examined cytology slides (gynecologic and nongynecologic) in the 100 slide workload limit.

(3) The laboratory must maintain records of the total number of slides examined by each individual during each 24-hour period and the number of hours spent examining slides in the 24-hour period irrespective of the site or laboratory.

(4) Records are available to document the workload limit for each individual.

(e) ***Slide examination and reporting.*** The laboratory must establish and follow written policies and procedures that ensure the following:

(1) A technical supervisor confirms each gynecologic slide preparation interpreted to exhibit reactive or reparative changes or any of the following epithelial cell abnormalities:

(i) Squamous cell.

(A) Atypical squamous cells of undetermined significance (ASC-US) or cannot exclude HSIL (ASC-H).

(B) LSIL-Human papillomavirus (HPV)/mild dysplasia/cervical intraepithelial neoplasia 1 (CIN 1).

(C) HSIL-moderate and severe dysplasia, carcinoma in situ (CIS)/CIN 2 and CIN 3 or with features suspicious for invasion.

(D) Squamous cell carcinoma.

(ii) Glandular cell.

(A) Atypical cells not otherwise specified (NOS) or specified in comments (endocervical, endometrial, or glandular).

(B) Atypical cells favor neoplastic (endocervical or glandular).

(C) Endocervical adenocarcinoma in situ.

(D) Adenocarcinoma endocervical, adenocarcinoma endometrial, adenocarcinoma extrauterine, and adenocarcinoma NOS.

(iii) Other malignant neoplasms.

(2) The report of gynecologic slide preparations with conditions specified in paragraph (e)(1) of this section must be signed to reflect the technical supervisory review or, if a computer report is generated with signature, it must reflect an electronic signature authorized by the technical supervisor who performed the review.

(3) All nongynecologic preparations are reviewed by a technical supervisor. The report must be signed to reflect technical supervisory review or, if a computer report is generated with signature, it must reflect an electronic signature authorized by the technical supervisor who performed the review.

(4) Unsatisfactory specimens or slide preparations are identified and reported as unsatisfactory.

(5) The report contains narrative descriptive nomenclature for all results.

(6) Corrected reports issued by the laboratory indicate the basis for correction.

(f) ***Record and slide retention.***

(1) The laboratory must retain all records and slide preparations as specified in § 493.1105.

(2) Slides may be loaned to proficiency testing programs in lieu of maintaining them for the required time period, provided the laboratory receives written acknowledgment of the receipt of slides by the proficiency testing program and maintains the acknowledgment to document the loan of these slides.

(3) Documentation of slides loaned or referred for purposes other than proficiency testing must be maintained.

(4) All slides must be retrievable upon request.

(g) ***Automated and semi-automated screening devices.*** When performing evaluations using automated and semi-automated screening devices, the laboratory must follow manufacturer's instructions for preanalytic, analytic, and postanalytic phases of testing, as applicable, and meet the applicable requirements of this subpart K.

(h) ***Documentation.*** The laboratory must document all control procedures performed, as specified in this section.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

§ 493.1276 Standard: Clinical cytogenetics.

(a) The laboratory must have policies and procedures for ensuring accurate and reliable patient specimen identification during the process of accessioning, cell preparation, photographing or other image reproduction technique, photographic printing, and reporting and storage of results, karyotypes, and photographs.

(b) The laboratory must have records that document the following:

(1) The media used, reactions observed, number of cells counted, number of cells karyotyped, number of chromosomes counted for each metaphase spread, and the quality of the banding.

(2) The resolution is appropriate for the type of tissue or specimen and the type of study required based on the clinical information provided to the laboratory.

(3) An adequate number of karyotypes are prepared for each patient.

(c) Determination of sex must be performed by full chromosome analysis.

(d) The laboratory report must include a summary and interpretation of the observations, number of cells counted and analyzed, and use the International System for Human Cytogenetic Nomenclature.

(e) The laboratory must document all control procedures performed, as specified in this section.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

§ 493.1278 Standard: Histocompatibility.

Commented [WG33]: Note: Proposed changes to histocompatibility are included in the proposed rule. Additional discussion on this section is out of scope. https://www.federalregister.gov/documents/2022/07/26/2022-15300/clinical-laboratory-improvement-amendments-of-1988-clia-fees-histocompatibility-personnel-and

(a) ***General.*** The laboratory must meet the following requirements:

(1) An audible alarm system must be used to monitor the storage temperature of specimens (donor and beneficiary) and reagents. The laboratory must have an emergency plan for alternate storage.

(2) All patient specimens must be easily retrievable.

(3) Reagent typing sera inventory prepared in-house must indicate source, bleeding date and identification number, reagent specificity, and volume remaining.

(4) If the laboratory uses immunologic reagents (for example, antibodies, antibody-coated particles, or complement) to facilitate or enhance the isolation of lymphocytes, or lymphocyte subsets, the efficacy of the methods must be monitored with appropriate quality control procedures.

(5) Participate in at least one national or regional cell exchange program, if available, or develop an exchange system with another laboratory in order to validate interlaboratory reproducibility.

(b) ***HLA typing.*** The laboratory must do the following:

(1) Use a technique(s) that is established to optimally define, as applicable, HLA Class I and II specificities.

(2) HLA type all potential transplant beneficiaries at a level appropriate to support clinical transplant protocol and donor selection.

(3) HLA type cells from organ donors referred to the laboratory.

(4) Use HLA antigen terminology that conforms to the latest report of the World Health Organization (W.H.O.) Committee on Nomenclature. Potential new antigens not yet approved by this committee must have a designation that cannot be confused with W.H.O. terminology.

(5) Have available and follow written criteria for the following:

(i) The preparation of cells or cellular extracts (for example, solubilized antigens and nucleic acids), as applicable to the HLA typing technique(s) performed.

(ii) Selecting typing reagents, whether prepared in-house or commercially.

(iii) Ensuring that reagents used for typing are adequate to define all HLA-A, B and DR specificities that are officially recognized by the most recent W.H.O. Committee on Nomenclature and for which reagents are readily available.

(iv) The assignment of HLA antigens.

(v) When antigen redefinition and retyping are required.

(6) Check each HLA typing by testing, at a minimum the following:

(i) A positive control material.

(ii) A negative control material in which, if applicable to the technique performed, cell viability at the end of incubation is sufficient to permit accurate interpretation of results. In assays in which cell viability is not required, the negative control result must be sufficiently different from the positive control result to permit accurate interpretation of results.

(iii) Positive control materials for specific cell types when applicable (that is, T cells, B cells, and monocytes).

(c) ***Disease-associated studies.*** The laboratory must check each typing for disease-associated HLA antigens using control materials to monitor the test components and each phase of the test system to ensure acceptable performance.

(d) ***Antibody Screening.*** The laboratory must do the following:

(1) Use a technique(s) that detects HLA-specific antibody with a specificity equivalent or superior to that of the basic complement-dependent microlymphocytotoxicity assay.

(2) Use a method that distinguishes antibodies to HLA Class II antigens from antibodies to Class I antigens to detect antibodies to HLA Class II antigens.

(3) Use a panel that contains all the major HLA specificities and common splits. If the laboratory does not use commercial panels, it must maintain a list of individuals for fresh panel bleeding.

(4) Make a reasonable attempt to have available monthly serum specimens for all potential transplant beneficiaries for periodic antibody screening and crossmatch.

(5) Have available and follow a written policy consistent with clinical transplant protocols for the frequency of screening potential transplant beneficiary sera for preformed HLA-specific antibodies.

(6) Check each antibody screening by testing, at a minimum the following:

(i) A positive control material containing antibodies of the appropriate isotype for the assay.

(ii) A negative control material.

(7) As applicable, have available and follow written criteria and procedures for antibody identification to the level appropriate to support clinical transplant protocol.

(e) ***Crossmatching.*** The laboratory must do the following:

(1) Use a technique(s) documented to have increased sensitivity in comparison with the basic complement-dependent microlymphocytotoxicity assay.

(2) Have available and follow written criteria for the following:

(i) Selecting appropriate patient serum samples for crossmatching.

(ii) The preparation of donor cells or cellular extracts (for example, solubilized antigens and nucleic acids), as applicable to the crossmatch technique(s) performed.

(3) Check each crossmatch and compatibility test for HLA Class II antigenic differences using control materials to monitor the test components and each phase of the test system to ensure acceptable performance.

(f) ***Transplantation.*** Laboratories performing histocompatibility testing for transfusion and transplantation purposes must do the following:

(1) Have available and follow written policies and protocols specifying the histocompatibility testing (that is, HLA typing, antibody screening, compatibility testing and crossmatching) to be performed for each type of cell, tissue or organ to be transfused or transplanted. The laboratory's policies must include, as applicable -

(i) Testing protocols for cadaver donor, living, living-related, and combined organ and tissue transplants;

(ii) Testing protocols for patients at high risk for allograft rejection; and

(iii) The level of testing required to support clinical transplant protocols (for example, antigen or allele level).

(2) For renal allotransplantation and combined organ and tissue transplants in which a kidney is to be transplanted, have available results of final crossmatches before the kidney is transplanted.

(3) For nonrenal transplantation, if HLA testing and final crossmatches were not performed prospectively because of an emergency situation, the laboratory must document the circumstances, if known, under which the emergency transplant was performed, and records of the transplant must reflect any information provided to the laboratory by the patient's physician.

(g) ***Documentation.*** The laboratory must document all control procedures performed, as specified in this section.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

§ 493.1281 Standard: Comparison of test results.

(a) If a laboratory performs the same test using different methodologies or instruments, or performs the same test at multiple testing sites, the laboratory must have a system that twice a year evaluates and defines the relationship between test results using the different methodologies, instruments, or testing sites.

(b) The laboratory must have a system to identify and assess patient test results that appear inconsistent with the following relevant criteria, when available:

(1) Patient age.

(2) Sex.

(3) Diagnosis or pertinent clinical data.

(4) Distribution of patient test results.

(5) Relationship with other test parameters.

(c) The laboratory must document all test result comparison activities.

§ 493.1282 Standard: Corrective actions.

(a) Corrective action policies and procedures must be available and followed as necessary to maintain the laboratory's operation for testing patient specimens in a manner that ensures accurate and reliable patient test results and reports.

(b) The laboratory must document all corrective actions taken, including actions taken when any of the following occur:

(1) Test systems do not meet the laboratory's verified or established performance specifications, as determined in § 493.1253(b), which include but are not limited to -

Commented [WG34]: The SOM should be updated to clarify the comparison of test results requirements described under § 493.1281. The update should include:
- Information on what is considered as the same test using different methodologies or instruments.
- Examples of what is considered when something is regarded as the same analyte, e.g., different specimen types, different analytic targets (troponin I versus T or HS troponin), different analytic or therapeutic ranges, tests with different sensitivities, and qualitative versus quantitative tests.

(i) Equipment or methodologies that perform outside of established operating parameters or performance specifications;

(ii) Patient test values that are outside of the laboratory's reportable range of test results for the test system; and

(iii) When the laboratory determines that the reference intervals ~~(normal values)~~or expected result(s) for a test procedure are inappropriate for the laboratory's patient population.

(2) Results of control or calibration materials, or both, fail to meet the laboratory's established criteria for acceptability. All patient test results obtained in the unacceptable test run and since the last acceptable test run must be evaluated to determine if patient test results have been adversely affected. The laboratory must take the corrective action necessary to ensure the reporting of accurate and reliable patient test results.

(3) The criteria for proper storage of reagents and specimens, as specified under § 493.1252(b), are not met.

§ 493.1283 Standard: Test records.

(a) The laboratory must maintain an information or record system that includes the following:

(1) The positive identification of the specimen.

(2) The date and time of specimen receipt into the laboratory.

(3) The condition and disposition of specimens that do not meet the laboratory's criteria for specimen acceptability.

(4) The records and dates of all specimen testing, including the identity of the personnel who performed the test(s).

(b) Records of patient testing including, if applicable, instrument printouts, must be retained.

§ 493.1289 Standard: Analytic systems quality assessment.

(a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and when indicated, correct problems identified in the analytic systems specified in §§ 493.1251 through 493.1283.

(b) The analytic systems quality assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of analytic systems quality assessment reviews with appropriate staff.

(c) The laboratory must document all analytic systems quality assessment activities.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

Commented [WG35]: The use of "normal values" should be replaced with "expected result(s)" at §§ 493.1251(b)(10), 493.1253(b)(1)(ii), 493.1253(b)(2)(vi), 493.1282(b)(iii), and 493.1291(d). The term "reference intervals" does not equal "normal values" for genetic and other qualitative tests.

Commented [WG36]: The regulations related to the requirement for test records at § 493.1283 should be updated to include patient confidentiality requirements.

Commented [WG37]: The regulations related to the requirement for test records at § 493.1283(a) should be updated to include a requirement for specimen collection date and time, as some assays have a very short specimen viability window.

Postanalytic Systems

§ 493.1290 Condition: Postanalytic systems.

Each laboratory that performs nonwaived testing must meet the applicable postanalytic systems requirements in § 493.1291 unless HHS approves a procedure, specified in Appendix C of the State Operations Manual (CMS Pub. 7) that provides equivalent quality testing. The laboratory must monitor and evaluate the overall quality of the postanalytic systems and correct identified problems as specified in § 493.1299 for each specialty and subspecialty of testing performed.

§ 493.1291 Standard: Test report.

(a) The laboratory must have an adequate manual or electronic system(s) in place to ensure test results and other patient-specific data are accurately and reliably sent from the point of data entry (whether interfaced or entered manually) to final report destination, in a timely manner. This includes the following:

(1) Results reported from calculated data.

(2) Results and patient-specific data electronically reported to network or interfaced systems.

(3) Manually transcribed or electronically transmitted results and patient-specific information reported directly or upon receipt from outside referral laboratories, satellite or point-of-care testing locations.

(b) Test report information maintained as part of the patient's chart or medical record must be readily available to the laboratory and to CMS or a CMS agent upon request.

(c) The test report must indicate the following:

(1) For positive patient identification, either the patient's name and identification number, or a unique patient identifier and identification number.

(2) The name and address of the laboratory location where the test was performed.

(3) The test report date.

(4) The test performed.

(5) Specimen source, when appropriate.

(6) The test result and, if applicable, the units of measurement or interpretation, or both.

(7) Any information regarding the condition and disposition of specimens that do not meet the laboratory's criteria for acceptability.

(d) Pertinent “reference intervals” or ~~“normal” values~~expected result(s), as determined by the laboratory performing the tests, must be available to the authorized person who ordered the tests and, if applicable, the individual responsible for using the test results.

Commented [WG38]: The regulations related to the requirement for a test report at § 493.1291 should be clarified to include requirements for new processes, such as the distributive testing process and associated activities that can be performed as part of the testing process. The SOM should be updated to include examples of activities.

Commented [WG39]: The CLIA regulations should define “test report” to clarify that releasing information through other means, such as a patient portal or EHR, should have the same requirements as the “test report” requirements currently in CLIA.

Commented [WG40]: The regulations related to the requirement for the name and address of the laboratory location where the test was performed at § 493.1291(c)(2) should be updated to “location(s)” and clarified to allow for laboratories to use a code for testing address if performed in a home office.

Commented [WG41]: The “test report date” should be clarified at §493.1291(c)(3) to distinguish from the date all results are final or if each date that results are released is required.

Commented [WG42]: The use of “normal values” should be replaced with “expected result(s)” at §§ 493.1251(b)(10), 493.1253(b)(1)(ii), 493.1253(b)(2)(vi), 493.1282(b)(iii), and 493.1291(d). The term “reference intervals” does not equal “normal values” for genetic and other qualitative tests.

(e) The laboratory must, upon request, make available to clients a list of test methods employed by the laboratory and, as applicable, the performance specifications established or verified as specified in § 493.1253. In addition, information that may affect the interpretation of test results, for example test interferences, must be provided upon request. Pertinent updates on testing information must be provided to clients whenever changes occur that affect the test results or interpretation of test results.

(f) Except as provided in § 493.1291(l), test results must be released only to authorized persons and, if applicable, the persons responsible for using the test results and the laboratory that initially requested the test.

(g) The laboratory must immediately alert the individual or entity requesting the test and, if applicable, the individual responsible for using the test results when any test result indicates an imminently life-threatening condition, or ~~panic or alert values~~a critical or clinically impactful value.

(h) When the laboratory cannot report patient test results within its established time frames, the laboratory must determine, based on the urgency of the patient test(s) requested, the need to notify the appropriate individual(s) of the delayed testing.

(i) If a laboratory refers patient specimens for testing -

(1) The referring laboratory must not revise results or information directly related to the interpretation of results provided by the testing laboratory;

(2) The referring laboratory may permit each testing laboratory to send the test result directly to the authorized person who initially requested the test. The referring laboratory must retain or be able to produce an exact duplicate of each testing laboratory's report; and

(3) The authorized person who orders a test must be notified by the referring laboratory of the name and address of each laboratory location where the test was performed.

(j) All test reports or records of the information on the test reports must be maintained by the laboratory in a manner that permits ready identification and timely accessibility.

(k) When errors in the reported patient test results are detected, the laboratory must do the following:

(1) Promptly notify the authorized person ordering the test and, if applicable, the individual using the test results of reporting errors.

(2) Issue corrected reports promptly to the authorized person ordering the test and, if applicable, the individual using the test results.

(3) Maintain ~~duplicates of~~ the original report, or have the ability to recreate the original report, as well as the corrected report or addendums.

(l) Upon request by a patient (or the patient's personal representative), the laboratory may provide patients, their personal representatives, and those persons specified under 45 CFR

Commented [WG43]: The use of "panic or alert values" should be replaced with "a critical or clinically impactful value" at §§ 493.1241(c)(1), 493.1251(b)(11), 493.1251(b)(13), and 493.1291(g).

Commented [WG44]: The regulations related to the requirement for patient specimen referral for testing at § 493.1291(i) should be updated to include requirements for testing, such as using the distributive model and utilizing electronic test records.

Commented [WG45]: The regulations related to the requirement to maintain duplicates of the original test report at § 493.1291(k)(3) should be updated to "Maintain the original report or have the ability to recreate the original report, as well as the corrected report of addendums."

164.524(c)(3)(ii), as applicable, with access to completed test reports that, using the laboratory's authentication process, can be identified as belonging to that patient.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003, as amended at 79 FR 7316, Feb. 6, 2014]

§ 493.1299 Standard: Postanalytic systems quality assessment.

(a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess and, when indicated, correct problems identified in the postanalytic systems specified in § 493.1291.

(b) The postanalytic systems quality assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of postanalytic systems quality assessment reviews with appropriate staff.

(c) The laboratory must document all postanalytic systems quality assessment activities.

[68 FR 3703, Jan. 24, 2003; 68 FR 50724, Aug. 22, 2003]

Appendix 2

Total Testing Process Review: Inclusion of Variant Classification
(Information provided by a CLIA Regulations Assessment Workgroup Member)

Problem description

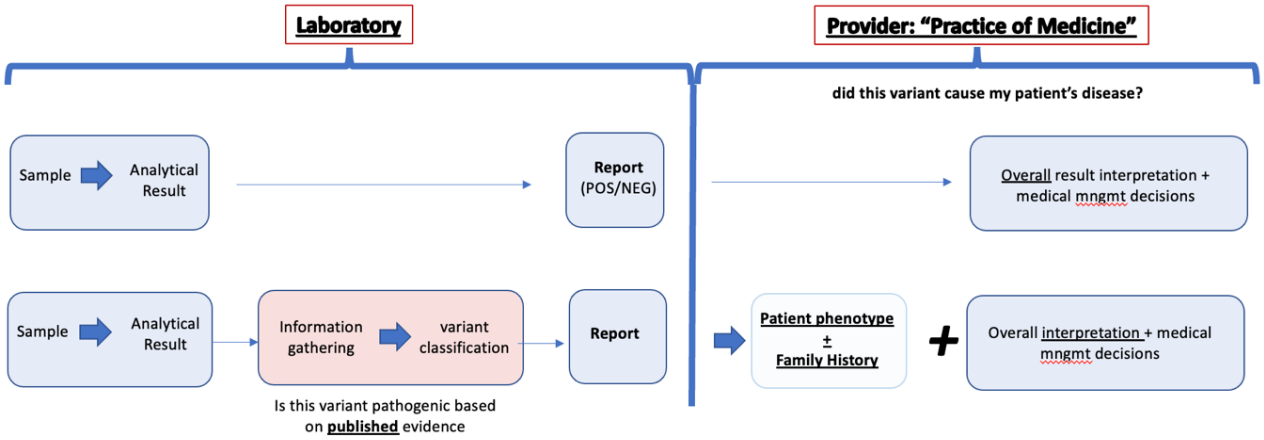

Figure 1: *The total testing process before (**top**) and after (**bottom**) the use of full gene sequencing and novel variant detection*

Historical laboratory testing process (Figure 1, TOP):

- CLIA regulations were introduced at a time when genetic testing was limited to variants that were already known to be pathogenic. At that time, the testing laboratory's role was limited to carrying out the assay, obtaining the analytical result, and reporting this to the ordering provider. When pathogenic variant(s) were detected, the result was labeled as "positive", otherwise as "negative". The provider used the laboratory result for clinical management, which included interpreting it in the context of the patient's clinical history.

Current laboratory testing process (Figure 1, BOTTOM):

- With the advent of full gene sequencing, laboratories began detecting NOVEL variants, and with that, the practice of VARIANT SCIENCE was born. Laboratory directors now needed to gather all available evidence for a given variant to determine whether it was strong enough to be classified as pathogenic. With this, laboratories introduced a tiered classification scheme, placing variants into one of five evidence-based categories (Pathogenic, Likely Pathogenic, Uncertain Significance, Likely Benign, or Benign). Positive reports were now issued for patients harboring Likely Pathogenic or Pathogenic variants.
- The process known as "variant assessment" includes two steps, which are carried out INDEPENDENT of the patient's phenotype: **(1)** evidence gathering (mining of all relevant data/evidence sources known to date). This requires scientific training, in-depth familiarity with specific resources, and search strategies. **(2)** Once all evidence has been obtained, laboratories evaluate the aggregate evidence using structured classification rules. Today, the community has largely settled on the ACMG/AMP variant classification framework. Both processes require detailed SOPs, not unlike all other, more traditional laboratory processes. Importantly, this process can be measured using the same CLIA performance metrics (including analytical sensitivity and specificity). *Important*: The skills

required to perform variant assessment and classification are usually NOT present among ordering providers.

- Some laboratories add an interpretive summary (which is a recommendation by CAP) – this entails reconciling the result with whatever clinical information was provided by the physician. This is more subjective and mimics what genetics literate providers have been doing for decades. *Important*: Because many ordering providers do not (yet) possess the necessary genetics literacy, some laboratories have been extending their role into the traditional "practice of medicine".

Summary and call to action

- The core process of variant assessment and classification (steps 1 and 2 outlined above) does NOT contain clinical interpretation (in the context of the patient's clinical findings).
- Prominent examples of misclassifying variants due to missing important evidence and/or not adhering to standard classification frameworks have led to negative patient outcomes.
- Until this process can be automated or be carried out by ordering providers, the community needs to ensure that labs, that have "organically" stepped into this space, have adequate expertise.
- It is imperative that we widen the concept of "analytical validity" beyond traditional "wet laboratory" processes.