Clinical **L**aboratory **I**mprovement **A**dvisory **C**ommittee

Summary Report

April 10, 2024

Atlanta, Georgia

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

Clinical Laboratory Improvement Advisory Committee (CLIAC) April 10, 2024, Summary Report

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RECORD OF ATTENDANCE

Committee Members Present

Dr. Jordan Laser (Chair)
Dr. Esther Babady
Mr. Michael Black
Dr. Chester Brown
Dr. Kimberle Chapin
Dr. James Crawford

Ms. Heather Duncan
Dr. Mary Edgerton
Dr. Tanner Hagelstrom
Dr. Yael Heher
Dr. David Koch
Dr. Hung Luu
Dr. Nirali Patel
Dr. Michael Pentella
Dr. Mark Tuthill
Dr. R.W. (Chip) Watkins
Ms. April Veoukas, AdvaMed (Liaison Representative)

Ex Officio Members
Dr. Collette Fitzgerald, CDC
Mr. Gregg Brandush, CMS
Dr. Courtney Lias, FDA

Designated Federal Officer
Dr. Reynolds Salerno, CDC

Executive Secretary
Ms. Heather Stang, CDC

In accordance with the provisions of Public Law 92-463, the meeting was open to the public. The meeting was attended via virtual Zoom webcast, and approximately 370 public citizens attended the meeting.

CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE (CLIAC) BACKGROUND

The Secretary of Health and Human Services (HHS) is authorized under Section 353 of the Public Health Service Act, as amended, to establish standards to ensure consistent, accurate, and reliable test results by all clinical laboratories in the United States and to establish advisory committees under Section 222.

The Clinical Laboratory Improvement Advisory Committee (CLIAC) was chartered in February 1992 to provide scientific and technical advice and guidance to the Secretary and the Assistant Secretary for Health pertaining to improvement in clinical laboratory quality and laboratory medicine practice. In addition, the Committee provides advice and guidance on specific questions related to possible revisions of the Clinical Laboratory Improvement Amendments of 1988 (CLIA) standards. Examples include providing guidance on studies designed to improve safety, effectiveness, efficiency, timeliness, equity, and patient-centeredness of laboratory services; revisions to the standards under which clinical laboratories are regulated; the impact of proposed revisions to the standards on medical and laboratory practice; and the modification of the standards and provision of non-regulatory guidelines to accommodate technological advances, such as new test methods and the electronic submission of laboratory information, and mechanisms to improve the integration of public health and clinical laboratory practices.

The Committee consists of 20 members, including the Chair. The Secretary selects members from authorities knowledgeable in the fields of microbiology, immunology, chemistry, hematology, pathology, and representatives of medical technology, public health, clinical practice, and consumers. In addition, CLIAC includes three ex officio members, or designees: the Director, Centers for Disease Control and Prevention (CDC); the Commissioner, Food and Drug Administration (FDA); the Administrator, Centers for Medicare & Medicaid Services (CMS); and such additional officers of the U.S. Government that the Secretary deems are necessary for the Committee to carry out its functions effectively. CLIAC also includes a non-voting liaison representative who is a member of AdvaMed and other non-voting liaison representatives that the Secretary deems necessary for the Committee to carry out its functions effectively.

Because of the different perspectives among its members, CLIAC is sometimes divided in the guidance and advice it offers to the Secretary. Even when all CLIAC members agree on a specific recommendation, the Secretary may not follow the Committee’s advice because of other overriding concerns. Thus, while some of the actions recommended by CLIAC may result in changes to the CLIA regulations or may lead to different actions taken by HHS, all of the Committee’s recommendations may not be accepted and acted upon by the Secretary.

CALL TO ORDER AND COMMITTEE INTRODUCTIONS

Dr. Reynolds Salerno, Designated Federal Officer (DFO), Clinical Laboratory Improvement Advisory Committee (CLIAC), and Director of the Division of Laboratory Systems (DLS), Office of Laboratory Science and Safety (OLSS), CDC, welcomed the Committee and the members of the public. Dr. Jordan Laser, CLIAC Chairperson, welcomed the Committee and reviewed the process for public comments, quorum requirements, and official CLIAC recommendations. Dr. Salerno introduced the new FDA Ex Officio, Dr. Courtney Lias. All members made self-introductions and financial disclosure statements relevant to the meeting topics. Dr. Laser stated that the agenda topics would include CDC, CMS, and FDA agency updates. In addition, the meeting would include presentations and discussions on the applicability of CLIA personnel requirements to preanalytic testing, the role of artificial intelligence and machine learning in the clinical laboratory, and the use of clinical standards to improve laboratory quality.

Recognition of Outgoing CLIAC Members ***Addendum 1***

Reynolds M. Salerno, PhD
Acting Associate Director for Laboratory Science and Safety
Acting Director, Office of Laboratory Science and Safety
Acting Director, Center for Laboratory Systems and Response
Centers for Disease Control and Prevention

Dr. Salerno recognized the CLIAC outgoing members, Dr. Mary Edgerton, Dr. Nirali Patel, Dr. Michael Pentella, and Dr. Chip Watkins, for their contributions to the Committee.

AGENCY UPDATES AND COMMITTEE DISCUSSION

Centers for Disease Control and Prevention (CDC) Update ***Addendum 2***

Collette Fitzgerald, PhD
Acting Associate Director for Science
Lead, Office of Science, Strategy and Evaluation
Center for Laboratory Systems and Response
Centers for Disease Control and Prevention

Dr. Fitzgerald began her CDC update by stating the importance of CLIAC recommendations and explaining that the update would cover six activities aligned with previous CLIAC meeting recommendations. She then provided an update on the new CLIAC Biosafety Workgroup and The Extension for Community Healthcare Outcomes (ECHO) Biosafety Project, including the upcoming meeting topics. She then discussed the newly formed CLIAC Next Generation Sequencing (NGS) Workgroup and reviewed the past and current work of the CDC-led Forum on Adoption of Standards for Laboratory Data. This forum is designed to help address CLIAC's recommendation in November 2021 related to the Systemic Harmonization and Interoperability Enhancement for Laboratory Data (SHIELD) initiative. This forum aims to provide a space for organizations to develop new relationships and discuss challenges and successes related to adopting laboratory data standards. Dr. Fitzgerald also highlighted several laboratory training and workforce development activities, including another major milestone in OneLab™ membership. As of November 2023, there were over 22,000 unique members across all OneLab™ elements. She also announced that the OneLab VR centrifuge safety practice scenario is available, and a new "Fundamentals of Handling Compressed Gas

Cylinders Safely" eLearning course was released in November 2023. Next, Dr. Fitzgerald mentioned the OneLab Summit, scheduled for April 16-18, 2024. The meeting theme will be Thrive: People, Planning, and Preparedness. She closed the presentation by discussing several activities related to partnerships, communication, and outreach, including announcing the May 22, 2024, CDC Clinical Laboratory Partners Forum, which will focus on the early diagnosis of chronic kidney disease (CKD) and how the clinical laboratory can play a central role in identifying patients at risk for CKD. She closed the presentation by highlighting DLS's activities during Medical Laboratory Professionals Week, honoring laboratory professionals' contributions to public health and patient care.

Centers for Medicare & Medicaid Services (CMS) Update ***Addendum 3***

Gregg S. Brandush, RN, JD
Director
Division of Clinical Laboratory Improvement and Quality
Quality, Safety, and Oversight Group
Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services

Mr. Brandush began by providing an update on the CMS Division of Clinical Laboratory Improvement and Quality (DCLIQ) leadership team, including two policy branches and three operations branches that have been restructured according to DCLIQ's primary activities. He then reviewed the current laboratory enrollment in the CLIA program based on certificate type, noting that Certificate of Waiver (CoW) sites continue to account for 81% of all CLIA-certified laboratories. Mr. Brandush described CMS' accomplishments for 2023 in four areas: improved processes, modernizing CLIA, assessing the use of enforcement discretion and flexibilities during the public health emergency (PHE) for COVID-19, and continued stakeholder engagement efforts, and described additional CMS accomplishments and ongoing activities related to the 2023 goals. As a follow-up from the November 2023 CLIAC meeting, he compared the top ten CLIA Certificate of Compliance deficiencies based on survey findings from October 2019 to September 2021, October 2021 to September 2023, and October 2023 to February 2024, noting that they continue to remain unchanged. Mr. Brandush introduced the CLIA goals for 2024, including reducing deficiencies commonly in the top ten every year by lowering survey inconsistencies, implementing a Lab Director University, and developing similar educational resources for other personnel positions. Mr. Brandush concluded his presentation with an overview of several new policy and administrative memos released since the last CLIAC meeting.

Food and Drug Administration (FDA) Update ***Addendum 4***

Courtney H. Lias, PhD
Acting Director
Office of In Vitro Diagnostic Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Dr. Lias began her presentation with a brief overview of the mission and key activities of the Office of In Vitro Diagnostic Devices. She discussed the recent Center for Devices and Radiological Health (CDRH) project to reclassify current class III (high risk) in vitro diagnostics (IVDs) into class II (moderate risk) since they have been available for an extended period and the risks and mitigation strategies have been determined. This

reclassification reduces the regulatory burden and provides a less complicated regulatory pathway. Next, Dr. Lias described an ongoing pilot program for companion diagnostics to ensure the availability of effective companion diagnostic tests for oncology drug treatment decisions. She then updated the Committee on the categories and number of PHE COVID-19 and mpox tests authorized as of April 1, 2024, and noted that the FDA is assessing the Avian Influenza (HPAI) A(H5N1) test detection capability and working with partners to monitor the current outbreak. Dr. Lias explained that FDA published two guidance documents to assist with transition plans for medical devices that were issued emergency use authorizations (EUAs) or fall within certain enforcement policies to support the response to the COVID-19 pandemic. She discussed the success of the Independent Test Assessment Program (ITAP) with COVID-19 tests and the current ITAP for hepatitis C virus RNA point-of-care diagnostics. She updated the Committee on recent authorizations, including one that uses artificial intelligence (AI) technology, a first-of-its-kind enzyme-linked immunosorbent assay (ELISA) intended for the qualitative determination of ADAMTS13 activity in platelet-poor human citrated plasma, a point-of-care test for the evaluation of suspected mild traumatic brain injury, and the first over-the-counter continuous glucose monitor. Dr. Lias concluded her presentation by providing helpful FDA links and contacts.

Clinical Laboratory Improvement Amendments of 1988 (CLIA) Fees; Histocompatibility, Personnel, and Alternative Sanctions for Certificate of Waiver Laboratories Final Rule

Penny Keller, BS, MB(ASCP)
Clinical Laboratory Scientist
Division of Clinical Laboratory Improvement and Quality
Quality, Safety, and Oversight Group
Centers for Clinical Standards and Quality
Centers for Medicare & Medicaid Services

Addendum 5

Ms. Penny Keller summarized the Clinical Laboratory Improvement Amendments of 1988 (CLIA) Fees, Histocompatibility, Personnel, and Alternative Sanctions for Certificate of Waiver Laboratories Final Rule that was published in the Federal Register on December 28, 2023. She presented several links for further information, including corrections to the rule. Ms. Keller explained the main features of the CLIA fees, including new definitions, new fees, and the fee schedule. She then discussed the modifications, revisions, removals, and updates to the histocompatibility regulations. Ms. Keller next detailed the new definitions added to this rule and described changes to the laboratory director, general supervisor, technical supervisor qualifications and responsibilities, and testing personnel qualifications. She summarized the algorithm from the rule to determine if a person is qualified based on their degree and credit hours for relevant classes. She finished explaining the alternative sanctions and resources for interested parties.

PRESENTATIONS AND COMMITTEE DISCUSSION

The Applicability of CLIA Personnel Requirements to Preanalytic Testing

Introduction to Topic ***Addendum 6***

Gregg S. Brandush, RN, JD
Director
Division of Clinical Laboratory Improvement and Quality
Quality, Safety, and Oversight Group
Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services

Courtney H. Lias, PhD
Acting Director
Office of In Vitro Diagnostic Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Tamara Pinkney
CLIA Program Lead/Policy Analyst
Division of Program Operations and Management
Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Mr. Brandush introduced the session, explaining the need to balance what is essential for safety while still being efficient, especially when considering preanalytic processes and high complexity testing personnel requirements. One situation described was when a test is categorized as high complexity, but has very simple preanalytical steps. Mr. Brandush asked the committee for their guidance and feedback on these nuances.

Dr. Lias noted the interesting intersection between personnel and test complexity and introduced Tamara Pinkney to give more details about the process of categorizing tests for CLIA. Ms. Pinkney explained that the reviewers scored seven criteria outlined in the CLIA regulations, each on a scale of one to three, and, based on the total score, determined if the test should be moderate or high complexity. She stated that the test is evaluated as a whole and, while the preanalytical steps are part of the review process, the test would not be considered moderate or high complexity based on those steps alone.

Public Comments
Addendum PC1 ***Addendum PC2***

Committee Discussion

- A Committee member asked for the seven criteria used by FDA when evaluating a test and what happens when the procedure of a test is very simple but the interpretation is complex. Ms. Pinkney provided the FDA CLIA Categorization website and clarified that the categorization of moderate and high complexity tests is based on the overall score. Waived tests are not determined through this process. Dr. Lias commented that FDA

examines if the interpretation of the test result itself has a complexity to it, adding that even a clinically complicated decision, if the test result itself is easy to interpret, may not lead to a higher complexity determination.

- A member asked if the current discussion was limited to high complexity tests. Mr. Brandush stated that personnel performing preanalytical testing steps for high complexity tests is the biggest concern since high complexity personnel requirements are more rigorous than for moderate complexity tests. The member commented that it is difficult to determine the personnel qualifications needed during the preanalytical steps since they can vary with each test system. The member added that the regulations may need to be revised to add the responsibility for determining personnel qualifications needed for the preanalytic phase of testing to the laboratory director.
- Multiple Committee members were concerned that it would be very difficult to determine personnel requirements for each test or to pull apart the total testing process. A member added that a CLIA requirement for personnel qualifications for preanalytic staff could exacerbate staffing challenges already experienced in the laboratory.
- A CLIAC member suggested that defining the starting point of a test may be helpful to better differentiate specimen handling from the preanalytical steps of the testing process. This definition could frame the issue and facilitate determining what personnel are needed.
- The CLIAC Chair discussed having a recommendation that some steps in a high complexity test may not require high complexity personnel and suggested the laboratory director could decide in some circumstances to use general guidance and information from the test insert.
- Members commented on the need for guidance documents and provided examples of preanalytic processes that should be defined.
- Committee members agreed that the preanalytic process should be separated from the analytic or postanalytic aspects of complex testing. The complexity of preanalytic processes should be determined by the CLIA laboratory director's assessment of the technology, risks, and other impactful factors
- A member suggested that a technical supervisor or general supervisor could perform competency assessments on the personnel who perform the preanalytic steps.

The Committee deliberated, voted, and approved the following recommendation based on the topic of *The Applicability of CLIA Personnel Requirements to Preanalytic Testing*.

Recommendation 1: CLIAC recommends that the CLIA laboratory director's responsibilities include determining the required competency of personnel who perform preanalytic phase processes, including documentation.

The Role of Artificial Intelligence and Machine Learning in the Clinical Laboratory

Introduction to Topic ***Addendum 7***

Heather L. Stang
Senior Advisor for Clinical Laboratories
Division of Laboratory Systems
Center for Laboratory Systems and Response
Office of Laboratory Science and Safety
Centers for Disease Control and Prevention

Courtney H. Lias, PhD
Acting Director
Office of In Vitro Diagnostic Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Ms. Stang introduced the topic of the role of artificial intelligence (AI) and machine learning (ML) in the clinical laboratory. She noted that AI was a CLIAC agenda topic for the first time at this meeting. Ms. Stang informed the Committee that the CLIAC Regulations Assessment Workgroup began discussions to address how the technologies that utilize AI play a role in the total testing process. During the workgroup discussions, members thought that it was essential to understand some of the basics of AI to help inform decisions, and a definition was needed to define AI as related to the clinical laboratory process to help determine CLIA applicability. She added that since the workgroup did not delve too deeply into the topic, it was brought to CLIAC. She concluded the presentation by providing an overview of the questions for CLIAC deliberation.

Dr. Lias provided an overview of AI/ML approaches at FDA's Center for Devices and Radiological Health, including the Digital Health Center of Excellence, which builds partnerships to advance healthcare by fostering responsible and high-quality digital health innovation. She noted the FDA publications Artificial Intelligence and Machine Learning in Software as a Medical Device and the Predetermined Change Control Plans for Machine Learning-Enabled Medical Devices: Guiding Principles and the draft guidance Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions as resources. Dr. Lias concluded by describing the types of devices that the FDA has reviewed.

The Basics of Artificial Intelligence and Machine Learning ***Addendum 8***

Alexis B. Carter, MD
Physician Informaticist
Molecular Genetic Pathologist
Children's Healthcare of Atlanta

Dr. Carter began by acknowledging that the presentation would cover only the basics of AI and ML; this technology has numerous applications in anatomic and clinical pathology, and pathologists must collaborate with data scientists to ensure the safe and effective use of these technologies. She defined AI as the ability of a computer or robot to perform tasks associated with intelligent beings and explained that ML is a subset of AI that allows

computers to learn without explicit programming. She added that deep learning is a type of ML designed to handle large amounts of data and often involves neural networks. Dr. Carter continued by providing definitions of other terms with examples. She compared ML and traditional statistical programming and summarized the uses and benefits of AI/ML in anatomic and clinical pathology. She discussed the challenges related to AI and ML, including data quality, ML model development problems, cybersecurity risks, lack of transparency, ethical issues, and other challenges, including the need for data scientists with experience in medicine or healthcare environments. Dr. Carter highlighted several guidelines to assist with addressing some of the challenges. She continued by providing an overview of several types of ML and discussed ML models, model evaluation strategies, the process of model development, and ML algorithms. Dr. Carter closed with a brief overview of artificial neural networks.

Public Comments

Addendum PC3 ***Addendum PC4*** ***Addendum PC5***

Committee Discussion

- A Committee member commented on the need to utilize alternate diagnoses to test against the input data in AI/ML. Dr. Carter responded that training the system with appropriate edge cases is critical. She added that obtaining the data sets needed to train the AI system entirely is difficult. She also stressed the need for IT developers who understand laboratory or medical science to have medical input as these tools are being developed.
- One member suggested that a workgroup be formed to start higher-level discussions on what questions need to be asked to assess the use of AI/ML in clinical laboratories. Another member added that this is a new opportunity to look at laboratory testing differently and identify where errors and potential for harm to the patients may occur.
- One CLIAC member suggested using the FDA test complexity process to develop a framework for assessing AI/ML systems.
- A few CLIAC members stated that since laboratory data may not be interoperable, there is a need to test the algorithm's robustness when using data imported from other sources.
- Committee members discussed the need for a workgroup and provided a list of topics for consideration, including:
    - Defining AI/ML and terminology around it in the context of laboratory medicine.
    - Crosswalking regulations and standards to determine where AI/ML aligns with current CLIA regulations.
    - Creating a best practice document or list of AI/ML resources.
    - Discussion on interoperability and data harmonization as related to AI/ML.
    - Developing a system to analyze the complexity of the AI/ML application
    - Addressing the need to establish performance specifications and continuous laboratory verification/validation of the systems.
    - Identifying data quality metrics.
    - Defining the personnel positions and requirements (i.e., data scientist)
    - Guiding where responsibility for AI/ML ends and responsibility for medical practitioners begins.
    - Learning from other medical disciplines (e.g., imaging) and looking at how AI/ML is employed in other industry areas.
    - Determining the appropriateness of patient development/deployment in the population.

The Committee deliberated, voted, and approved the following recommendation based on the topic of *The Role of Artificial Intelligence and Machine Learning in the Clinical Laboratory*.

Recommendation 2: CLIAC recommends creating a workgroup to explore the current and future intersection between artificial intelligence and machine learning in the clinical laboratory, specifically regarding implementing and deploying tools in the clinical laboratory.

The Use of Clinical Standards to Improve Laboratory Quality

Introduction to Topic ***Addendum 9***

Víctor R. De Jesús, PhD
Chief, Quality and Safety Systems Branch (QSSB)
Division of Laboratory Systems (DLS)
Office of Laboratory Science and Safety (OLSS)
Centers for Disease Control and Prevention (CDC)

Dr. De Jesús introduced the session on using clinical standards to improve laboratory quality. He explained that, although the CLIA regulations do not specifically address the use of voluntary standards in addition to the mandatory quality standards, there is a role for clinical standardization programs and consensus standards to help laboratories strive for high-quality testing. He mentioned specific regulation citations that suggest the use of standardization programs to evaluate and correct identified problems, as well as the use of consensus standards to establish and verify performance specifications. Dr. De Jesús concluded the presentation by introducing the session speakers and providing questions for the Committee to consider during their deliberations.

CDC's Clinical Standardization Programs: Ensuring the Accuracy and Reliability of Chronic Disease Biomarker Tests ***Addendum 10***

Hubert W. Vesper, PhD
Director, CDC Clinical Standardization Programs
Clinical Chemistry Branch
Division of Laboratory Sciences
The National Center for Environmental Health
Agency for Toxic Substances and Disease Registry

Dr. Vesper opened his presentation by discussing the clinical standardization program developed by CDC to address concerns and problems with certain biomarkers. He presented data on various biomarkers, such as vitamin D, estradiol, and free thyroxine, to highlight the variability in measurements across different laboratories. He explained that their voluntary program aims to improve disease diagnosis, treatment, and prevention by standardizing CLIA laboratory measurements. He added that this is accomplished by creating traceable measurement results on an accuracy basis, which are comparable across methods, locations, and over time. Dr. Vesper described that the standardization process involves establishing a reference system, assessing and improving assay performance, and verifying end-user test performance. He emphasized the ongoing nature of standardization and the need for continuous monitoring. Dr. Vesper discussed the unique features of their program, including customized samples provided to participants and detailed reports on measurement bias. He showcased how their program has helped detect trends and addressed problems in laboratory testing. Dr. Vesper highlighted the importance of standardized tests in patient care

and research settings and described how the program collaborates with stakeholders to educate the laboratory communities about the importance of assay standardization.

Clinical and Laboratory Standards Institute (CLSI): Consensus Standards to Support Operational Excellence and Regulatory Compliance

Barb Jones, PhD — ***Addendum 11***
Chief Executive Officer
Clinical and Laboratory Standards Institute

Dr. Jones began her presentation by discussing the importance of using accredited standards development organizations for laboratory standards. She then briefly explained the difference between CLIA regulatory standards and the Clinical and Laboratory Standards Institute (CLSI) consensus standards. She then provided a list of CLSI standards documents to assist laboratories in addressing CLIA regulations related to establishing performance specifications. Dr. Jones then explained that CLSI is a not-for-profit global leader in setting clinical laboratory standards and has been accredited by the American National Standards Institutes since 1977. She emphasized the rigorous consensus process followed by CLSI, which involves vetting experts, public comment periods, and appeals processes. She highlighted the role of CLSI in harmonizing standards across professions, government bodies, and industry stakeholders. Dr. Jones discussed how CLSI supports CLIA by providing documents and guidances that directly apply to the CLIA quality regulations. She provided examples of how federal agencies can use consensus standards either through incorporation by reference, which is difficult to achieve, or recognition of the standard where the agency has the discretion to define the process, the procedure, and the requirements. Dr. Jones closed her presentation by providing suggestions for CLIAC to consider regarding using consensus standards.

Public Comments
Addendum PC6

Committee Discussion

- One CLIAC member inquired about the support and financial resources needed to fund CDC's clinical standardization programs and CLIA program activities. Dr. Vesper responded that funding has been minimal for the last ten years, and expanding the programs to include other biomarkers is difficult. He added that it would be helpful if CLIAC and other organizations recognized the effort of the program participants to improve quality either through the inclusion of program participation on checklists or as part of a quality assessment indicator.
- A member inquired about whether test manufacturers have responded in any way to the CDC program's efforts. Dr. Vesper responded that manufacturers are generally supportive, noting that when manufacturers introduce or update a new test, they may implement changes identified by participants in the standardization program. Dr. Lias added that the FDA has incentivized standardization through a lower regulatory bar, adding that vitamin D assays are exempt from premarket review if standardized through the vitamin D clinical standardization program provided by CDC.
- A CLIAC member noted that it is difficult to determine how many laboratories utilize CLSI standards, to what extent they have incorporated them into their processes, or if they are keeping them on hand for reference.
- Dr. Lias commented that many laboratories participating in the CDC clinical standardization program utilize laboratory developed tests. Also, manufacturers will

participate in the program so that they can offer and promote the availability of standardized tests to their customers.

- Another member commented that CMS review recognized consensus standards to identify standards for consideration for future incorporation into CLIA.
- One member highlighted the work of The International Consortium for Harmonization of Clinical Laboratory Results, which provides a list of the different efforts that are ongoing to improve the harmonization of results from clinical laboratory measurement procedures for measurands (analytes) that do not have reference measurement procedures and provides a resource center for information on global activities to harmonize and standardize clinical laboratory measurement procedures.
- A CLIAC member mentioned that while encouraging vendors to conduct traceability studies and achieve harmonization is essential, it is equally crucial to have a system to flag and communicate these harmonized results effectively, as this information is currently not included in the test results. The member added that there is a significant effort to determine whether a test result is harmonized or comparable and noted that the Systemic Harmonization and Interoperability Enhancement for Laboratory Data (SHIELD) initiative is developing a harmonization indicator that can be attached to results.
- A member suggested that CLIA agencies promote clinical laboratory participation in clinical standardization programs by initiating or supporting published studies showing enhanced patient care when standardized methods produce the laboratory data.

The Committee deliberated, voted, and approved the following recommendations based on the topic of *The Use of Clinical Standards to Improve Laboratory Quality*.

Recommendation 3: CLIAC recommends CMS/CDC/FDA to engage professional societies (e.g., harmonization.net) to encourage test developers to participate in existing clinical standardization programs.

Recommendation 4: CLIAC recommends that CDC create a marketing campaign to raise awareness of standardization/harmonization efforts and their benefits.

CLIAC APRIL 10, 2024 MEETING AGENDA *Addendum 12*

CLIAC MEETING TRANSCRIPT *Addendum 13*

ADJOURN

Drs. Laser and Salerno acknowledged the staff who assembled the meeting agenda and organized the meeting. They also thanked the CLIAC members and partner agencies for their support and participation.

I certify that this summary report of the April 10, 2024, CLIAC meeting accurately and correctly represents the meeting.

Dr. Jordan Laser, CLIAC Chair Date

Division of Laboratory Systems

CLIAC Outgoing Member Recognition

Reynolds M. Salerno, PhD
Acting Associate Director for Laboratory Science and Safety
Acting Director, Office of Laboratory Science and Safety
Acting Director, Center for Laboratory Systems and Response
CLIAC Designated Federal Officer

CLIAC 2023 OUTGOING MEMBERS

Mary E. Edgerton, MD, PhD

Nirali M. Patel, MD

Michael A. Pentella, PhD, MS, SM(ASCP), CIC, D(ABMM)

R. W. (Chip) Watkins, MD, MPH, FAAFP

Mary E. Edgerton, MD, PhD

Dr. Edgerton's experience in anatomic and clinical pathology and clinical informatics, including research in data mining, bioinformatics, and mathematical modeling, provided the physician informatician perspective on various Committee discussions. Dr. Edgerton was instrumental in drafting recommendations on many topics, including laboratory data exchange and harmonization, remote selection, interpretation, and reporting of patient results, and standardization of test result communication. We thank Dr. Edgerton for her service to the Committee.

Nirali M. Patel, MD

Dr. Patel's experience as a board-certified molecular geneticist, anatomic and clinical pathologist, and laboratory director provided a diverse perspective to many CLIAC discussions. Her experience leading and providing compliance oversight within multiple regulatory frameworks led to CLIAC recommendations on many topics, including remote selection, interpretation, and reporting of patient results, the laboratory workforce, and the role of the laboratory in diagnostic and antimicrobial stewardship. She is currently serving as the Chair of the Next Generation Sequencing Workgroup. We thank Dr. Patel for her commitment to CLIAC.

Michael A. Pentella, PhD, MS, SM(ASCP), CIC, D(ABMM)

Dr. Pentella's experience as a board-certified medical microbiologist and expertise in biosafety in clinical and public health laboratories was very beneficial to many CLIAC topic discussions. He was instrumental in leading recommendations related to the partnership between clinical and public health laboratories, laboratory data exchange, the laboratory workforce, and laboratory training and education. He is currently serving as the Chair of the Biosafety Workgroup. We thank Dr. Pentella for his commitment to the Committee.

R. W. (Chip) Watkins, MD, MPH, FAAFP

Dr. Watkins' experience as a physician and laboratory director, including his diverse clinical experience spanning academics, corporate, and private practice medicine, has provided the physician perspective on numerous CLIAC topics. He was instrumental in discussions to develop recommendations related to the laboratory workforce, training and education, the role of the laboratory in diagnostic and antimicrobial stewardship, and efforts to address the CLIA top ten deficiencies. We thank Dr. Watkins for his commitment to CLIAC.

Thank you!

CDC Update

Collette Fitzgerald, PhD
Deputy Director for Science
Division of Laboratory Systems
Center for Laboratory Systems and Response

CLIAC Spring Meeting 2024

CLIAC Recommendations

DLS Initiative	Category	CLIAC Meeting
CLIAC Biosafety Workgroup ECHO Biosafety Program	Biosafety	April 2016
CLIAC Next Generation Sequencing Workgroup	Next Generation Sequencing	November 2021
Forum on Adoption of Standards for Laboratory Data Exchange	Laboratory Data Exchange and Harmonization	November 2021
OneLab Initiative	Laboratory Workforce	April 2022 November 2022
Clinical Laboratory Partners Forum Meeting	The Laboratory's Role in Advancing Health Equity	April 2023

CLIAC recommendation table can be found at https://www.cdc.gov/cliac/meeting.html

CLIAC Biosafety Workgroup

Workgroup Charge

Charged with providing input to CLIAC for consideration in making recommendations to the Department of Health and Human Services (HHS) on the potential additions to the CLIA regulations and the need for solutions that will provide a safe working environment for the nation's clinical and public health laboratories.

https://www.cdc.gov/cliac/workgroups/biosafety.html

Chair

- Dr. Michael A. Pentella

DFO

- Dr. Víctor R. De Jesús

Ex Officio Members

- Dr. Nancy Cornish (CDC)
- CDR Lane Vause (CMS)
- Ms. Amy Zale (FDA)

CLIAC Member Representative

- Ms. Heather Duncan

ECHO Biosafety Program

Upcoming Sessions

- **April 30** - Planning: Developing and Achieving Biorisk Management Objectives
- **May 28** - Support: Resources, Competence, and Awareness
- **June 25** - Support: Communication and Documented Information

www.cdc.gov/safelabs/resources-tools/echo-biosafety.html

CLIAC Next Generation Sequencing Workgroup

Workgroup Charge

Charged with providing input to CLIAC for consideration in making recommendations to the Department of Health and Human Services (HHS) on education, training, experience, and competencies that CLIA should require to qualify personnel who perform next generation sequencing bioinformatic data analysis and interpretation.

https://www.cdc.gov/cliac/workgroups/ngs.html

Chair

- Dr. Nirali Patel

DFO

- Ms. Heather Stang

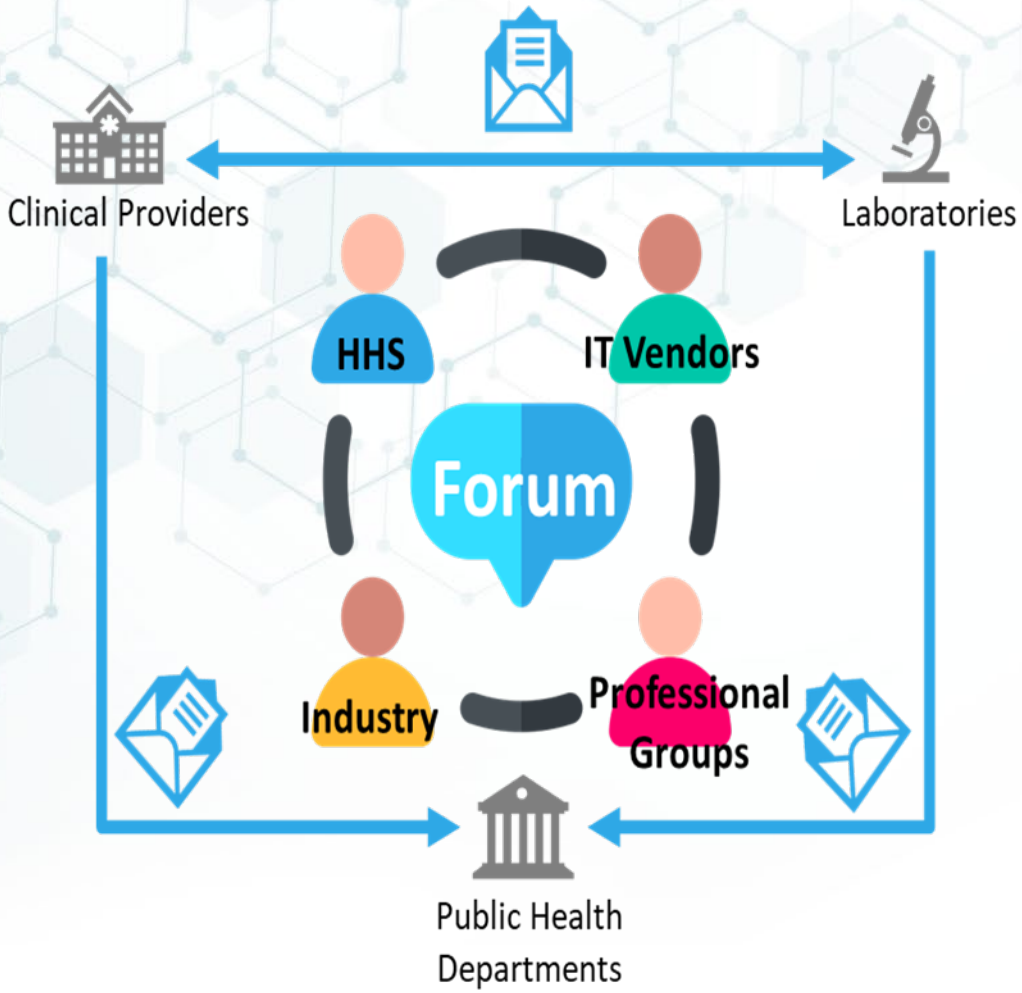
Ex Officio Members

- Dr. Diego Arambula (CDC)
- Ms. Penny Keller (CMS)
- Ms. Amy Zale (FDA)

CLIAC Member Representatives

- Dr. Chester Brown
- Dr. Tanner Hagelstrom

Forum on Adoption of Standards for Laboratory Data



Challenges Presented

- Frequent updates to informatics standards
- Financial burden on laboratories
- Knowledge gaps of end users

Suggestions Provided by the Forum

- Increase informatics expertise within laboratories
- Create incentive programs for funding standards implementation
- Develop educational resources

Solutions In Progress

- Resource depicting laboratory data exchange standards in public health

OneLab Initiative

OneLab has experienced **83% membership** growth since November 2023, now totaling over **22,000 unique members**!

OneLab Resources

- OneLab training materials – eLearning and VR courses, job aids, webinars, videos, etc. – have attracted over **168,000 registrations** in the first two quarters of FY24 – just 3,000 short of FY23 total in half the time
- OneLab VR "Centrifuge Safety" practice scenario is live
- "Fundamentals of Handling Compressed Gas Cylinders Safely" eLearning course released in November 2023

OneLab REACH™ — **20,000+ learners** with **9,000 new learners** in the past six months

OneLab Network — **9,700+ members** with **3,000 new members** in the past six months

OneLab TEST — **3,700+ members** with **1,700 new members** in the past six months

www.cdc.gov/onelab

Register for next week's OneLab Summit!

April 16-18, 2024

OneLab Summit

Thrive: People, Planning, Preparedness

OneLab Summit is a free, annual virtual event that connects laboratory professionals in real time to support a unified response to laboratory education and training needs

OneLab Summit attendees will

- Increase their knowledge of laboratory training development tools and practices
- Gain insights from the clinical and public health laboratory community's success and resilience
- Collaborate and connect with CDC and laboratory education and training peers

www.cdc.gov/onelab

Clinical Laboratory Partners Forum

Next Meeting

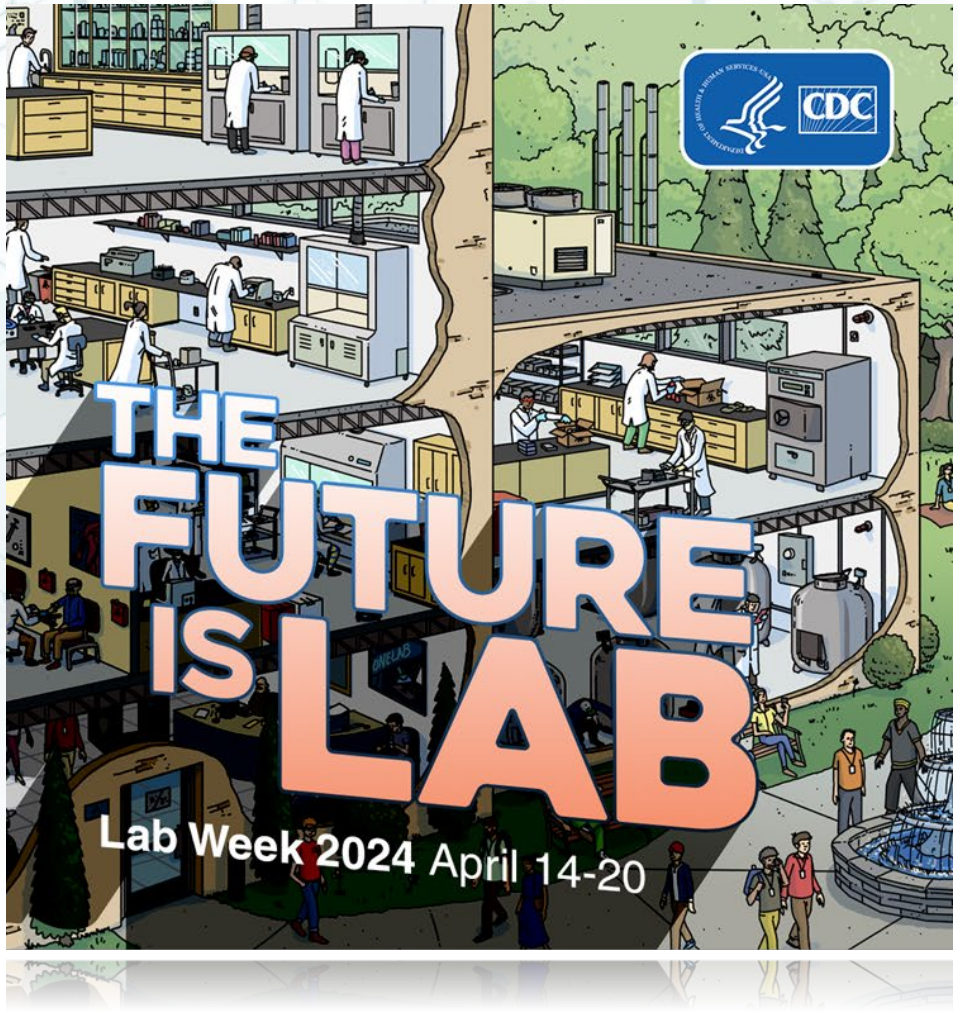
- May 22, 2024
- Theme: Early diagnosis of chronic kidney disease (CKD) and how the clinical laboratory can play a central role in identifying patients at risk for CKD

Topics

- Standardization of use of CKD-EPI 2021 eGFR race-free equation across clinical laboratories
- Creation of a specific Kidney Panel combining eGFR and urine Albumin-Creatinine Ratio (ACR) for screening
- Standardization of test name for ACR to Albumin-Creatinine Ratio, Urine

https://www.cdc.gov/csels/dls/strengthening-clinical-labs/clin-lab-partners-forum.html

Medical Laboratory Professionals Week: April 14-20



Join DLS in celebrating Lab Week 2024 by

- Showing thanks to a laboratory professional
- Participating in DLS's Lab Week activities
- Accessing our digital toolkit and content

www.cdc.gov/csels/dls/lab-week/

For more information contact CDC
1800-cdc-info (232-2636)
TTY: 1-888-232-6348 www.cdc.gov

CMS CLIA Update

Gregg Brandush

Division of Clinical Laboratory Improvement and Quality

April 10, 2024

Disclaimer

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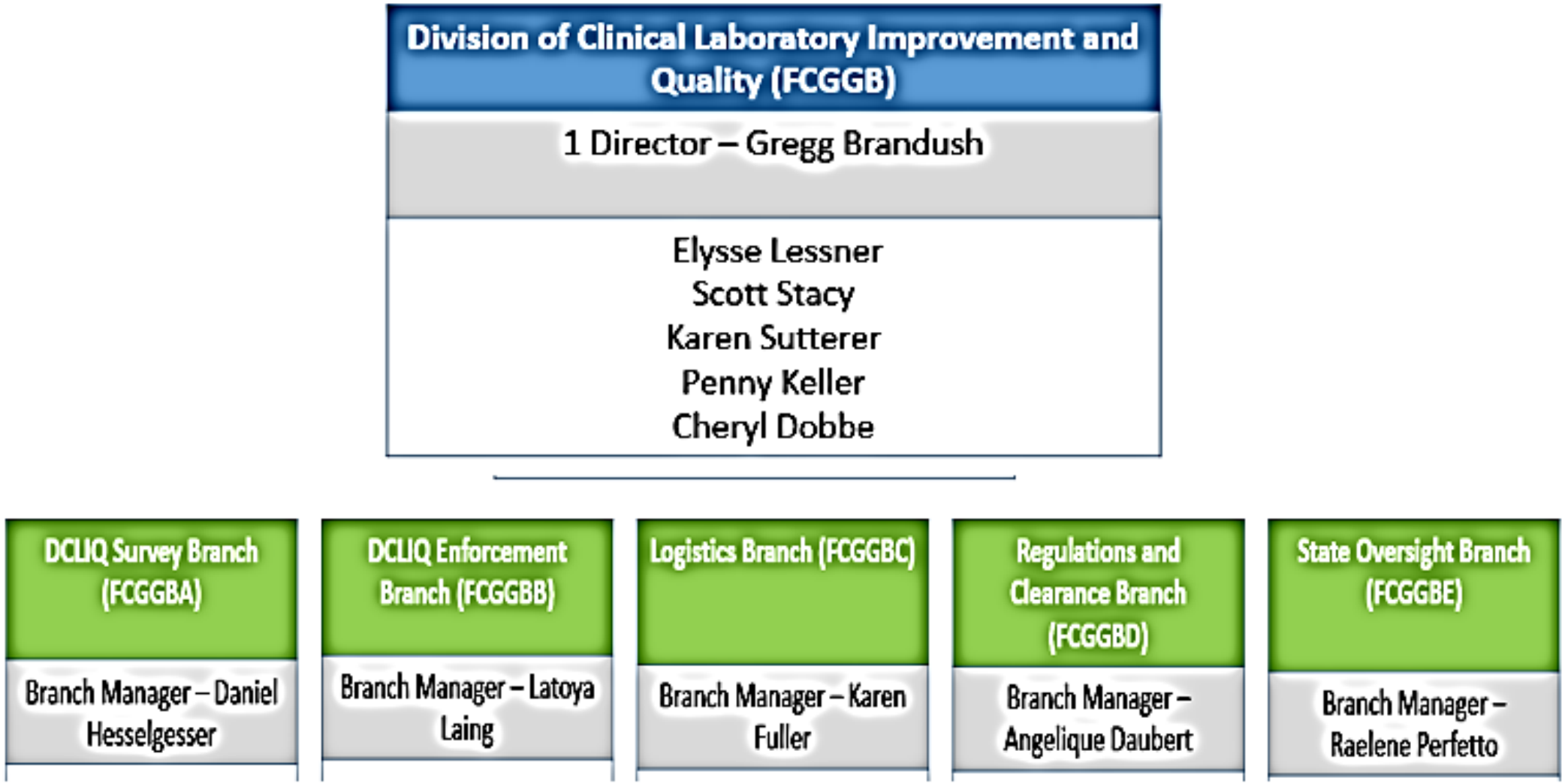
CMS DCLIQ REORGANIZATION

- DCLIQ Reorganization--what has changed:
- 2 Policy Branches and 3 Operations Branches have been restructured
- New structure consists of 5 branches along the primary product lines:
  - Survey Branch
  - Enforcement Branch
  - Logistics Branch
  - Regulations and Clearance Branch
  - State Oversight Branch

CMS CENTERS FOR MEDICARE & MEDICAID SERVICES

CLIA

CMS DCLIQ REORGANIZATION

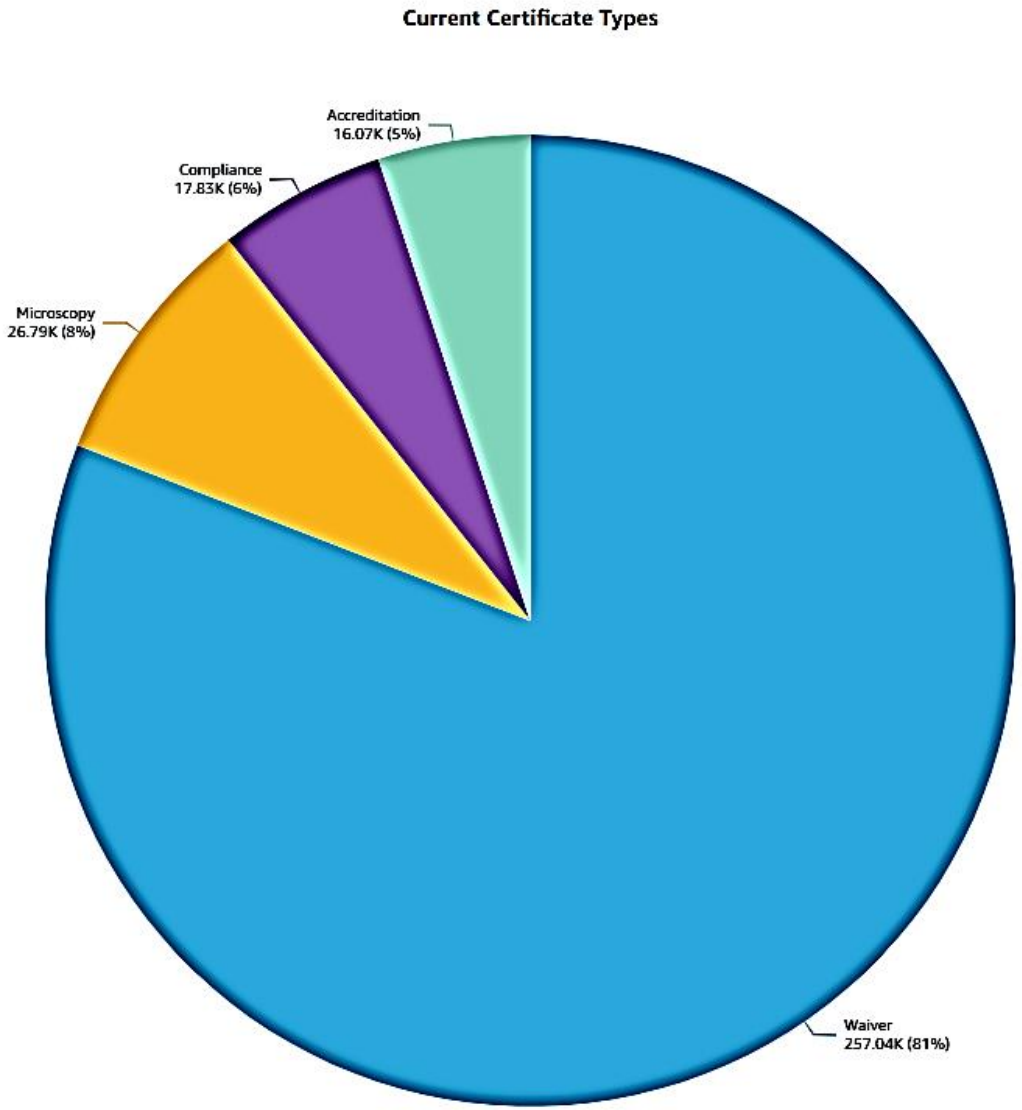


How many labs are there?

Approximate Number—Laboratories	317,740
Exempt States (New York and Washington)	14,508
Total Non-Exempt	303,232
CoC	17,833
CoW	257,043
CoA	16,073
PPM	26,791

Source: CMS database—February 2024

Visual Breakdown of Certificate Types



CMS CLIA goals for 2023

- Improved processes
  - Use of data to identify outliers in terms of survey findings, time spent on survey, team size
  - Adherence to enforcement timelines
  - Enhanced state oversight activities
- Modernizing CLIA
  - PT Rule implementation
  - Electronic Certificates
- Assessing the use of enforcement discretion and flexibilities during the PHE:
  - Remote review of pathology slides/data
  - Expedited review of CLIA applications
  - Contiguous site flexibilities
  - University non-CLIA COVID testing
  - COW testing authorization as soon as CLIA application is filed
  - COVID test result reporting
- Continuing our stakeholder engagement efforts

Additional CMS accomplishments FY23

- Electronic Certificates and QCOR links
- CDC Data Exchange
- Fee rule
- RFI (*Histopathology, Cytology, and Clinical Cytogenetics Regulations)*
- Budget process
- Backlog plan
- Dashboards

A-19s

- Emergency Waiver Authority Proposal:
  - Would mirror Section 1135 of the Social Security Act that grants CMS the authority to waive regulations that are not explicit Statutory Requirements for providers and suppliers that comply with CMS regulations as a Medicare participation requirement
  - No corresponding CLIA authority in the PHSA
  - Would allow the CLIA program to respond more rapidly in times of emergency
  - Currently, the mechanism is enforcement discretion

Certificate of Compliance survey findings

Top Ten Conditions Nationwide (10/1/19 to 9/30/21):

Tag Number	Count	Tag Identification
2016	1,263	**Condition: Successful PT participation**
6000	839	**Condition: Lab Director qualifications and responsibilities for moderate complexity testing at 493.1405 and 493.1407.**
6076	452	**Condition: Lab Director qualifications and responsibilities for high complexity testing at 493.1443 and 493.1445.**
5400	380	**Condition: Analytic Systems—Must meet requirements at 493.1251-1289.**
2000	298	**Condition: PT enrollment and testing of samples**
6033	257	**Condition: Technical Consultant qualifications and responsibilities for moderate complexity testing at 493.1411 and 493.1413.**
6063	230	**Condition: Testing personnel qualifications and responsibilities for moderate complexity testing at 493.1423 and 493.1425.**
6168	204	**Condition: Labs performing high complexity testing; testing personnel**
3000	169	**Condition: Facility Administration—must meet 493.1101-1105.**
6108	103	**Condition: Technical Supervisor qualifications and responsibilities for high complexity testing at 493.1449 and 493.1451.**

Certificate of Compliance survey findings

Top Ten Conditions Nationwide (10/1/21 to 9/30/23):

Tag Number	Count	Tag Identification
2016	1,538	**Condition: Successful PT participation**
6000	1,091	**Condition: Lab Director qualifications and responsibilities for moderate complexity testing at 493.1405 and 493.1407.**
6076	573	**Condition: Lab Director qualifications and responsibilities for high complexity testing at 493.1443 and 493.1445.**
5400	547	**Condition: Analytic Systems—Must meet requirements at 493.1251-1289.**
6033	350	**Condition: Technical Consultant qualifications and responsibilities for moderate complexity testing at 493.1411 and 493.1413.**
2000	342	**Condition: PT enrollment and testing of samples**
6168	258	**Condition: Labs performing high complexity testing; testing personnel**
6063	253	**Condition: Testing personnel qualifications and responsibilities for moderate complexity testing at 493.1423 and 493.1425.**
3000	218	**Condition: Facility Administration—must meet 493.1101-1105.**
6108	136	**Condition: Technical Supervisor qualifications and responsibilities for high complexity testing at 493.1449 and 493.1451.**

Certificate of Compliance survey findings

Top Ten Conditions Nationwide (10/1/23 to 2/29/24):

Tag Number	Count	Tag Identification
2016	234	**Condition: Successful PT participation**
6000	166	**Condition: Lab Director qualifications and responsibilities for moderate complexity testing at 493.1405 and 493.1407.**
6076	100	**Condition: Lab Director qualifications and responsibilities for high complexity testing at 493.1443 and 493.1445.**
5400	76	**Condition: Analytic Systems—Must meet requirements at 493.1251-1289.**
6033	55	**Condition: Technical Consultant qualifications and responsibilities for moderate complexity testing at 493.1411 and 493.1413.**
2000	75	**Condition: PT enrollment and testing of samples**
6033	55	**Condition: Technical Consultant qualifications and responsibilities for moderate complexity testing at 493.1411 and 493.1413.**
6063	55	**Condition: Testing personnel qualifications and responsibilities for moderate complexity testing at 493.1423 and 493.1425.**
3000	26	**Condition: Facility Administration—must meet 493.1101-1105.**
6108	21	**Condition: Technical Supervisor qualifications and responsibilities for high complexity testing at 493.1449 and 493.1451.**

CMS CLIA goals for 2024

Year One Goals	Year Three Goals	Year Five Goals
• 50% of CLIA certificates will be electronic and available on-line • Issue Interpretive Guidance on the new Fee, histocompatibility, Personnel and Alternative Sanction rule. • Initiate action plan to address data that demonstrates survey inconsistencies related to team size, time spent on survey, citation rates. • Track enforcement actions to ensure consistency • Make CLIA Certificate of Compliance survey findings available of QCOR	• Implement Lab Director University • Revise enforcement letters for plain language and readability • Assess state budget allocations for consistency and fairness	• Develop other educational resources such as Technical Supervisor University, Technical Consultant University, etc. • Develop standardized survey process that is objective, consistent and computer assisted.

New Guidance

Three memos were released since the last meeting:

- QSO-24-03-CLIA Final Rule (Fee, Histocompatibility, Personnel, Alternative Sanctions)
- Admin Info: 24-09-CLIA (Onsite/Offsite Follow-up/Revisit Guidance)
- Admin Info: 24-08-CLIA (Survey Team Composition and Workload Report)

Additional questions?

Thank you!

Gregg Brandush

Gregg.Brandush@CMS.HHS.GOV

312-353-1567

FDA Update

CLIAC

April 10, 2024

Courtney H. Lias, Ph.D.
Acting Office Director, Office of In Vitro Diagnostics
(OHT7 – Office of Health Technology 7)
Office of Product Evaluation and Quality (OPEQ)
CDRH | Food and Drug Administration

OHT7 Key Activities

Premarket Activities

- PMA, 510(k), De novo request reviews
- Investigational Device Exemptions
- Humanitarian Device Exemptions
- Pre-submissions
- Breakthrough designation requests
- Premarket inspections
- CLIA waiver applications
- CLIA categorizations

Postmarket Activities

- Monitoring and Surveillance
- Postmarket Inspections
- Postmarket Studies
- Recalls
- Compliance and Enforcement Actions
- Safety communications

External Engagement & Outreach

- External training and engagement
- Public meetings
- Conferences
- Town Halls
- Inquiry responses

Emergency Use

- Emergency Use Authorizations
- Cross-agency collaborations
- Stakeholder engagement, including Town Halls

Guidance

- Issue new guidances
- Update existing guidances
- Training and webinars

Program Development & Operations

- Internal training
- Performance tracking
- Data reporting

CDRH Intends to Initiate the Reclassification Process for Most High Risk IVDs

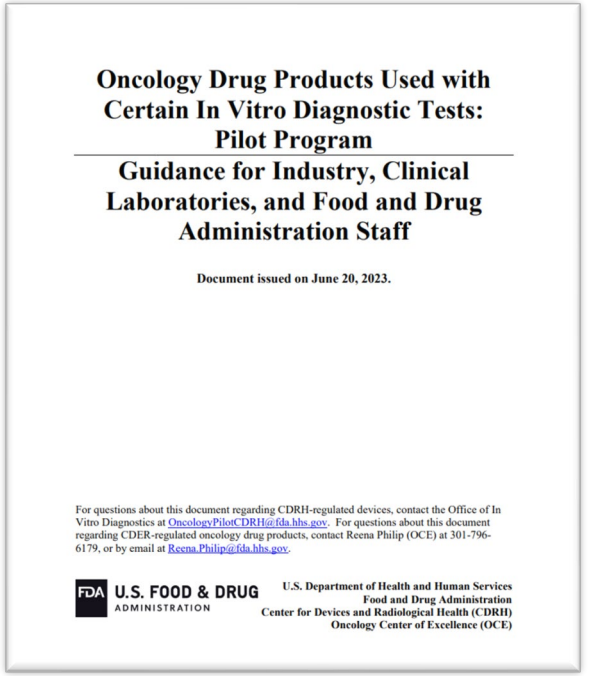
- Proposed reclassification for most IVDs that are currently class III (high risk) into class II (moderate risk)
  - Primarily infectious disease and companion diagnostic IVDs
- Premarket review of reclassified tests under the 510(k) pathway
  - High risk mitigated through special controls
- Microbiology Devices Panel meeting held on September 7, 2023. The Panel recommended FDA should reclassify from Class III to Class II the following types of devices:
  - Hepatitis B tests
  - Parvovirus antibody assays
  - M. tuberculosis assays
- Reclassifications may lead to increased access

Medical Devices News and Events

Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program

FDA is piloting a new approach to provide greater transparency regarding minimum performance characteristics that certain tests for certain oncology drugs should meet

- Goal is to assure the availability of effective companion diagnostic tests for oncology drug treatment decisions.
- This pilot does not alter the standards for approval of the oncology drug products or for marketing authorization of the corresponding companion in vitro diagnostics.
- At this time, the scope of this voluntary pilot program is limited to 9 drug sponsors and where:
  - A test is needed to identify the intended patient population of an oncology drug product for which no satisfactory alternative exists;
  - such a test uses the same technology as a previously FDA-authorized companion diagnostic;
  - the accuracy of such a test can be supported by a well-validated reference method, comparator, or materials; and
  - the anticipated benefits of the drug are so pronounced as to outweigh the risks of approval without contemporaneous approval of a companion diagnostic.


Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program

Guidance for Industry, Clinical Laboratories, and Food and Drug Administration Staff

Document issued on June 20, 2023.

For questions about this document regarding CDRH-regulated devices, contact the Office of In Vitro Diagnostics at OncologyPilotCDRH@fda.hhs.gov. For questions about this document regarding CDER-regulated oncology drug products, contact Reena Philip (OCE) at 301-796-6179, or by email at Reena.Philip@fda.hhs.gov.

U.S. FOOD & DRUG ADMINISTRATION

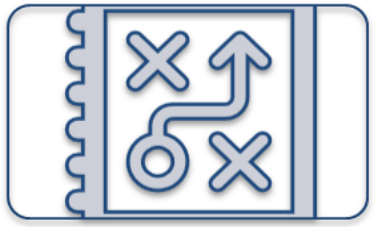
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

https://www.fda.gov/media/169616/download

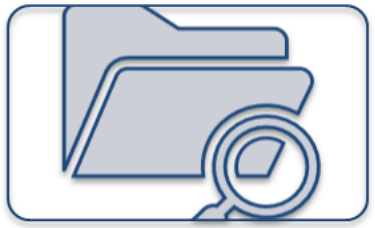
Oncology Diagnostics Pilot Program

FDA will request performance information for the tests used to enroll patients into the clinical trials that support drug approval

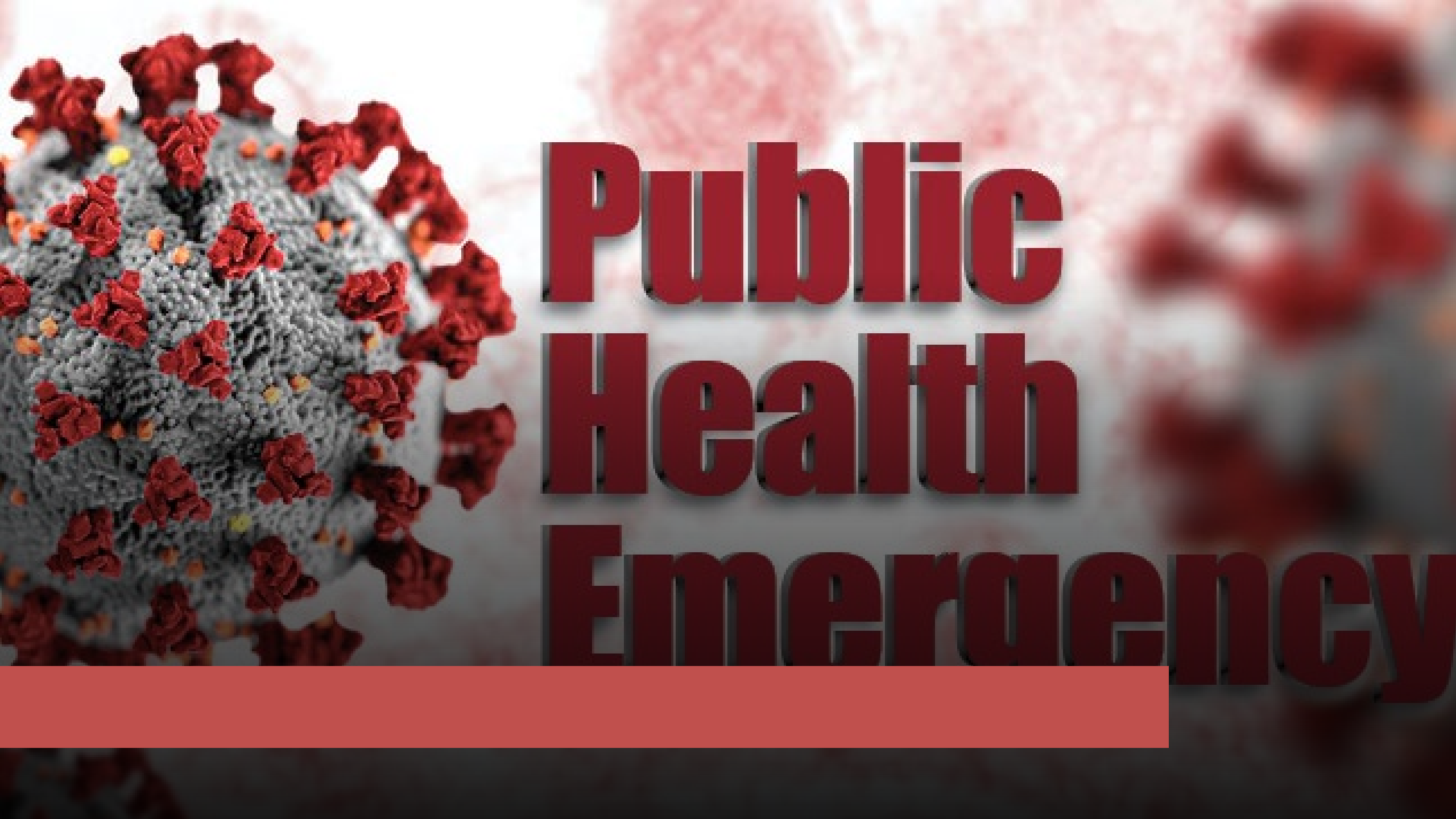
FDA will post to its website the minimum performance characteristics recommended for similar tests that may be used to select patients for treatment with the approved drug



Healthcare professionals may use this information to guide their choice of companion diagnostic test



This transparency aims to help facilitate better and more consistent performance of these tests, resulting in better drug selection and improved care for patients with cancer


Public
Health
Emergency

PHE Tests Authorized as of April 1, 2024

299

COVID Molecular diagnostic tests

Including:

- 26 Multi-analyte (i.e., SARS-CoV-2 + Influenza)
- 24 Point-of-care
- 72 Home collection
  - 16 Direct-to-consumer
  - 5 Multi-analyte
  - 14 Saliva home collection
- 5 Over-the-counter (OTC) at-home tests

78

COVID-19 Serology and other immune response tests

69

COVID-19 Antigen diagnostic tests

Including:

- 63 Point-of-care
- 33 Over-the-counter (OTC) at-home tests
- 8 Multi-Analyte

8

mpox NAAT diagnostic tests

Including:

- Automated
- Point-of-care
- Tests developed in collaboration with ITAP

Highly Pathogenic Avian Influenza (HPAI) A(H5N1)

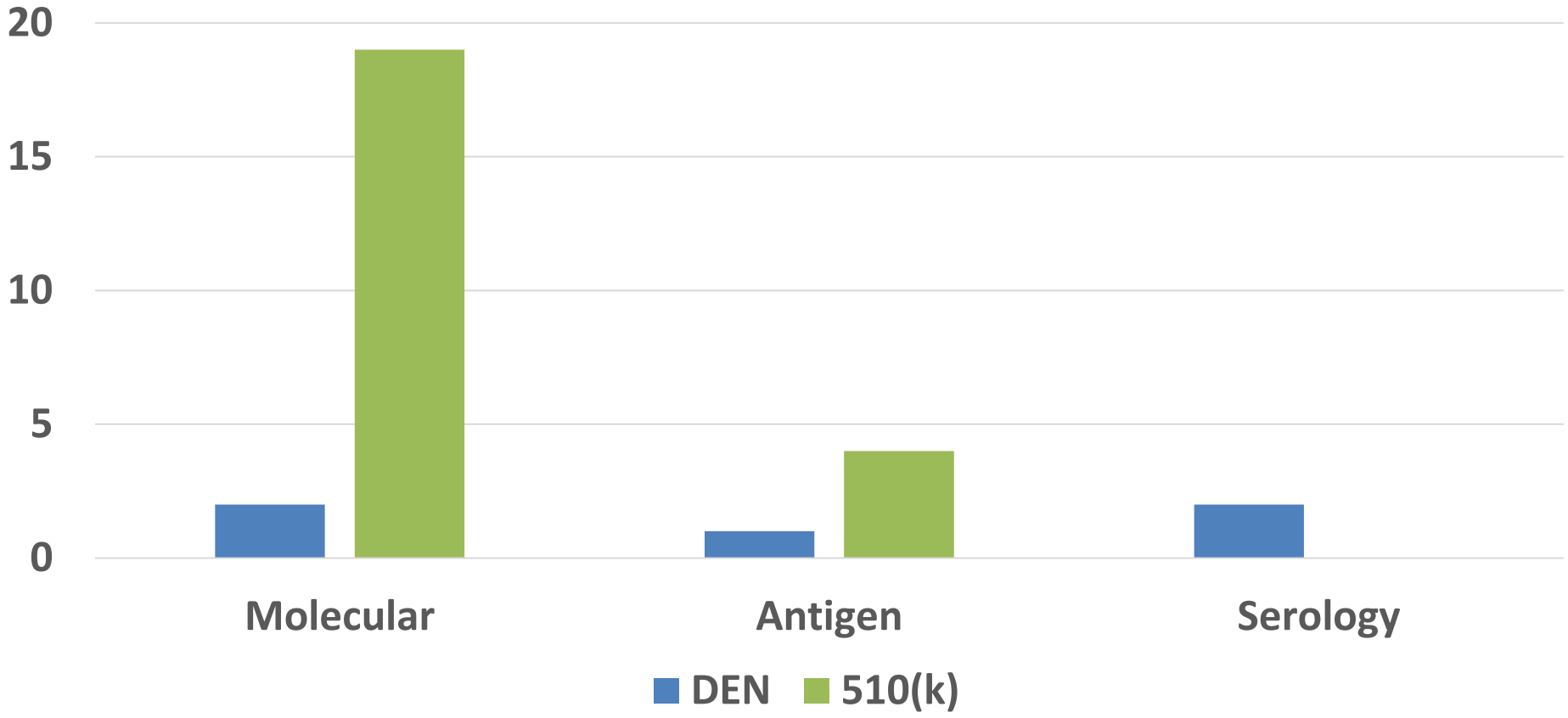
- Current assessment of test detection capability
- Working closely with Federal Partners to monitor the situation

Final COVID-19 Transition Guidances

- On March 27, 2023, CDRH issued two guidance documents to assist with transition plans for medical devices that were issued EUAs or fall within certain enforcement policies issued to support the response to the COVID-19 pandemic
  - *Transition Plan for Medical Devices Issued Emergency Use Authorizations (EUAs) Related to Coronavirus Disease 2019 (COVID-19)*
    - Referred to as "EUA Transition Guidance"
  - *Transition Plan for Medical Devices That Fall Within Enforcement Policies Issued During the Coronavirus Disease 2019 (COVID-19) Public Health Emergency*
    - Referred to as "Enforcement Policies Transition Guidance"
    - FDA's Policy for Coronavirus Disease-2019 Tests (Revised) and Policy for Evaluating Impact of Viral Mutations on COVID-19 Tests (Revised) are outside scope

*This slide presents high level discussion points. Please refer to the guidance documents for the details and official policies.

COVID-19 Tests Granted Traditional Marketing Authorization



[COVID-19 Tests Granted Traditional Marketing Authorization by the FDA | FDA]

Data as of 4/1/2024

Independent Test Assessment Program (ITAP) provides support for FDA authorization of rapid IVD tests

- Collaboration between the FDA and the NIH RADx program
- To date, FDA has authorized 13 COVID-19 tests, four COVID-19/Flu combo tests, and one mpox test after being evaluated through ITAP
- **Sekisui OSOM Flu SARS-CoV-2 Combo Home Test**: Authorized February 29, 2024
  - Intended for qualitative detection and differentiation of SARS-CoV-2, influenza A, and influenza B protein antigens
  - First OTC antigen test that detects both flu and COVID-19 viruses to receive an EUA following collaboration with the NIH ITAP

ITAP for Hepatitis C Virus (HCV) RNA Point-of Care POC Diagnostics

In collaboration with FDA, the National Institutes of Health (NIH) Rapid Acceleration of Diagnostics (RADx) Tech program solicited proposals to accelerate the validation, regulatory authorization, and commercialization of innovative point-of-care (POC) tests (CLIA Waived) for hepatitis C virus RNA (HCV RNA) detection and quantitation.

Independent Test Assessment Program (ITAP) | National Institute of Biomedical Imaging and Bioengineering (nih.gov)

ITAP for HCV POC Diagnostics - POCTRN - GAITS

HCV RNA Tests: End Goal

- Support Viral Hepatitis Elimination in the US by making an HCV RNA first line diagnostic test available in the US market→ Test and Treat

Goal

Advantages

- Diagnose individuals who may not normally go to doctor
- Treat individuals same visit and minimize loss to follow up

VISION

The United States will be a place where new viral hepatitis infections are prevented, every person knows their status, and every person with viral hepatitis has high-quality health care and treatment and lives free from stigma and discrimination.

This vision includes all people, regardless of age, sex, gender identity, sexual orientation, race, ethnicity, religion, disability, geographic location, or socioeconomic circumstance.

https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf

FDA Grants Marketing Authorization for Cytology Test Based on Artificial Intelligence (AI) Technology

Hologic Genius Digital Diagnostics System with the Genius Cervical AI algorithm:
Granted January 31, 2024

- Intended for the creation and viewing of digital images of scanned ThinPrep Pap Test glass slides
- Aid in cervical cancer screening for the presence of atypical cells, cervical neoplasia, including its precursor lesions, carcinoma, as well as all other cytological categories, as defined by The Bethesda System for Reporting Cervical Cytology
- Includes the Genius™ Digital Imager, Genius™ Image Management Server (IMS), the Genius™ Review Station, and the Genius™ Cervical AI algorithm

FDA Roundup

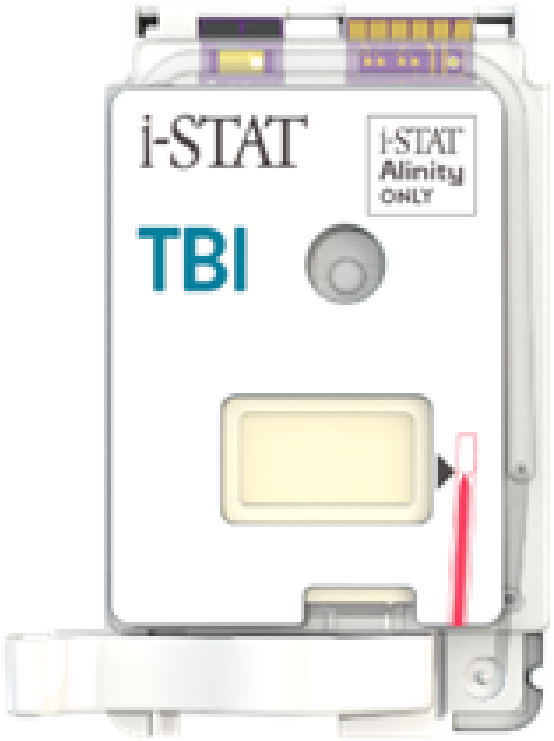
FDA Grants Marketing Authorization for First-of-a-Kind IVD Test for ADAMTS13 Activity

Technoclone Technozym ADAMTS13 Activity: Granted February 28, 2024

- First-of-a-kind enzyme-linked immunosorbent assay (ELISA) intended for the qualitative determination of ADAMTS13 activity in platelet poor human citrated plasma
- Used in conjunction with other clinical and laboratory findings, the test is intended as an aid in the diagnosis of thrombotic thrombocytopenic purpura (TTP) in patients with thrombotic microangiopathy (TMA)
- The assay is measured on microplate readers capable of detecting a wavelength of 450 nm

[FDA Roundup]

FDA Clears POC IVD for the Evaluation of Suspected Mild Traumatic Brain Injury (mTBI)



Abbott Point of Care i-STAT TBI Cartridge:
Cleared March 27, 2024

- For the quantitative measurements of glial fibrillary acidic protein (GFAP) and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) in whole blood using the **i-STAT Alinity** instrument
- The interpretation of test results is used, in conjunction with other clinical information, to aid in the evaluation of patients, 18 years of age or older, presenting with suspected mild traumatic brain injury (Glasgow Coma Scale score 13-15) within 24 hours of injury, to assist in determining the need for a CT scan of the head

FDA Roundup

FDA Clears First Over-the-Counter Continuous Glucose Monitor

FDA News Release

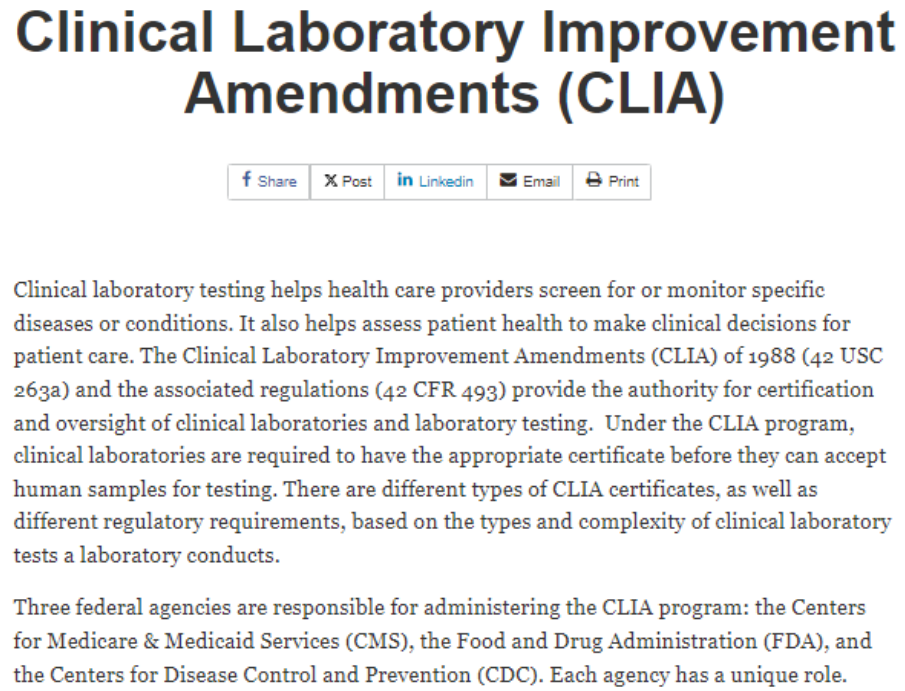
Dexcom Stelo Glucose Biosensor System: Cleared March 5, 2024

- First over-the-counter (OTC) integrated Continuous Glucose Monitor (iCGM) intended for anyone 18 years and older who does not use insulin
- System uses a wearable sensor, paired with an application installed on a user's smartphone or other smart device, to continuously measure, record, analyze and display glucose values
- Helps the user better understand how lifestyle and behavior modification, including diet and exercise, impact glucose excursion

Summary

Ways to interact with us:

- FDA CLIA Webpage
- Office of In Vitro Diagnostics Webpage
- Medical Device Safety Communications
- Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program
- For CLIA-related questions: CLIA@fda.hhs.gov
- For COVID-19 Diagnostics questions: Covid19DX@fda.hhs.gov
- For mpox Diagnostics questions: MPXdx@fda.hhs.gov



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Thank You

CLIA Fees, Histocompatibility, Personnel, Alternative Sanctions Final Rule, CMS-3326-F

Penny Keller

Technical Advisor,

Regulations and Clearance Branch,

CMS/QSOG/Division of Clinical Laboratory Improvement and Quality

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Objectives

After the presentation, you will be able to:

- State the two effective dates of the CMS-3326-F Final Rule provisions
- Describe the finalized requirements:
  - CLIA Fees
  - Histocompatibility
  - Personnel
  - Alternative Sanctions for Certificate of Waiver (CoW) laboratories

CMS-3326-F Final Rule Is Published!

Clinical Laboratory Improvement Amendments of 1988 (CLIA) Fees, Histocompatibility, Personnel, and Alternative Sanctions final rule (CMS-3326-F) was published in the Federal Register on **December 28, 2023**.

- General *Federal Register* link: Federal Register
- Direct link to CMS-3326-F Final Rule: CMS-3326-F
- CLIA ListServ: CMS-3326-F final rule announcement
- QSO Memo: QSO-24-03-CLIA Fees/Histocompatibility/Personnel/Alternative Sanctions final rule (CMS-3326-F)
- Correction notices: CMS-3326-CN and CMS-3326-CN2

CMS CENTERS FOR MEDICARE & MEDICAID SERVICES

CLIA

Two Effective Dates

1) Effective 30 days after the FRN publication date, on January 27, 2024:

- CLIA Fees and Alternative Sanctions regulations
- Also include definitions for *replacement certificate* and *revised certificate*

Two Effective Dates

2) One year after the FRN publication date; on December 28, 2024:

- Histocompatibility and Personnel regulations
- Also include definitions for *continuing education (CE) credit hours, doctoral degree, experience directing or supervising, laboratory training or experience, and midlevel practitioner*

CLIA FEES
SUBPART F, General Administration
§§ 493.638 thru 493.680

Finalized Requirements - CLIA Fees

§ 493.2 includes two new definitions:

1. "*Replacement certificate*" means an active CLIA certificate that is reissued with no changes made.
2. "*Revised certificate*" means an active CLIA certificate that is reissued with changes to one or more fields displayed on the certificate, such as the laboratory's name, address, laboratory director, or approved specialties/subspecialties. For purposes of this part, revised certificates do not include the issuance, renewal, change in certificate type, or reinstatement of a terminated certificate with a gap in service.

Finalized Requirements - CLIA Fees

- Establishes new but currently authorized fees that have not been previously assessed.
- Fees will be assessed when the following activities are performed:
  - Follow-up surveys to confirm correction of deficiencies.
  - Review and approval of testing when a laboratory adds a new specialty or subspecialty of testing.
  - Complaint surveys when the findings are substantiated.
  - Desk reviews involving unsuccessful laboratory proficiency testing.
  - Issuing revised or replacement certificates.

Finalized Requirements - CLIA Fees

- Apply a 18 percent across-the-board increase to the current fee.
- Apply a $25 certificate fee increase on Certificate of Waiver (CoW) laboratories to recover the cost of categorizing waived tests by the FDA.
- Apply a formula to assess user fees every two years to account for inflation if needed to meet program obligations.

Finalized Requirements - CLIA Fees

TABLE 6: CMS Proposed Fee for Issuance of Revised Certificate

Certificate Type	Fee
CoW	$95.00
CoA	$95.00
CoR	$150.00
CoC	$150.00
PPM	$150.00

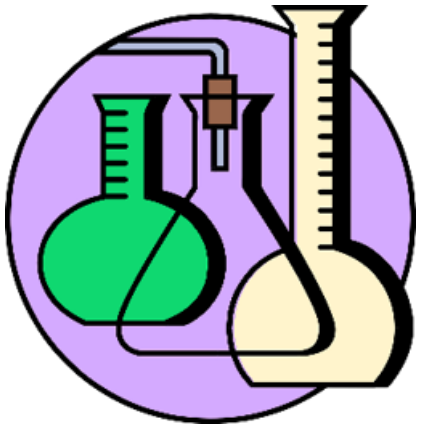
Finalized Requirements - CLIA Fees

CLIA website, CLIA Certificate Fee Schedule:

CLIA CERTIFICATE FEE SCHEDULE
Effective January 27th, 2024

Type of Lab	Number of Specialties	Annual Test Volume	Biennial Certificate Fee
Waived	N/A	N/A	$248
PPM	N/A	N/A	$297
Low Vol. A	N/A	2,000 or fewer	$223

HISTOCOMPATIBILITY
SUBPART K, QUALITY SYSTEMS
§ 493.1278



Finalized Requirements - Histocompatibility

- Remove histocompatibility-specific requirements that are already addressed by the general requirements regarding quality control materials and procedures for all test systems.
- Revise the name at § 493.1278(d) from “Antibody Screening” to “Antibody Screening and Identification” for clarification, as both processes apply to histocompatibility testing.
- Revise the words “transfusion” and “transfused” to “infusion” and “infused,” respectively.

Finalized Requirements - Histocompatibility

- Remove three requirements regarding the laboratory having crossmatch procedures and controls; already addressed by the general requirements for all test systems under §§ 493.1445(e)(1), 493.1251, and 493.1256.
- Modify the following terminologies to reflect current practices: “cadaver donor” is replaced by “deceased donor,” “transfused” is replaced by “infused,” and “combined” is replaced by “paired.”

Finalized Requirements- Histocompatibility

- Update the name of the World Health Organization (WHO) committee that determines HLA nomenclature to “Nomenclature Committee for Factors of the HLA System,” in the regulatory text.
- Add the requirement to obtain a recipient specimen prior to transplantation for crossmatch on the day of the transplant, if possible.

PERSONNEL
SUBPART M
§§ 493.1359, and 493.1405 thru 493.1491

Finalized Requirements - Personnel

§ 493.2 includes five new definitions:

1. "*Midlevel practitioner*" was amended by adding a nurse anesthetist and clinical nurse specialist.
2. "*Continuing education (CE) credit hours*" means either continuing medical education (CME) or continuing education (CE) units. The 20 CEs must be obtained before qualifying as a laboratory director.

Finalized Requirements - Personnel

§ 493.2 includes five new definitions :

3. *"Doctoral degree"* means an earned post-baccalaureate degree with at least 3 years of graduate-level study that includes research related to clinical laboratory testing or advanced study in clinical laboratory science or medical technology.

   - Doctoral degrees would not include doctors of medicine (MD), doctors of osteopathy (DO), doctors of podiatry, doctors of veterinary medicine (DVM), or honorary degrees
   - DCLS (Doctor of Clinical Laboratory Science) degrees would be included in doctoral degrees

Finalized Requirements - Personnel

§ 493.2 includes five new definitions:

4. "*Laboratory training or experience*" means that the training or experience must be obtained in a facility that meets the definition of a laboratory under § 493.2 and is not excepted from CLIA under § 493.3(b).

5. "*Experience directing or supervising*" means that the director or supervisory experience must be obtained in a facility that meets the definition of a laboratory under § 493.2 and is not excepted under § 493.3(b).

Finalized Requirements - Personnel

PPM laboratory director responsibilities (§ 493.1359):

- Modify the PPM laboratory director's responsibilities to include competency assessment (CA). The same CA intervals as in §§ 493.1413(b)(8) and 493.1451(b)(8) would apply.

Finalized Requirements - Personnel

Laboratory Director qualifications/responsibilities (§§ 493.1405, 1407, 1443, 1445):

- Remove “or possess qualifications that are equivalent to those required for such certification” related to the American Board of Pathology and American Osteopathic Board of Pathology.
- Include 20 CEs to moderate and high complexity laboratory director qualifications.
- Add “directing and supervising experience” to the high complexity, laboratory director’s doctoral degree qualification requirements.
- Remove the residency provision; however, relevant experience in a residency or fellowship would continue to be acceptable experience and training for qualifying individuals.

Finalized Requirements - Personnel

Laboratory Director qualifications/responsibilities (§§ 493.1405, 1407, 1443, 1445):

- Update the regulations addressing laboratory director responsibilities to require the director to be on-site at the laboratory at least once every six months, with at least a four month interval between the two on-site visits.
- Update the language of the regulations addressing laboratory director qualifications to specify that an individual qualifying under the doctoral degree algorithm must have an earned doctoral degree.

Finalized Requirements - Personnel

Technical Supervisors qualifications (§ 493.1449):

- Combine the provisions with identical Technical Supervisor requirements into a combined requirement.
- Remove the reference to the American Society of Cytology as it has not provided certification for cytology since 1998.
- Update the *immunohematology* test specialty requirement to allow individuals with doctoral, master's, and bachelor's degrees with appropriate training and experience to qualify as a Technical Supervisor for immunohematology.

Finalized Requirements - Personnel

General Supervisor qualifications and responsibilities (§§ 493.1461, 1463):

- Revise the language to allow the delegation to the General Supervisor for performing all (semiannual and annual) CA.

Finalized Requirements - Personnel

Cytotechnologist qualifications (§ 493.1483):

- Replace “CAHEA” with CAAHEP (Commission on Accreditation of Allied Health Education Programs) and remove “or other organization approved by HHS” in the introductory regulatory text.

Finalized Requirements - Personnel

Testing Personnel qualifications (§§ 493.1423, 1489):

- Add the nursing degree for testing personnel, moderate complexity, as proposed for § 493.1423.
- However, for § 493.1489, a nursing degree does not automatically meet high complexity testing personnel qualifications.

Finalized Requirements - Personnel

Testing Personnel qualifications (§§ 493.1423, 1489):

- Add the blood gas testing personnel for moderate complexity.
- Move the military provision out of the April 24, 1995, grandfather provision for high complexity, and make it a mechanism that individuals will be able to qualify for high complexity testing personnel.
- Move Department of Health, Education and Welfare (HEW)-qualified individuals to 493.1489.

Finalized Requirements - Personnel

Degrees:

- Add an educational algorithm qualification option for both moderate and high complexity testing for bachelor's, master's, and doctoral degrees.
- Remove the reference to a physical science degree from subpart M.
- Add an approved thesis/research with the educational option.

Finalized Requirements - Personnel

Grandfathering:

- Remove the “grandfather” provisions at §§ 493.1406 (MC LD), 493.1443(b)(3)(ii) thru (b)(6) (HC LD), 493.1461(c)(5) and 493.1462 (HC GS), 493.1489(b)(5) and 493.1491 (HC TP).
- Add a new grandfather provision for all qualified individuals employed in a given personnel position before the date of the final rule. However, we intend to require all individuals becoming employed by a laboratory or changing assignments within a laboratory after the final rule's effective date to qualify under the new personnel provisions.

Finalized Requirements - Personnel related…

Other Conforming Amendments:

- Update the regulatory cross-references at §§ 493.945(b)(2), 493.945(b)(3)(i), 493.945(b)(3)(ii)(C), 493.945(b)(3)(ii)(F), 493.1273(b), and 493.1274(c)(1), 493.1417(a), 493.1451(c), 493.1455(a), 493.1469(a) to be consistent with the finalized regulations to the updated Personnel subpart M regulations.

Finalized Requirements - Personnel

Updated regulations:

- § 493.1359; (b)(2); (c); (d); Standard; PPM laboratory director responsibilities
- § 493.1405; (b); Standard; Laboratory director qualifications, moderate complexity
- § 493.1407; (c); Standard; Laboratory director responsibilities, moderate complexity
- § 493.1411; (b); Standard; Technical consultant qualifications, moderate complexity
- § 493.1423; (b); Standard; Testing personnel qualifications, moderate complexity
- § 493.1443; (b); Standard: Laboratory director qualifications, high complexity

Finalized Requirements - Personnel

Updated regulations:

- § 493.1445; (c); (e)(10); Standard; Laboratory director responsibilities, high complexity
- § 493.1449 Standard; Technical supervisor qualifications, high complexity
- § 493.1461; (c); (d)(3)(i); (e); Standard: General supervisor qualifications, high complexity
- § 493.1463; (b)(4); Standard: General supervisor responsibilities, high complexity
- § 493.1483; introductory text; (b); Standard: Cytotechnologist qualifications
- § 493.1489; (b); Standard: Testing personnel qualifications, high complexity

Finalized Requirements - Personnel

Remove “grandfather” provisions:

- § 493.1406 Laboratory Director qualifications on or before February 28, 1992
- § 493.1443 (b)(3)(ii) thru (b)(6) Laboratory Director qualifications on or before February 28, 1992 or February 24, 2003
- § 493.1461(c)(5) General supervisor qualifications on or before September 1, 1992
- § 493.1462 General supervisor qualifications on or before February 28, 1992
- § 493.1489(b)(5) Technologist qualifications on or before September 1, 1997
- § 493.1491 Technologist qualifications on or before February 28, 1992

ALTERNATIVE SANCTIONS
SUBPART R, ENFORCEMENT PROCEDURES
§ 493.1804(c)(1)

Finalized Requirements - Alternative Sanctions

Update the regulation at § 493.1804(c)(1) to allow CMS to impose alternative sanctions on Certificate of Waiver laboratories, as appropriate.

Summary

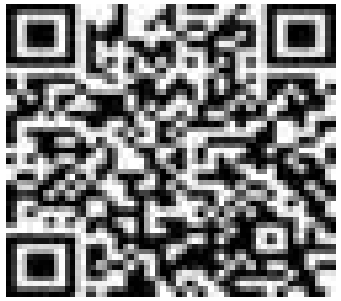
- Clinical Laboratory Improvement Amendments of 1988 (CLIA) Fees, Histocompatibility, Personnel, and Alternative Sanctions final rule (CMS-3326-F) was published in the Federal Register on **December 28, 2023**.
- Updated CLIA requirements include:
  - CLIA Fees
  - Histocompatibility
  - Personnel
  - Alternative Sanctions for CoW laboratories
- Effective dates of the CMS-3326-F Final Rule provisions:
  - January 27, 2024- CLIA fees and Alternative Sanctions for CoW laboratories
  - December 28, 2024- Histocompatibility and Personnel
- General *Federal Register* link: Federal Register

Resources

- **Email address**: LabExcellence@cms.hhs.gov

- **CLIA website**: https://www.cms.gov/medicare/quality/clinical-laboratory-improvement-amendments
    - Online Payment
    - CLIA Laboratory Lookup
    - CLIA Communications ListServ

- **QR code to CLIA website**:



Questions?

Pre-analytic Testing and Personnel Requirements

Gregg Brandush

Division of Clinical Laboratory Improvement and Quality

April 10, 2024

Pre-analytic Testing and Personnel Requirements

Fundamental Question:

- Should CMS CLIA High Complexity Personnel Requirements apply to all aspects of a High Complexity test including Pre-analytic Testing?
  - Considerations in making this assessment:
    - Pre-analytic testing for some high complexity tests merely require instrument loading and many labs do not use HC Personnel for this function.
    - Should HC Personnel requirements apply to HC testing where there is no required manipulation or processing of the specimen beyond centrifuging and storage; there are no calculations or precision pipetting required.
    - No specimen rejection requirements that require individual assessment (i.e., hemolysis, clots, lipemia, blood to anticoagulant ratios, etc.)
    - Modular systems where modules can be taken off-line if quality issues are encountered

COLLEGE of AMERICAN PATHOLOGISTS

Statement to the
Clinical Laboratory Improvements Advisory Committee
Meeting April 10, 2024

Applicability of CLIA personnel requirements to preanalytic testing

The College of American Pathologists (CAP) appreciates the opportunity to provide written comments to the Clinical Laboratory Improvement Advisory Committee (CLIAC). As the world's largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, the CAP serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide.

As such, the CAP recommends that the current scope of CLIA be maintained and that personnel requirements related to the pre-analytics of testing remain outside of the scope of CLIA regulations.

At the November 2023 CLIAC meeting, CLIAC approved a recommendation to include histology under CLIA. The CAP disagreed with this recommendation as through our own monitoring and oversight of laboratories, we have no detected quality issues. Furthermore, the study cited during the last meeting was from overseas, so not necessarily reflective of laboratories in the US, but was also focused on the impact to digital pathology implementation and not a pathologist's ability to render a high-quality diagnosis. Increasing the scope of CLIA regulations is not needed, as there is no consensus supporting the assertion that there are quality issues that would warrant such an expansion. Thus, more discussion, and further study of U.S. laboratories, should take place before expanding CLIA oversight to new areas.

The CAP provides oversight for over 8000 laboratories, providing a firsthand view into how they operate. While issues do arise during the pre-analytical phase of testing, they are not the result of personnel being unqualified. Typically the pre-analytical steps that can compromise the quality of analysis are associated with the time to stabilization of tissue and time to processing the sample. This indicates that laboratory and personnel could benefit from process improvements, not increased qualifications, and our concern is that increased regulation will not solve these issues but could likely exacerbate them.

Some pre-analytic activities are appropriately within the purview of CLIA, such as Test Requests, Specimen submission, handling, and the laboratories systems quality assessment. However, instituting CLIA oversight of preanalytic testing personnel would mean increased regulatory burden for laboratories while reducing the flexibilities available to laboratory directors, who must make decisions on laboratory workflow based on the best interest of the patient balanced with the realities of constricting financial resources. Additionally, as laboratories continue to adapt to workforce challenges, automation is rapidly changing the field of laboratory medicine, and thus it may be premature to develop regulations as practices remain in flux and issues with quality have yet to be identified.

College of American Pathologists
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Washington, DC 20001
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The CAP does support increased consistency of application and interpretation of existing CLIA regulations and requirements. CLIA is appropriate and needed to regulate testing, which can be defined as producing a test result. We would support and encourage efforts to make interpretation of regulations more consistent; for example, guidance documents to address laboratory questions and consistency of surveyor interpretation from state to state on preanalytic duties that may be performed by laboratory assistants, defined as individuals that help perform testing, versus those requiring further knowledge and judgement that must be performed by qualified testing personnel. This would help laboratories remain compliant with CLIA requirements while also allowing for the use of laboratory assistants to meet workforce needs. However, regulating personnel qualifications for individuals involved in pre-analytic testing would be challenging from a functional standpoint, and unnecessary.

The CAP welcomes the opportunity to discuss our concerns and recommendations for implementation at your earliest. Please contact Andrew Northup at anorthu@cap.org or 202.297.3726.

Closing,

The College of American Pathologists

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National Society for Histotechnology
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E: histo@nsh.org
www.nsh.org

April 10, 2024

Heather Stang MS, MLS (AMT)
Executive Secretary
Clinical Laboratory Improvement Advisory Committee
Centers for Disease Control and Prevention
CLIAC@cdc.gov

RE: Virtual Comments for April 10, 2024 Spring Virtual Clinical Laboratory Improvement Advisory Committee Meeting, the Applicability of CLIA Personnel Requirements to Preanalytic Testing

The National Society for Histotechnlogy appreciates the opportunity to provide comments concerning the Applicability of CLIA Personnel Requirements to Preanalytic Testing on behalf of its membership. The National Society for Histotechnology is a non-profit member organization that supports histotechnicians and histotechnologists worldwide through education, collaboration and innovation.

When CMS last revisited the CLIA regulations in 1992, it excluded from oversight many histological pre-analytic, analytical and post-analytical processes because they were deemed relatively simple, minimal risk procedures that did not require a Histotechnologist to produce an independent result. However much has changed in the last 30 years. The field of histotechnology has witnessed unprecedented technical advances including innovative approaches, methodologies, and automation in traditional areas as well as in the fields of immunohistochemistry, in situ hybridization, molecular diagnostics, and computer-assisted digital image analysis, all of which are critical to patient diagnosis and treatment. For example, loading slides on an immunohistochemistry instrument is not a simple task. Loading an instrument requires the selection of proper reagents, insuring appropriate controls are in place, programing the instrument and reviewing results. Multiple individuals may be involved at any time throughout the work shift in this process and all must be capable of executing the entire task for a successful test. In addition, many laboratories have a varied menu of pre-diluted reagents and concentrates as well as other reagents for special stains requiring the ability to do complex dilutions and calculations. Histologists also manipulate specimens. Grossing is the most obvious but processing, embedding, sectioning and staining all change the specimen in ways that can influence diagnosis. Histologists also reject specimens for a variety of reasons including if a specimen cannot be embedded as required, sectioned as indicated or if tissue falls of a slide or a stain is not working. Histologists must use their experience to determine if the specimen is adequate for further processing. This occurs at multiple points throughout the sample workflow. In addition, when test systems fail, there is a critical need for an individual with high complexity skills to troubleshoot the problem and bring the test system back on line. As noted, histology procedures and methods have become highly complex, and with personalized medicine becoming the standard of care, the entire test system is critical to deliver high quality patient care. There is sufficient evidence that quality outcomes depend on the quality of input and as such, preanalytical steps should be considered part of the high complexity *Total Test* approach (1).

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NSH strongly believes that the definition of a "test," specifically as it relates to histology, needs reexamination. The complexity designation should include the pre analytical and analytical phase steps of the total test approach.

Essential to providing quality patient healthcare in today's complex medical laboratory environment are educated, trained, professional histotechnicians and histotechnologists. The NSH strongly believes that histologists should have post-secondary education that confers a degree and training culminating in national certification or licensure to demonstrate competency and meet CLIA's high complexity personal requirements, consistent with the American Society of Clinical Pathology Board of Certification credential requirements. Given the complexity of contemporary histology laboratories, we strongly feel that the current level of education required in CFR 42 §492.20 does not adequately provide the education and expertise necessary to provide high quality patient care and outcomes.

The National Society for Histotechnology advocates that the CLIA recommendations be amended to include Histotechnicians and Histotechnologists under CLIA's oversight therefore requiring histology laboratory personnel to meet CLIA's high complexity personal requirements.

The National Society for Histotechnology strongly believes that CLIA should increase its oversight of histology laboratories by requiring those facilities or entities that perform histologic processing of anatomic tissues to be classified as CLIA-certified high complexity laboratories. In this way, the procedures are performed in an appropriately accredited CLIA laboratory and by personnel who meet CLIA personnel requirements in order to provide high quality personalized care, today and in the future.

The National Society for Histotechnology is the largest a non-profit member organization, representing histotechnicians and histotechnologists worldwide. NSH is the leading provider of histotechnology education designed to demonstrate continuing competence in an increasingly complex laboratory-testing environment. We look forward to CLIAC's response to these issues and continued discussion in order to advance the histotechnology profession and provide the highest quality care to the patients we serve. We thank the committee for the prior work, ongoing efforts, and consideration.

1. Taylor, C.R., *Quality assurance and standardization in immunohistochemistry. A proposal for the annual meeting of the Biological Stain Commission, June, 1991.* Biotech Histochem, 1992. **67**(2): p. 110-7.

The Role of Artificial Intelligence and Machine Learning in the Clinical Laboratory

Introduction

Heather L. Stang, MS, MLS(AMT)
Senior Advisor for Quality and Safety
CLIAC Executive Secretary

CLIAC Regulations Assessment Workgroup

Chairs

Dr. Kimberle C. Chapin
Dr. Gregory N. Sossaman

Workgroup Charge

The CLIA Regulations Assessment Workgroup provides input to CLIAC for deliberation on how the CLIA might specifically be updated, considering the April 2019 reports by the Personnel Regulations, Non-Traditional Workflow Models, and NGS workgroups. The workgroup is charged with providing advice to CLIAC for consideration in making recommendations to HHS on revising the CLIA regulations.

https://www.cdc.gov/cliac/workgroups/regulations-assessments.html

CLIAC Regulations Assessment Workgroup: Total Testing Process Evaluation

Workgroup Questions

- 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?

Presentation

The Basics of Artificial Intelligence and Machine Learning

Alexis B. Carter, MD
Physician Informaticist and Molecular Pathologist
Pathology and Laboratory Medicine
Children's Healthcare of Atlanta

Questions to CLIAC

1) What are the challenges to applying the CLIA regulations to technologies utilizing artificial intelligence and machine learning?
2) Should a CLIAC workgroup be formed to discuss the requirements that should be added or revised in CLIA to ensure the quality of testing when artificial intelligence and machine learning are part of the total testing process?

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Heather Stang (404)498-2769 or btg0@cdc.gov

The Basics of Artificial Intelligence and Machine Learning

Alexis B. Carter, MD
Physician Informaticist and Molecular Genetic Pathologist
Presentation for CLIAC on April 10, 2024

Disclosures

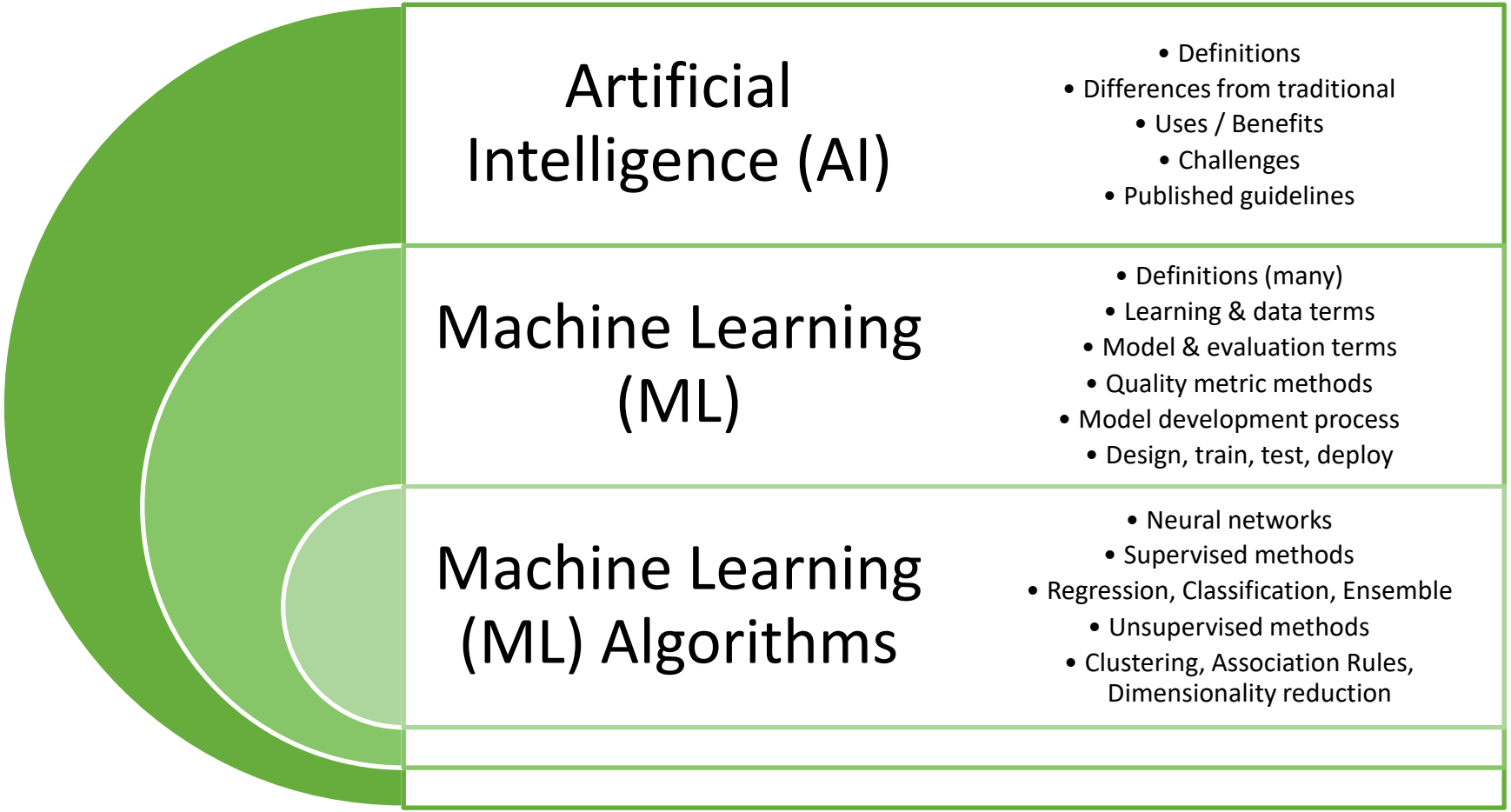
In the past 12 months, I have not had any significant financial interest or other relationship with the manufacturers of the products or providers of the services that will be discussed in my presentation.

Having said that, attendees should be aware that:

- I am a paid faculty member of the AMIA Clinical Informatics Board Review Course.
- My spouse received consulting fees from Sysmex International, Inc.
- I am the immediate past Secretary/Treasurer for AMP
- I am on committees of several professional societies (CAP, AMP, CLSI) and one federal working group for CLIAC.

Goals and Objectives

- VERY high-level overview of Artificial Intelligence and Machine Learning (AI/ML)
- Describe current and future potential applications of AI/ML
  - Anatomic Pathology
  - Clinical Pathology
- Understand why it is critical for pathologists and laboratories to bring in data scientists to use AI/ML wisely

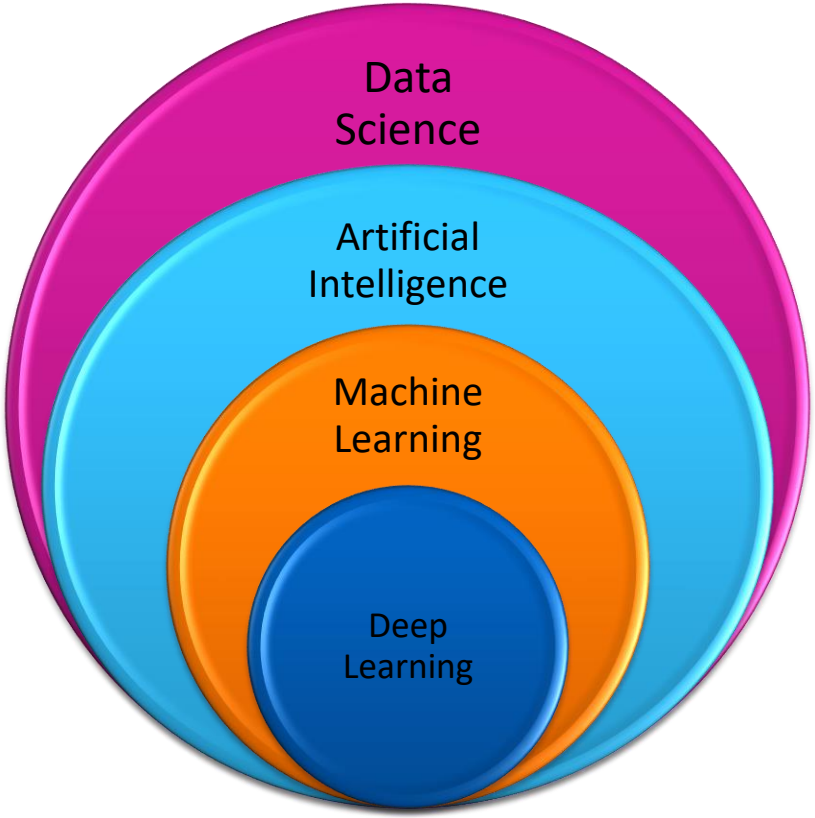

Artificial Intelligence (AI)
• Definitions
• Differences from traditional
• Uses / Benefits
• Challenges
• Published guidelines
Machine Learning (ML)
• Definitions (many)
• Learning & data terms
• Model & evaluation terms
• Quality metric methods
• Model development process
• Design, train, test, deploy
Machine Learning (ML) Algorithms
• Neural networks
• Supervised methods
• Regression, Classification, Ensemble
• Unsupervised methods
• Clustering, Association Rules, Dimensionality reduction

Artificial Intelligence

Definitions

Definitions

- **Data Science:** Science of organizing / analyzing massive amounts of data (In pathology = computational pathology)
- **Artificial intelligence (AI**): ability of a computer or computer-controlled robot to perform tasks commonly associated with intelligent beings https://www.britannica.com/technology/artificial-intelligence
- **Machine Learning (ML):** Algorithms which allow computers to learn with**out** explicit programming
- **Deep Learning**: Specific set of ML tools designed to handle big data (e.g., specific neural networks)



Definitions

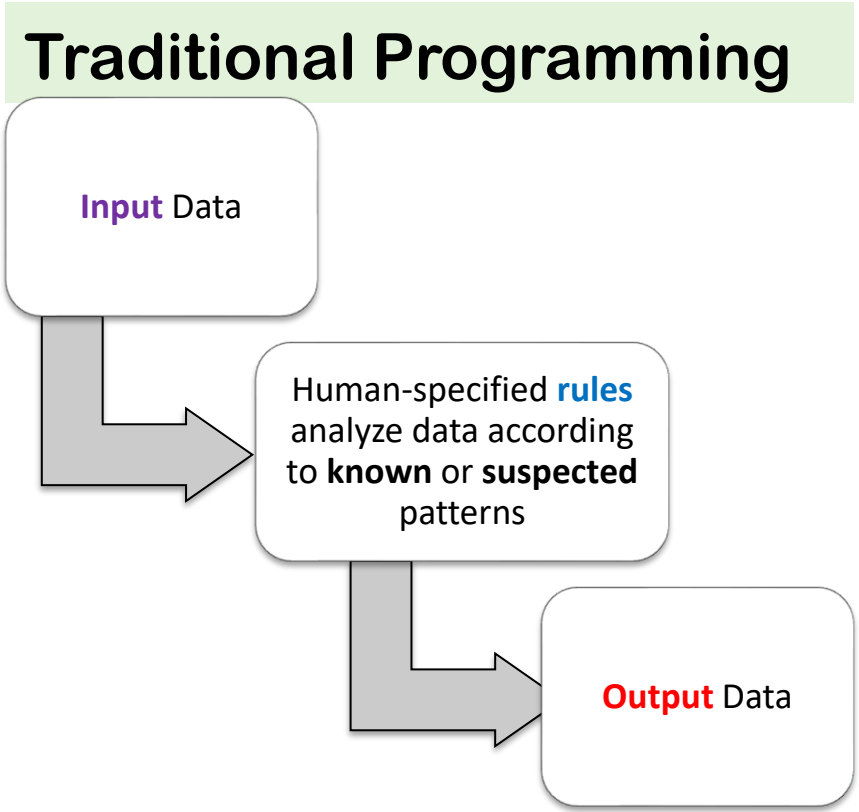
- **Narrow AI***
  - The machine can perform a **single** specific task better than a human
- **General AI**
  - The machine can perform **any intellectual task** with the **same** accuracy as a human
- **Strong AI**
  - The machine **outperforms** humans in **many** tasks

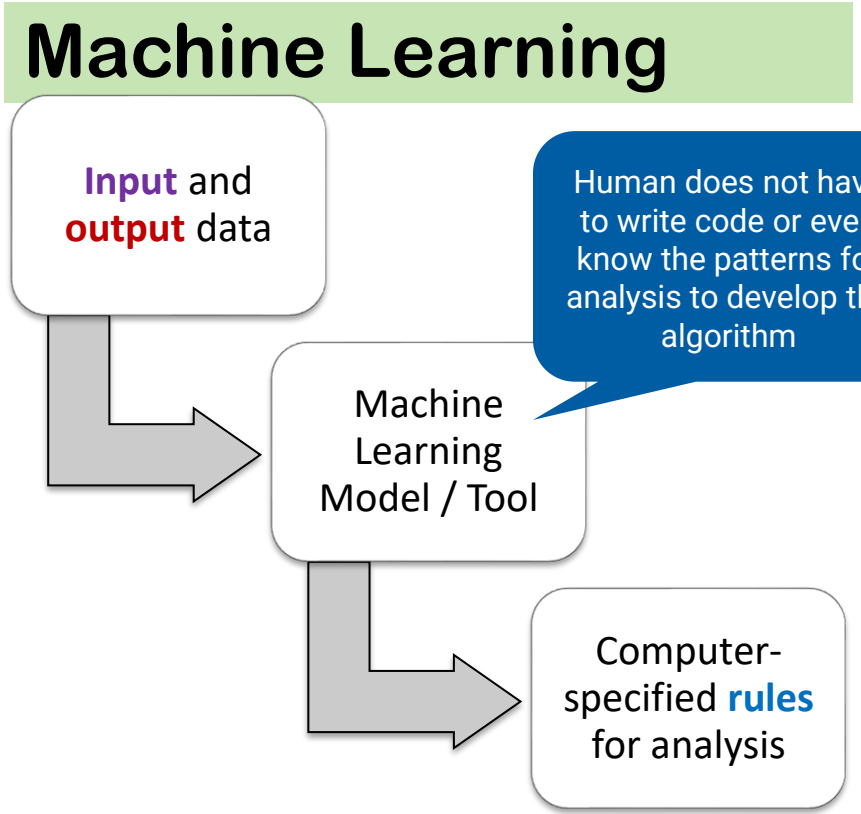
*** All currently deployed AI tools are only narrow AI.**

- "**AI Effect**" and "**Tesler's theorem**"
  - AI is whatever hasn't been done yet
  - Optical character and voice recognition, automated pap smear and peripheral blood smear readers, bioinformatics pipelines → no longer considered AI
- **Autonomous intelligence**
  - AI is making the decisions (no "human-in-the-loop")
- **Augmented intelligence**
  - AI is used to augment and/or assist humans in their work
  - Maintains "human-in-the-loop"; human ultimately making decisions

Why is Artificial Intelligence different?

Machine Learning vs. Traditional Programming





Machine Learning vs. Traditional Statistics

Function	Traditional Statistics	Machine Learning
Defines explicit mathematical relationship between inputs and outputs	Yes	Not usually
Makes assumptions about characteristics and distribution of the data fed to it •Parametric vs. Non-parametric •Normal distribution vs. Non-normal distribution	Yes	Not usually
Handles large # input variables	Not usually	Yes
Can use complex multifactorial data	Not usually	Yes
Reason for output is clear and explainable	Yes	Not usually **(black box problem)**

Uses and Benefits of Artificial Intelligence and Machine Learning (AI/ML)

Uses and Benefits – Anatomic Pathology

- Classifications
  - Current Hype
    - Histopathologic diagnosis through image analysis (active research area)
  - Actual current and possible uses
    - Smart assistive technology for pathologists to make diagnoses better, faster
      - Counting mitoses
      - Finding tiny metastases
      - Detecting sneaky microorganisms
- Predictions based on histologic features
  - Prognosis of patient
  - Molecular sub-characterization
- Anomaly detection
  - Detecting errors in data (e.g., pathology reports…Ye JJ, Tan MR*, J Pathol Inform*, 2019; 10:20)

Uses and Benefits – Clinical Pathology

- Predictions
  - Lurking medical diagnoses from general laboratory test results (e.g., future anemia from CBC trends)
  - Patient volumes → adjust staffing
  - Determination of optimal future state workflows / functional gaps in process redesign
  - Predicting, detecting and subverting malware attacks
- Classifications
  - Pattern detection (e.g., diagnoses), feature detection (images)
  - NGS variant pathogenicity algorithms
  - Variant prioritization of variants determined through exomes and genomes
- Decision support
  - Making prior authorization decisions
- Signal conversion
  - E.g., natural language processing, voice recognition, optical character recognition
- Anomaly detection
  - Problem-solving for unexpected laboratory results
  - Monitoring for shifts and trends in live result data that may indicate instrument problem before the next QC run

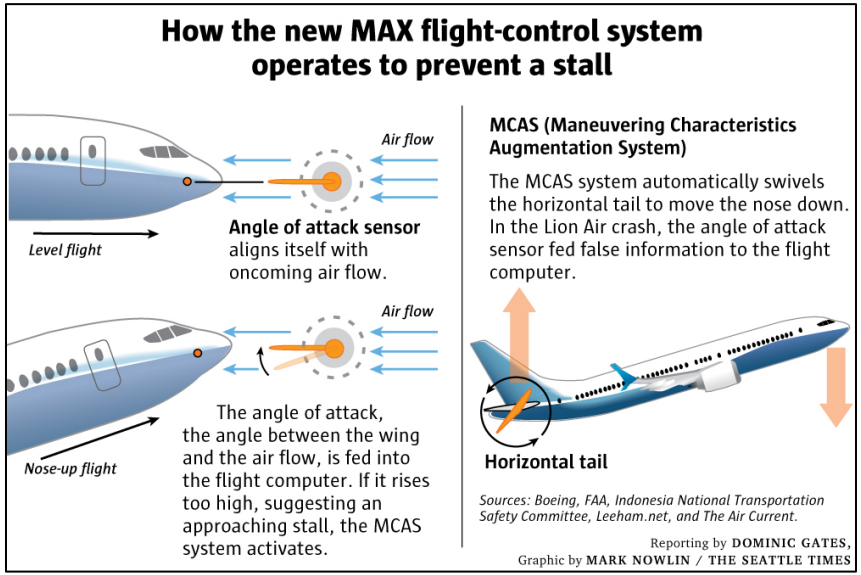
Challenges

Challenges

- Some challenges similar to other non-AI software
  - Cybersecurity risks
  - Software can be developed with bad data or bad science
  - **Automation bias** – assumption that the computer is right, even when it doesn't make sense
    [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3240751/]
  - Inaccurate assumptions about data accuracy and representation
    - https://spectrum.ieee.org/how-ibm-watson-overpromised-and-underdelivered-on-ai-health-care

Challenges Illustrated - Story of Harm

- **Boeing 737 MAX flight control system**
  - Two plane crashes killing all 346 passengers in Oct 2018, Mar 2019
  - **Faulty** angle-of-attack **sensors** fed bad data to system
  - **No redundant sensors** required to detect when sensor was faulty
  - **No usable human override mechanism**
  - **Default configuration did not show alerts** for mismatched sensor data (when >1 sensor present)
  - **System was not set to disengage** when multiple errors generated at once
  - **Similar errors during simulations not reported to FAA** by Boeing because they were considered "advisory" rather than "critical"
  - FAA, citing lack of funding and resources, over the years had delegated increasing authority to Boeing to assess its own work during certification processes



- Image from: https://arffwg.org/max-737-sensor-w/
- https://arffwg.org/max-737-sensor-w/
- https://www.washingtonpost.com/transportation/2019/05/15/faa-chief-be-pressed-boeing-max-while-would-be-replacement-faces-questions-his-approach-air-safety/?noredirect=on&utm_term=.ffb046749452
- https://www.faa.gov/foia/electronic_reading_room/boeing_reading_room/media/737_RTS_Summary.pdf

Challenges – Data Quality

- Good quality data is **critical**
  - bad data → bad model
  - Some models need large amount of training data
- Data have insufficient quantity / variability for context
  - Especially problematic for models finding less common patterns (e.g., disease screening, anomaly detection)
  - Underrepresented populations → non-generalizable rules (socioeconomic, gender, race, ethnic and other disparities)
- Data labels represent human bias / false beliefs
  - e.g., court sentences, hiring / firing decisions
  - Can promulgate or exacerbate inequality
- Data have incomplete, inaccurate and/or variable labels
  - Different terms or metrics for same label due to human inconsistency
- Critical input data may be missing
  - **Polanyi's Paradox**:
    - Human decision-making beyond explicit understanding or description
  - Human may not realize which data contributed to human decision
  - Critical inputs may not be represented in AI training data

Challenges – ML Model Problems

- Models can be brittle
  - Small changes in input → big changes in output
  - Unable to see the forest for the trees (double-edged sword)
  - Humans are BETTER at generalization and situational awareness
- Small changes to input introduced by hackers (**adversarial examples**) led to wrong output [https://www.nature.com/articles/d41586-019-03013-5]
- Models can also degrade over time
  - Similar concept for laboratory tests (drift, shift)

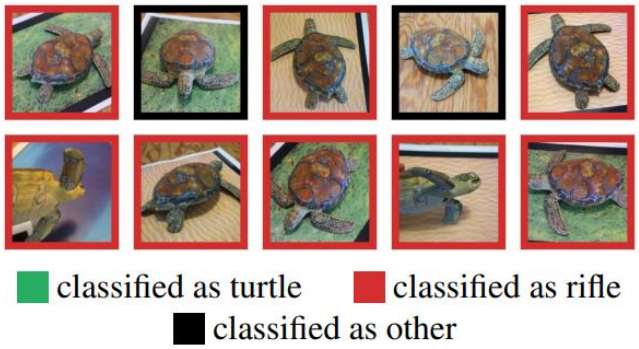


Figure 1. Randomly sampled poses of a 3D-printed turtle adversarially perturbed to classify as a rifle at every viewpoint[2]. An unperturbed model is classified correctly as a turtle nearly 100% of the time.

Athalye et al. 2018.
https://arxiv.org/pdf/1707.07397.pdf

Challenges - Cybersecurity

- AI can be hacked just like any other software
  - Robotic surgical systems (https://www.ncbi.nlm.nih.gov/pubmed/30397993)
- Hacked systems have potential for unauthorized disclosure, patient harm
- Human autonomy ("human-in-the-loop") may help detect malfunctions
- US national efforts for AI cybersecurity
  - National Security Commission on Artificial Intelligence (https://www.nscai.gov/)
    - Established 2018 by John S. McCain National Defense Authorization Act (Public Law 115-232)

Challenges - Transparency

- Definitions (multiple)
  - For AI developers: Reasons for model's performance are **known** and **understood**
  - For end-users (ethics): Sufficient information is published such that model's performance can be audited [https://www.who.int/publications/i/item/9789240029200]
- Lack of transparency (**Black box problem**)
  - Rules developed by the AI algorithm
    - May be indecipherable after model is trained, even to the developer(s)
    - May not be able to determine why algorithm generated certain output
    - May generally work well but some output may be inexplicably wrong

Challenges - Ethics

- Hot topic because of some noted failures
  - https://georgetownsecuritystudiesreview.org/2021/05/06/racism-is-systemic-in-artificial-intelligence-systems-too/
  - https://technologyandsociety.org/bias-and-discrimination-in-ai-a-cross-disciplinary-perspective/
  - https://www.technologyreview.com/2019/01/21/137783/algorithms-criminal-justice-ai/
- **Beneficence:** Maximize benefits; minimize risks and harms
  - AI can propagate and exacerbate human bias
  - Protect human autonomy in decisions (**"human-in-the-loop"**)
    - ACR and RSNA recommendation → do not approve autonomous AI until sufficient human-supervised AI experience obtained
- **Auditability**: Audit the tool to verify performance, ensure ethics followed
- **Accountability**: Who or what is accountable when something goes wrong
  - Medicolegal liability
    - AI is not standard of care
    - Regulations not yet developed in US
    - EU paper (https://pubmed.ncbi.nlm.nih.gov/33489979/) that discusses that liability is based on physician using standard of care

Challenges – Ethics (cont.)

- **Intelligibility**
  - Achieved through Transparency and eXplainability
    - https://nvlpubs.nist.gov/nistpubs/ir/2020/NIST.IR.8312-draft.pdf
  - **Transparency** [https://www.who.int/publications/i/item/9789240029200]
    - Sufficient information **published** before the design or deployment of an AI technology
      - Describes how technology is designed, intended use, data used, etc.
    - Also means that a person knows when AI is being used on them
  - **eXplainability** (XAI)
    - Providing the human user an explanation of how the AI tool works

Other Challenges

Personnel

- Medicine lacks sufficient data scientists
- Many data scientists lack expertise in medicine and/or healthcare environment

Organizational

- Lack AI strategies
  - Right tasks
  - Right data
  - Right evidence standard(s)
  - Right approaches for integration
- Deploying models in clinical environments is challenging (patient safety, population differences between locations)

Financial

- Lack of reimbursement mechanisms
- Harder to define returns on investment

Technical

- Lack of adequate computational infrastructure
- Introduces new cybersecurity threats that aren't yet addressed

Response to Challenges → Guidelines

- Guideline for machine learning model development (US, Canada, UK Guideline – Oct 2021)
  - https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles
  - Multidisciplinary expertise throughout
  - Good software/security practices
  - Data representative of intended patient population
  - Training data independent of testing data
  - Reference data is well characterized
  - Model design tailored to available data and reflects intended use
  - Focus on keeping the human in the loop (human AI team)
  - Testing demonstrates performance during clinically relevant conditions
  - Users provided clear essential information for use
  - Deployed models are monitored for performance in the real world
- AI Ethics Guidelines and White Papers
  - WHO Ethics Guidelines for AI https://www.who.int/publications/i/item/9789240029200
  - UNESCO https://unesdoc.unesco.org/ark:/48223/pf0000379920.page=14
  - EU guidelines https://digital-strategy.ec.europa.eu/en/library/ethics-guidelines-trustworthy-ai
  - https://www.intelligence.gov/artificial-intelligence-ethics-framework-for-the-intelligence-community

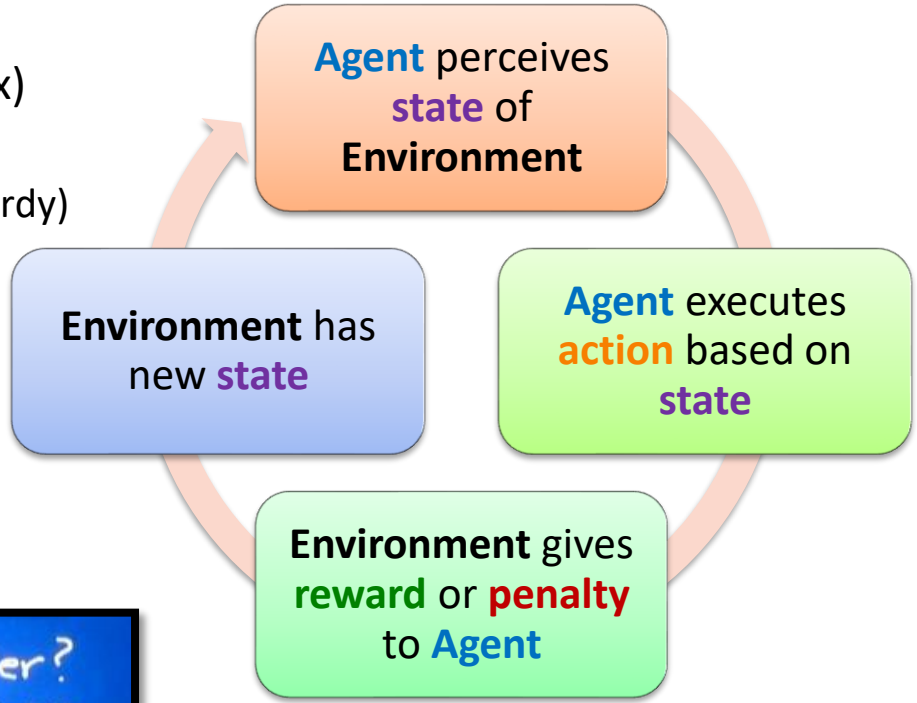
Machine Learning Rudimentary Basics

ML Definitions – Types of Learning

Supervised learning	Trains on classified and/or labeled data • Goal → train model to generate **known** answers, patterns or relationships
Fully supervised	All data labeled to same extent (degree of detail)
Semi-supervised	Some data are labeled while other data are not • Unlabeled data may be auto-labeled to match patterns on labeled data
Weakly supervised	Small amount of data have detailed labels; rest of data have fewer labels
Unsupervised learning	Data which have **not** been classified or labeled • Goal → model discovers **new** (previously **unknown**) patterns or relationships

ML Definitions – Types of Learning

- **Reinforcement learning**
  - Used to learn how to reach a (complex) goal
    - Game playing (IBM Watson and Jeopardy)
    - Speech to text, financial trading



ML Definitions – Types of Learning

- **Transfer learning**
  - Separate category vs. subtype of supervised learning
  - Data used for training the model are transferred from a different related domain
    - Data were developed for use in a domain different than the one intended for the model
    - Example: Using natural images from ImageNet (https://image-net.org/) to train a models for medical images [Alzubaidi et al 2021 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8036379/]
  - Coarse training done on transferred data
  - Fine tune training with smaller data directly related to domain of use
  - Reasons
    - Data are expensive
    - Higher quality and quantity data may be more available, cheaper in another domain

ML Definitions - Data

- **Instance**
  - Single event in a data set
  - # instances required to train a model depends on the problem and model used
  - **Outlier**
    - Instance which is significantly different from the remaining instances in the population
    - Can skew results
    - Different models have different sensitivities to outliers
- **Label** – observed value for a feature of an individual instance
- **Feature**
  - An aspect (variable) of the training data
  - Called a **dimension** in unsupervised learning

	Feature 1	**Feature 2**	**Feature 3**
Instance 1	Red	Slow	Yes
Instance 2	Red	Fast	No
Instance 3	Green	Medium	No

Red, Green, Slow, Fast, Medium, Yes and No are all **labels** in this data set.

ML Definitions - Models

- **Algorithm**
  - Repeatable process used to train a model from a given set of training data
- **Parameter**
  - Internal values inside machine learning that the model derives based on training data
  - e.g., weights, bias values
- **Model** = algorithm + parameters
  - When a model is used for classification, it is called a **classifier** [https://towardsdatascience.com/machine-learning-classifiers-a5cc4e1b0623]
  - **Weak learner (weak model):** model whose performance only slightly > random chance
  - Good model: model that **generalizes well** (it performs the same on new data as it did on the training (and test) data)
- **Epoch**
  - 1 epoch = 1 pass through the training data

ML Definitions – Model Evaluation

Signal

The true underlying pattern you are trying to learn from the data

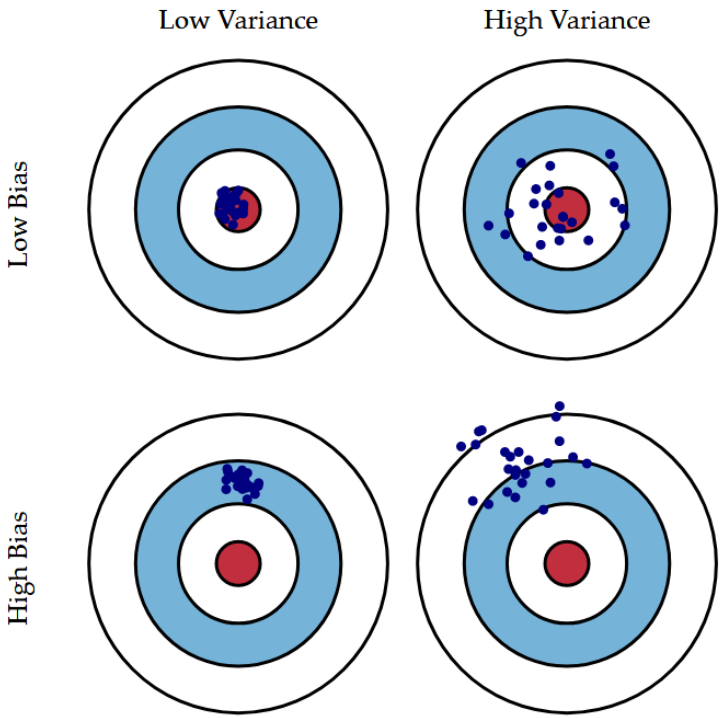
Well designed machine learning separates signal from noise

Noise

Irrelevant information or randomness in a data set

Irreducible error

Bias	Variance	Irreducible error
• Measure of inaccuracy • High bias + low variance ➔ consistently inaccurate results	• Measure of imprecision (lack of reproducibility) • High variance + low bias ➔ inconsistently accurate results	• Noise that cannot be reduced by optimizing algorithms



https://devopedia.org/bias-variance-trade-off

ML Definitions – Model Evaluation

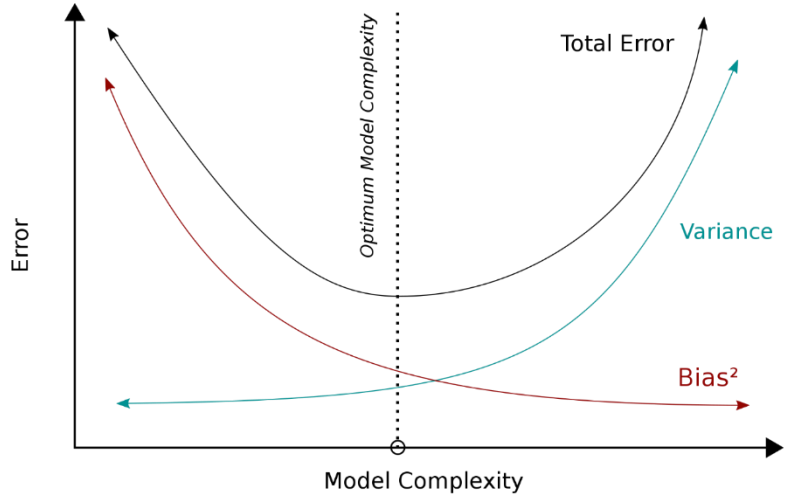
Bias

- *Not just an ethical term…*
- Amount of **inaccuracy** in the model's performance after training
- High bias → model is inaccurate (underfit)
- Low bias → model is accurate (but may be overfit)

Variance

- Amount of **imprecision** (square of standard deviation (σ) → σ^2)
- Due to model's sensitivity to small fluctuations in the training set
- High variance → model is imprecise (and likely overfit)
- Low variance → model is precise (but may not be accurate and may be underfit)

ML Definitions – Model Evaluation



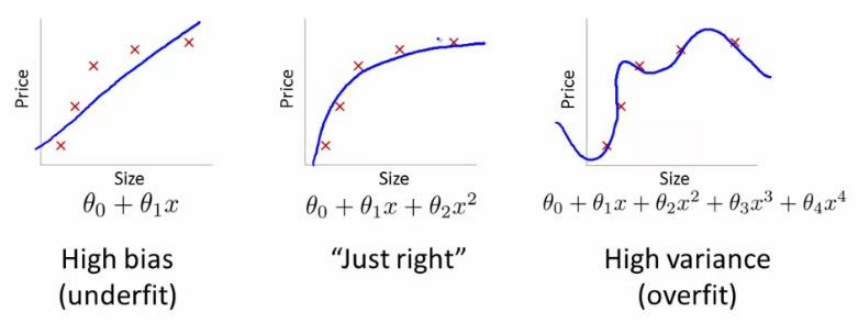
- **Bias-Variance Trade-Off**
  - Things that reduce variance increase bias
  - Things that reduce bias increase variance

$$Total\ error = (bias^2) + variance + irreducible\ error$$

https://en.wikipedia.org/wiki/Bias%E2%80%93variance_tradeoff
https://towardsdatascience.com/understanding-the-bias-variance-tradeoff-165e6942b229

ML Definitions – Model Evaluation

- **Goodness of fit**
  - How closely a model's output values match the observed (true) values
- **Underfitting**
  - Model does not accurately predict output for the data fed to it
    - high bias, low or high variance
- **Overfitting**
  - Occurs when statistical model exactly fits training data BUT…
    - Does not fit new data well (test or production data)
  - Training set has low error rate but test set has high error rate = high variance
  - **Most common problem** for any statistical model using a training set



https://datascience.stackexchange.com/questions/361/when-is-a-model-underfitted

ML Definitions – Model Evaluation

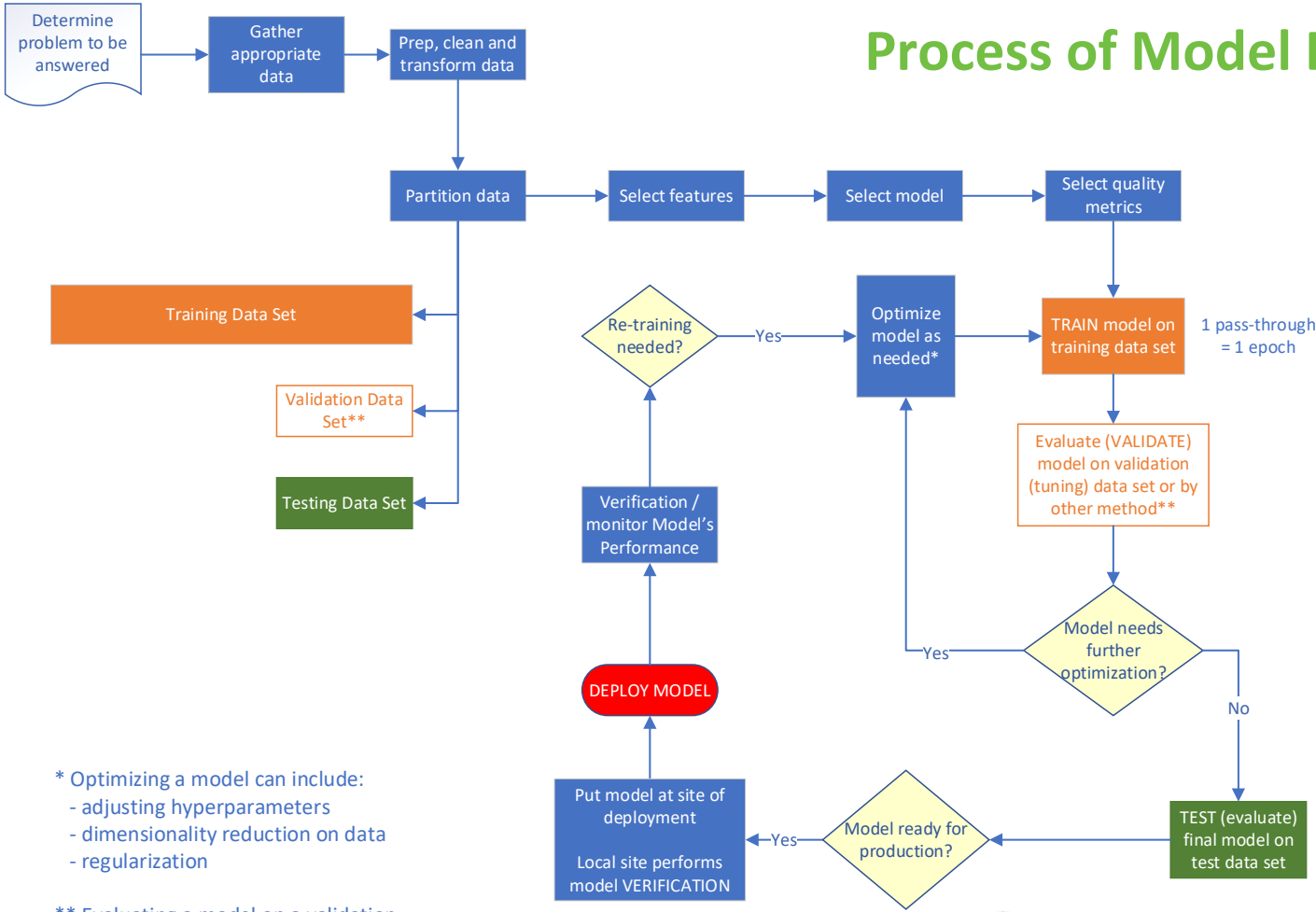
- **Null error rate**
  - For classification methods, rate of being wrong if you ALWAYS pick the majority class
  - If the majority class has 105 instances out of 165 total instances
    - Null error rate = (165 – 105)/165 = 36%
  - **Accuracy paradox**
    - Best classifier for the intended use may have a higher error rate than the null error rate
    - Occurs when condition or outcome is very low percentage of overall data set (e.g., 1%)
    - Model can correctly predict absence of the condition in 99% of cases – hooray! BUT…
    - May completely fail to detect the condition being sought
      - 100% failure of detecting the condition (but null error rate is only 1%)
    - Take home point → Use different statistical methods when trying to screen for low incidence conditions

Process of ML Model Development

- Many ways that a model can be trained → tested → deployed
  - Depends on model, amount of data, and other factors
- Phases of model development have variable nomenclature between authors
  - E.g., learning phase, inference phase
- A few definitions to resolve possible confusion

	What it means in machine learning…	**What it means in a hospital laboratory…**
Validation	Evaluating preliminary (non-final) *model* • Results of evaluation lead to tweaking (tuning) the model	Final evaluation of a *laboratory test* where no further changes to the test procedure are expected
Testing	Final evaluation of a *machine learning model* where no further changes to the model are expected	Evaluating preliminary (non-final) *laboratory test* OR Performing live clinical testing

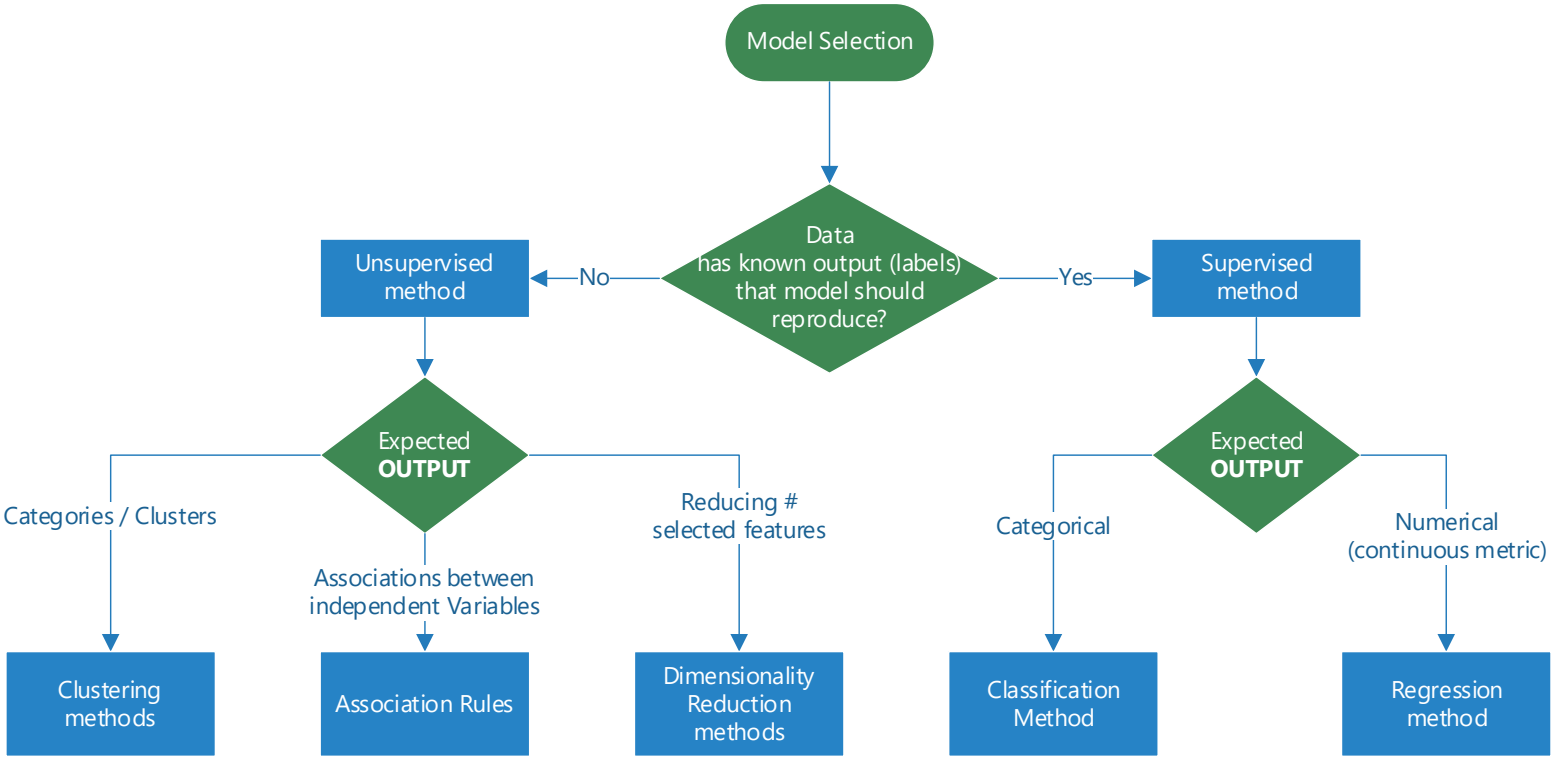
Process of Model Development



* Optimizing a model can include:
  - adjusting hyperparameters
  - dimensionality reduction on data
  - regularization

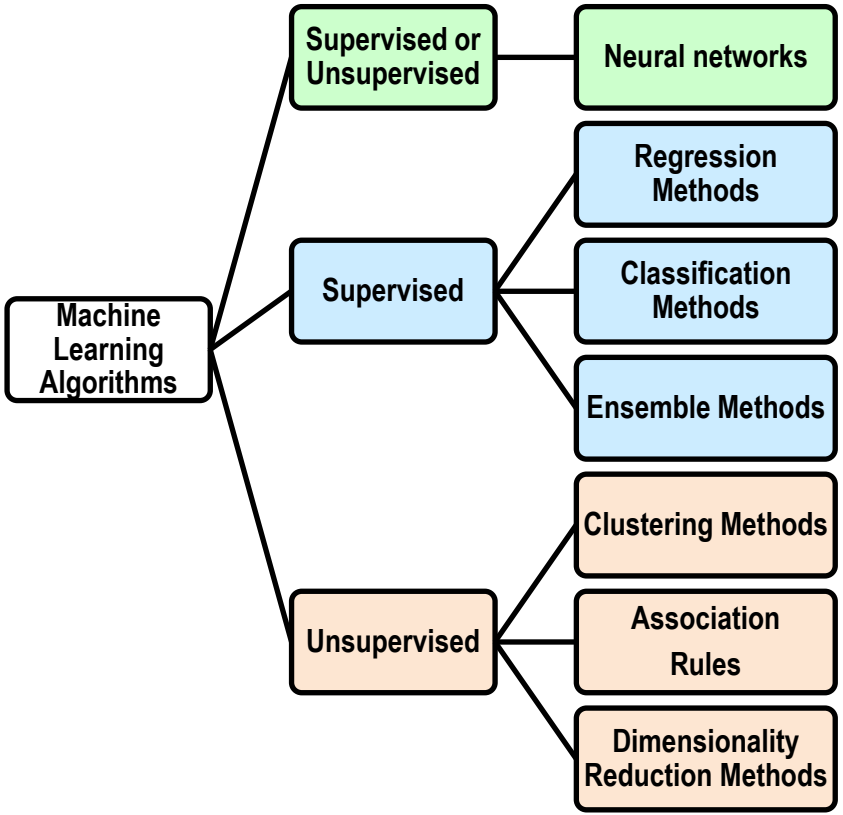
** Evaluating a model on a validation data set may not always be needed.

Process of Model Development



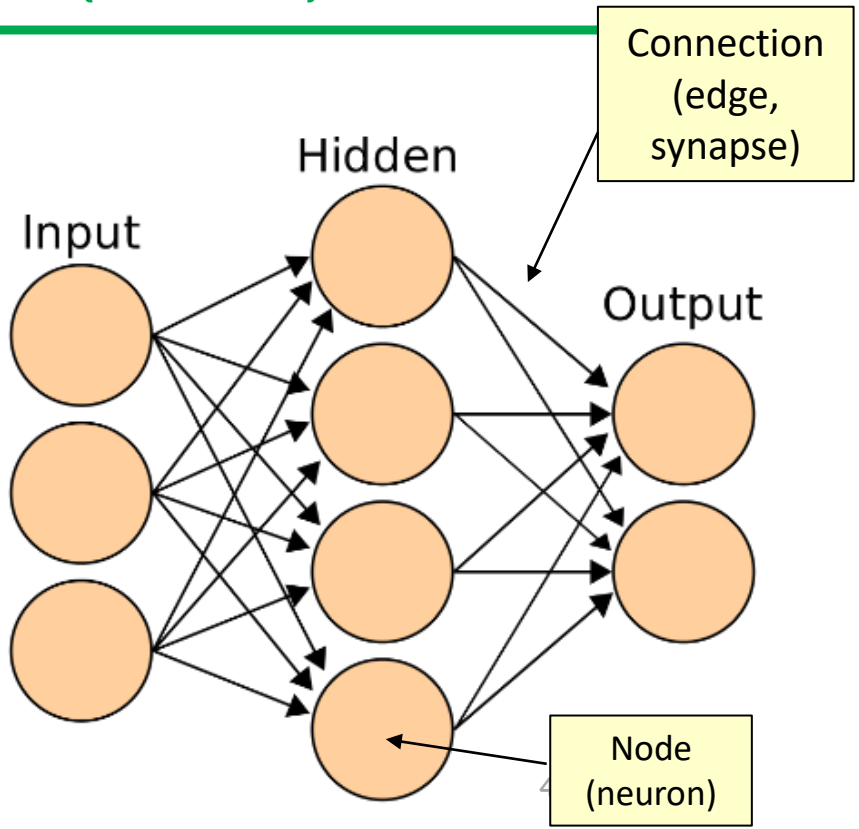
Machine Learning Algorithms

- Each category has algorithms that are primarily used for that purpose
- However, classification algorithms may sometimes be used for regression and vice versa
- Unsupervised algorithms may sometimes be used with supervised learning



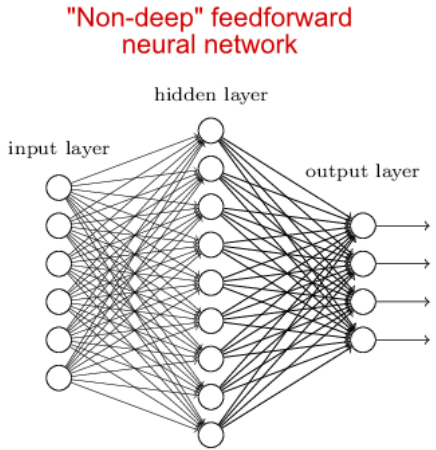
Artificial Neural Networks (ANNs)

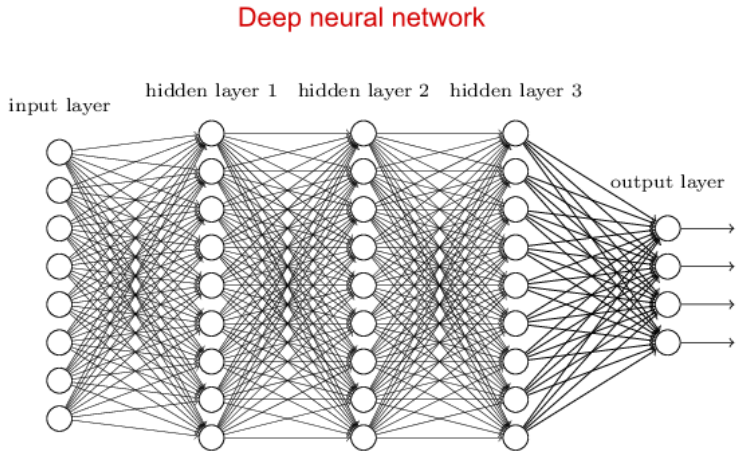
- Goal: Solve problems like a human
- Operate via flow through neural nets, akin to biological networks
  - Handles large amounts of complex data
  - Computationally intensive
  - Unraveling the pathways after training is completed can be difficult to impossible → **Black Box Problem**
- **Nodes** (akin to neurons) → transfer functions
- **Connections** (akin to synapses, a.k.a. edges)
- **Back-propagation** (nice YouTube (https://www.youtube.com/watch?v=Ilg3gGewQ5U) video)
  - Learns mistakes based on output
- Layers (nodes in each layer *usually* have same activation function)
  - **Input layer**: # nodes = # features selected in data
  - **Output layer**: # nodes = # output categories of data
  - **Hidden layer(s): Shallow networks** usually have 1; **Deep networks** have >3



ANN – Deep Learning

- **Deep Learning** (a.k.a. deep networks; deep nets)
  - Goal: *imitate the human brain* in processing data and decision-making patterns
  - Usually multiple (Some say > 1 to >3 to hundreds to thousands) of hidden layers
    - Thousands to millions of interconnections; large number non-linear computations
  - Means more in-depth processing, *not* more in-depth knowledge





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Questions?

COLLEGE of AMERICAN PATHOLOGISTS

Statement to the Clinical Laboratory Improvements Advisory Committee Meeting April 10, 2024

The role of artificial intelligence (AI) and machine learning (ML) in the clinical laboratory

The College of American Pathologists (CAP) appreciates the opportunity to provide written comments to the Clinical Laboratory Improvement Advisory Committee (CLIAC). The CAP is the world's largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, and continually strives to improve and advocate for excellence in the practice of pathology and laboratory medicine worldwide in service to our patients and members, practicing pathology and laboratory medicine worldwide.

The CAP believes the training and use of artificial intelligence and machine learning (AI/ML) algorithms introduces a fundamentally new kind of data analysis into the healthcare workflow that requires an appropriate regulatory framework. By virtue of their influence on pathologists and other physicians in selection of diagnoses and treatments, the outputs of these algorithms can critically impact patient care. The data patterns identified by these systems are often not exact, as there is no perfect separation of classes or predictions. Thus, there are analogies with sensitivity, specificity, and predictive value of other complex tests performed by clinical laboratories. However, in machine learning the patterns in data are identified by software and often are not explicitly revealed. Biases or subtle errors may be incorporated inadvertently into machine learning systems, and these must be identified and mitigated prior to deployment. Naturally occurring variations in healthcare context such as case mix changes, updated tests or sample preparation, or new therapies, may also change the input data profile and reduce the accuracy of a previously well-functioning machine learning system.

The CAP anticipates that in the near future AI/ML-based technologies will power highly useful applications in a broad range of medical settings including some that are performance-critical, particularly those termed Machine Learning-enabled Device Software Function (ML-DSF). For success and safe operation, the performance quality of these applications must be verified after installation and monitored over time. Performance problems may occur if there are differences in the details of local data in comparison with the data used to train the software or if the characteristics of local data drift over time. Updates to software affecting the machine learning components inherently re-define the relationship between the training and local data and require a practical and appropriate re-verification of performance to ensure safe and effective operation. Hence, ML-DSF are analogous to high complexity diagnostic testing in requiring verification at installation and robust quality control/quality assurance procedures. Because of the partial analogy of these new technologies with current diagnostic testing, the expected impact of these technologies on the practice of pathology and laboratory medicine, and the need to adhere to CLIA in the laboratory setting, the CAP has a keen interest in the regulatory approach for AI/ML technologies.

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CAP members have extensive expertise in providing and directing laboratory services under the Clinical Laboratory Improvement Amendments (CLIA) regulations, which require compliance with requirements through a quality system approach for overall operations and administration of the clinical laboratory. This includes the verification and validation of any new or modified tests and devices. It is important to note that there are quality practices in the laboratory specified by CLIA that are separate from operational requirements defined by a manufacturer of a medical device and approved by the FDA. While CLIA regulations are not directly applicable to other medical specialties, they may inform thinking about performance quality goals in ways that strengthen current efforts to develop AI/ML regulations and improve the consistency of their application across medical specialties. As these tools support the decision-making of providers, the role of pathologists and other specialties to interpret results must be defined.

We encourage CLIAC to work with the FDA in drafting regulation to ensure harmonization and consistency across all requirements. The FDA proposed to regulate types of AI/ML-based software as a medical device (SaMD) modifications including (1) clinical and analytical performance improvements, (2) changes in data inputs and (3) intended use of the software. The details of these kinds of modifications and the requirements for local verification and re-verification are critical and need to be better specified. Furthermore, data inputs to SaMD may be subject to variation in the real world, for example, laboratory test results can vary based on testing kit or instrument platform produced by various vendors or microscope slides produced and stained by different histology laboratories and scanned with different devices.

As such, an effective and equitable regulatory framework for machine learning in healthcare will 1) define requirements based on risk and tailored to the likelihood and magnitude of possible harm from each machine learning application, 2) require best practices for system developers including bias assessment and mitigation, 3) define appropriate best practices for verification of system performance at deployment sites, such as local laboratories, 4) define best practices for monitoring the performance of these AI/ML systems over time and mitigating performance problems that may develop, and 5) clearly assign responsibility for problems if and when they occur .

Many considerations must be addressed before regulations can be drafted. It must be determined, for example, if a SaMD will require explicit validation for use with test kits or scanning devices. If a laboratory test that is used as one of several inputs for an AI/ML predictive algorithm is changed for cost reasons to a similar test from a different vendor, would that change or invalidate a SaMD or require local re-verification? If the latter, what form of re-verification would be acceptable? In a setting where multiple algorithms are deployed, to what extent do the requirements for validation of those algorithms “lock in” methodologies and workflows for the clinical data elements upon which they depend? This kind of lock-in has the potential to reduce the organizational agility that the FDA is hoping to promote with these regulatory changes. Can general purpose validation and performance monitoring practices be defined that identify and mitigate these kinds of problems? Should data input devices such as whole slide imaging systems and chemistry and hematology analyzers be held to reproducibility standards (e.g.

color reproduction, resolution, adsorption, etc.) that keep them within some performance envelope that all SaMD manufacturers can target?

Lastly, these systems must ensure excellent performance monitoring and maintenance. Given the inherent black box nature of the advanced mathematical approaches that underpin the SaMD applications in question and the potential for drift over time there must be a robust quality control, quality assurance and quality improvement processes, including strict delta checks and a high frequency of mandatory "result" review prior to verification. Furthermore, any modification of inputs and/or intended uses, including the SaMD Pre-Specifications concept, should be viewed as an entirely new product in need of FDA approval.

Once again thank you the time to discuss the CAP's concerns and recommendations and we welcome the opportunity for further dialogue. Please contact Andrew Northup at anorthu@cap.org or 202.297.3726.

Closing,

The College of American Pathologists

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April 10, 2024

Heather Stang MS, MLS (AMT)
Executive Secretary
Clinical Laboratory Improvement Advisory Committee
Centers for Disease Control and Prevention
CLIAC@cdc.gov

RE: Virtual Comments for April 10, 2024 Spring Virtual Clinical Laboratory Improvement Advisory Committee Meeting, the Role of Artificial Intelligence and Machine Learning in the Clinical Laboratory

The National Society for Histotechnology (NSH) appreciates the opportunity to provide comments concerning the Role of Artificial Intelligence and Machine Learning in the Clinical Laboratory on behalf of its membership. The National Society for Histotechnology is a non-profit member organization that supports histotechnicians and histotechnologists worldwide through education, collaboration and innovation.

When CMS last revisited the CLIA regulations in 1992, it excluded from oversight many histological pre-analytic, analytical, and post-analytical processes because they were deemed relatively simple, minimal risk procedures that did not require a Histotechnologist to produce an independent result. As NSH has commented in previous letters to CLIAC much has changed in the last 30 years, and an educated, well-trained Histotechnician and Histotechnologist is essential to arrive at an accurate diagnosis of anatomic pathology samples. The field of histotechnology has witnessed unprecedented technical advances over the last two decades, including innovative approaches, methodologies, and automation in traditional areas (tissue processing, histochemistry) as well as in the fields of immunohistochemistry, molecular diagnostics, and computerized assisted digital analysis (artificial Intelligence and machine learning) all critical to patient diagnosis and treatment.

The medical profession continues to expand and utilize artificial intelligence and machine learning to aid patient diagnosis and treatment by extracting quantitative data from digitized whole slide images. The accuracy of this data is dependent upon the quality of the histology preparations. To achieve accurate and reproducible results from whole slide imaging to routine image analysis solutions to those that utilize artificial intelligence and machine learning, high quality histology is a necessity playing a significant role in the *Total Test* approach (1-4).

There are numerous challenges to applying current CLIA regulations to the technologies using artificial intelligence and machine learning. Histotechnicians and Histotechnologists perform a critical role in the process and are not currently under CLIA's oversight nor meet CLIA's high complexity personnel requirements. The National Society for Histotechnology advocates that the CLIA recommendations be amended to include Histotechnicians and Histotechnologists under CLIA's oversight therefore requiring histology laboratory personnel to meet CLIA's high complexity personal requirements.

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As technology continues to advance at a rapid pace, NSH strongly recommends that a CLIAC workgroup be formed to discuss the requirements that should be added or revised in CLIA to ensure the quality of testing when artificial intelligence and machine learning are a part of the total testing process. Furthermore, NSH strongly recommends that a histology professional be included on that workgroup.

The National Society for Histotechnology is the largest a non-profit member organization, representing histotechnicians and histotechnologists worldwide. NSH is the leading provider of histotechnology education designed to demonstrate continuing competence in an increasingly complex laboratory-testing environment. We look forward to CLIAC's response to these issues and continued discussion in order to advance the histotechnology profession and provide the highest quality care to the patients we serve. We thank the committee for the prior work, ongoing efforts, and consideration.

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CLIAC Public Comment April 10, 2024

Thank you for the opportunity to offer public comment as a citizen and laboratory informaticist. I am clinically trained as a medical laboratory scientist with experience in academic medical centers to smaller clinic settings especially in different needs therein. My PhD is in Health Informatics and I have a passion for laboratory data interoperability and usability of laboratory data for a variety of clinical, public health and research purposes. I'm also the first laboratory professional who is a Fellow of the American Medical Informatics Association.

Regarding the topic of Artificial Intelligence (AI) and Machine Learning (ML), I want to thank Dr. Carter for her presentation on these topics that are gaining in popularity. My doctoral training in Health Informatics includes courses in Artificial Intelligence which includes AI and ML methods in Dr. Carter's presentation, Clinical Decision Support including Tools and Impacts on Decision Making, Healthcare Data Standards to name a few. These tools can be utilized for many great applications, as well as cause harm or bad decisions if not designed/set up correctly or "hallucinate" with black box outputs. I created a simple neural network to classify anemia based upon common complete blood count parameters for a course project so these are easy to develop by many, including those without laboratory expertise.

As applications flood the market or even in those applications that one may create or customize, the question becomes how do we know these tools are functioning as expected across different care settings, sources of data, patient populations, etc. and safely, not resulting in bad outputs, patient harm, or bad decisions or recommendations? They need to be clinically validated that they are "fit for purpose" and generate quality data and outputs. I want to emphasize one of Dr. Carter's points that **quality of data is critical**. It's critical to have good data to avoid GIGO: garbage in, garbage out.

As CLIAC deliberates what may be needed to support their safe use, one consideration is where and how are they being used? Are they low risk decisions like a spell checker in software or high risk decisions such as patient care aspects? Are we even aware where they are being used within software products, whether health IT (EHR, LIS) or ancillary systems, software on IVD devices, etc.?

In my work in standards development, specifically with HL7 FHIR standards, discussion has occurred on how traceability of laboratory data and decisions occur in laboratory workflows. For example, autovalidation tables are often set up within a LIS or middleware

to autoverify and release results that are “normal.” The LIS distinguishes between human verified results and those that are autovalidated by the “software.” This provides traceability for root cause analysis and other quality needs and governance.

With Point of Care testing, how do we indicate that a human, either a consumer or health professional performed a test, versus those with companion applicaition usually on a smartphone that “interprets” result values? It may be in conjunction with a camera reader for a urine dipstick result value or a calculation within the device. These may not “visible” to the consumer or health professional buried within the software application or smartphone device itself.

Are these test results comparable if no human intervention is used in their interpretation? Trust of consumer performed and perhaps some health professional performed testing is a concern across the health ecosystem. Are we more apt to trust those without human intervention that may be used in health professional decision making? For consumer performed testing, preanalytical aspects such as specimen quality, as well as performance of the test are all factors impacting trust as downstream users of the data do not know if data quality is compromised if the test was performed on the patient’s pet or another person or invalidated if expired, etc. Consumers may not exercise the same rigor as trained health professionals regarding specimen rejection or acceptability criteria. We know these preanalytical issues can impact test performance and results interpretation whether by humans or machine learning algorithms.

The FDA sponsored Synensys report of the laboratory ecosystem assessed from a systems approach makes the recommendation that laboratory professionals and expertise be involved in many of these informatics based processes so that laboratory needs are considered.

I ask CLIAC to consider what is needed to ensure laboratory data quality and decisions with use of machine learning and make any recommendations to federal agencies to help ensure they are considered by those with AI/ML evaluation processes and regulations.

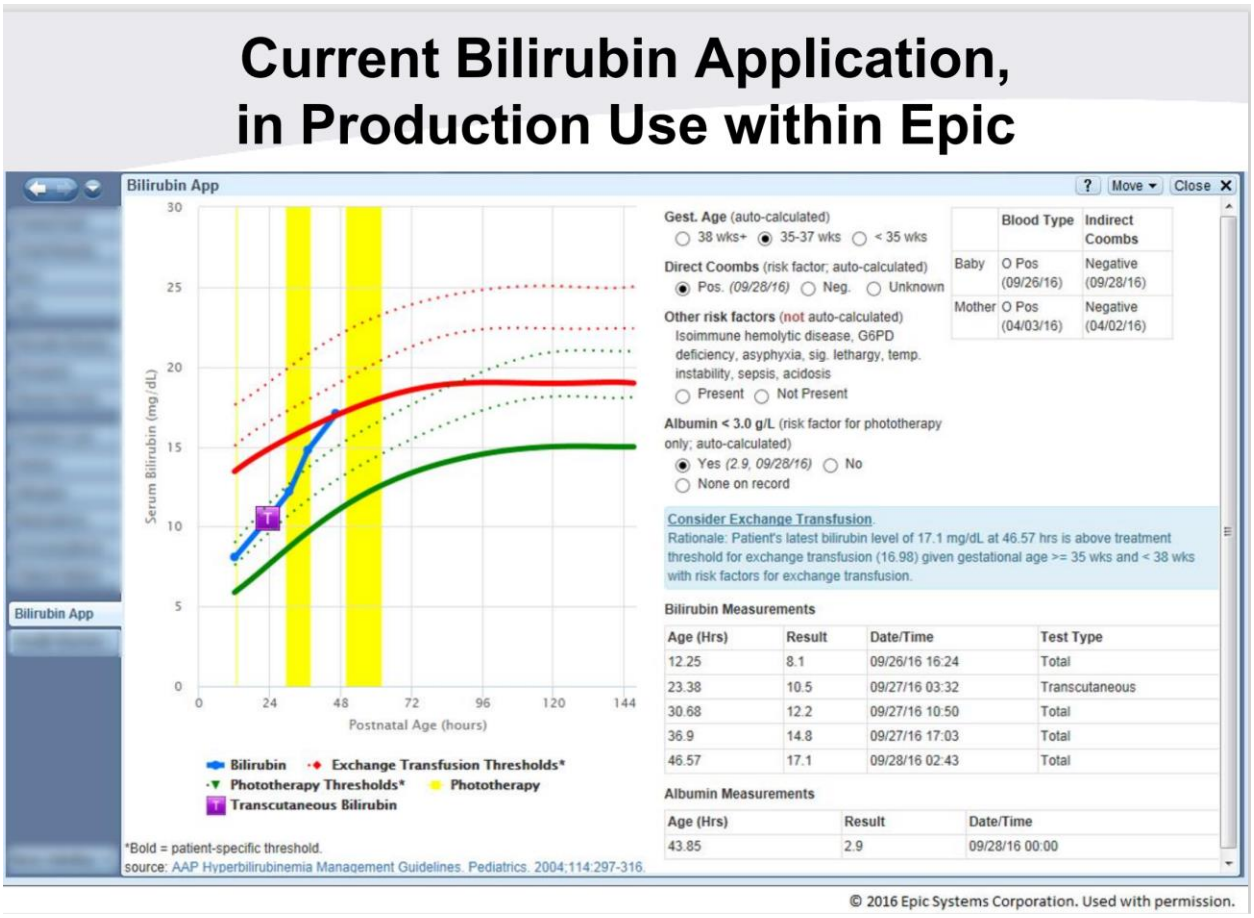
Secondly, with regard to the standards topic. I support standardization and harmonization of laboratory assays and testing to global standards for comparability and interoperability. Those test methods which are not comparable also need to distinguished so all users are aware and do not inadvertently comingle them in a variety of data uses, especially AI/ML. AI/ML trained on lab result values that have clinically significantly different methods/specimens, etc. can introduce bias into algorithms, AI/ML, as well as human assessments and use, as we see happening today. AI/ML will likely magnigy these issues

similar to the transformations we saw when paper based design or data issues were magnified with electronic implementations if they were not addressed.

Harmonization and standardization is a term used by many in the informatics and Healthcare IT space as well. Generally, it is used to mean how do I group the many ways a single lab test is performed into single term or code that I can use to refer to this item, no matter the variety of test names used by each performing laboratory. It is akin to the generic vernacular we use in talking about laboratory tests. We don't usually mention details like specimen or method when we speak about laboratory tests.

Clarity is needed by CLIAC in addressing the Standards questions and options as to which standards might be utilized. Is the focus on standards related to test performance quality as indicated by the FDA standards list showing CLSI documents referenced? Or will standards include terminology/codesystem standards for laboratory data (providing computer processable meaning) and/or data exchange standards used for laboratory data? If the latter, guidance is recommended for how quality implementations and use of the standards will be determined, which use cases or areas of laboratory medicine they will be utilized, and guidance for those inspecting to know especially with newer technologies which are compliant or not? This is an area where caution is needed as the nuances in laboratory testing may not yet warrant a single broad application, but perhaps a smaller scope that may be piloted or phased in. The initial focus may be on simpler areas of testing with lower risk too. CLIAC may also want to recommend that coordination with federal agencies, entities, states and accreditation may be warranted to help ensure definitions, uses, etc of laboratory data are the same/aligned by different entities too.

While I'm not aware of any LIS that has FHIR functionality, much less CLIA Compliant FHIR implementations, there are laboratories using FHIR for ancillary purposes and a vendor who is working on a FHIR LIS. Downstream from the LIS, EHRs and Health IT are certified to meet ONC requirements which includes FHIR and for laboratory data. There is great variability in the quality of laboratory data in these applications. For example, here's a baby bilirubin application where transcutaneous values are listed/graphed with laboratory performed values. (Slide 1 (hl7.org)) On the left scale serum bilirubin is listed, even though a transcutaneous value is not performed on serum. There are many other laboratory data quality issues about this example.



	Blood Type	Indirect Coombs
Baby	O Pos (09/26/16)	Negative (09/28/16)
Mother	O Pos (04/03/16)	Negative (04/02/16)

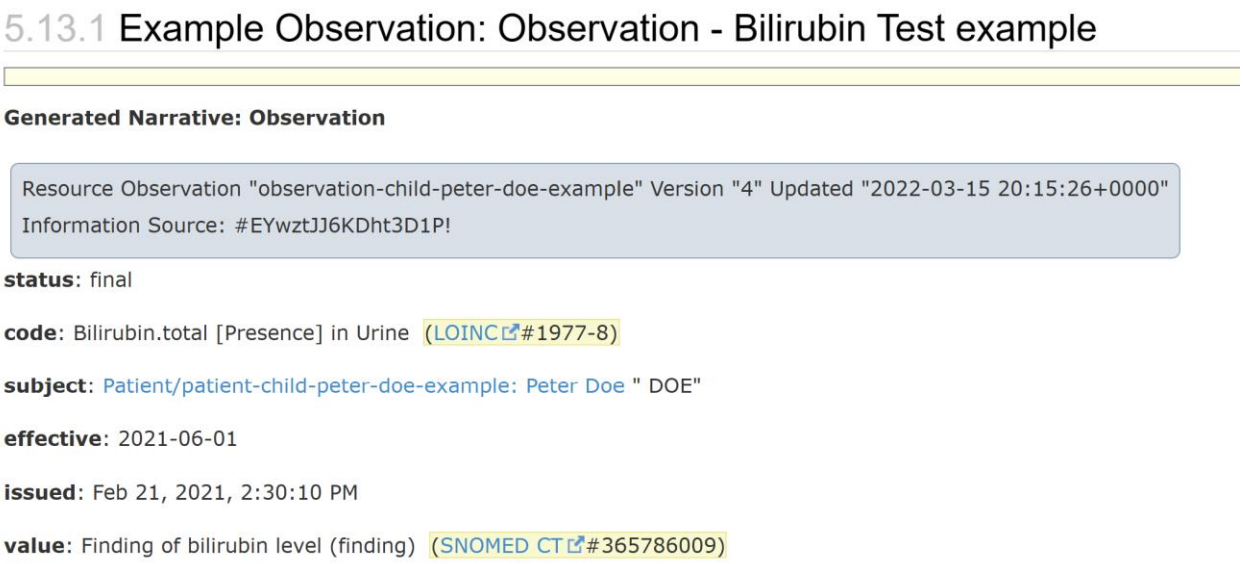
Age (Hrs)	Result	Date/Time	Test Type
12.25	8.1	09/26/16 16:24	Total
23.38	10.5	09/27/16 03:32	Transcutaneous
30.68	12.2	09/27/16 10:50	Total
36.9	14.8	09/27/16 17:03	Total
46.57	17.1	09/28/16 02:43	Total

Age (Hrs)	Result	Date/Time
43.85	2.9	09/28/16 00:00

Consider another example in the screenshot below and link provided, which is named "Bilirubin Test," but is reflected as a qualitative Urine Bilirubin result represented by the LOINC Long Name under "code." (see HL7.FHIR.US.MIHR\Observation - Bilirubin Test example - FHIR v4.0.1) This example doesn't even reflect the lab test name, as it only represents the test with the LOINC (not advised by the LOINC User Guide.) The value is encoded to the wrong SNOMED CT code (it should be from the qualitative value hierarchy). Thus a computer using this code may attribute the wrong meaning to the result value. This test is rarely performed in the US, and there are other LOINCs for the Ictotest and dipstick/test strip methods that provide more detail and clarity. It's unclear whether the effective and issued dates correspond to the specimen collection date, or when the laboratory received the specimen or verified the results in accord with CLIA. The danger is many developers may not know these are important data quality and coding issues and implement these examples "as is," and perpetuate these issues.

A recommendation is for HL7 implementation guides to be developed for laboratory data/use cases with clarity for implementers on how to avoid these issues and have quality implementations. FHIR implementation guides for orders and results be developed with review by CLIA to ensure the end product is compliant with CLIA regulations similar to how

the ONC S&I framework Implementation Guides were developed for lab ordering, (LOI), resulting (LRI), compendiums (eDOS) and ELR Public Health Reporting exchanges. Laboratory expertise is needed in the development of these guides, including from a variety of lab settings to reflect these lab needs too.



5.13.1 Example Observation: Observation - Bilirubin Test example

Generated Narrative: Observation

Resource Observation "observation-child-peter-doe-example" Version "4" Updated "2022-03-15 20:15:26+0000"
Information Source: #EYwztJJ6KDht3D1P!

status: final

code: Bilirubin.total [Presence] in Urine (LOINC#1977-8)

subject: Patient/patient-child-peter-doe-example: Peter Doe " DOE"

effective: 2021-06-01

issued: Feb 21, 2021, 2:30:10 PM

value: Finding of bilirubin level (finding) (SNOMED CT#365786009)

Thank you for your consideration of these comments and helping to ensure the quality and safe use of laboratory and pathology results.

Andrea Pitkus, PhD, MLS(ASCP)CM, FAMIA

Division of Laboratory Systems

The Use of Clinical Standards to Improve Laboratory Quality

Introduction

Víctor R. De Jesús, PhD
Acting Director, Division of Laboratory Systems
Chief, Quality and Safety Systems Branch

CLIAC Spring 2024 Meeting
April 10, 2024

CLIA Does Not Address the Use of Standards

- **§ 493.1230 Condition: General laboratory systems.**
  - 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.*

- **§ 493.1253 Standard: Establishment and verification of performance specifications.**
  - (b2) ***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 and standardized methods such as text book procedures), 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*…

Presentation

CDC's Clinical Standardization Programs: Ensuring the Accuracy and Reliability of Chronic Disease Biomarker Tests

Hubert Vesper, PhD

Director, Clinical Standardization Programs
Division of Laboratory Sciences
Centers for Disease Control and Prevention

Presentation

Clinical and Laboratory Standards Institute (CLSI): Consensus Standards to Support Operational Excellence and Regulatory Compliance

Barb Jones, PhD

Chief Executive Officer
Clinical and Laboratory Standards Institute

Questions to CLIAC

1) Clinical standardization programs (CSPs) improve the accuracy and reliability of laboratory tests for key chronic disease biomarkers. How can the CLIA program agencies promote participation in CSPs by laboratories and test manufacturers to improve analytical performance?

2) Currently, the FDA provides a list of Recognized Consensus Standards related to medical devices. What are other ways that the CLIA program agencies and professional organizations can promote the use of standardization programs and standards?

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Víctor R. De Jesús, PhD (770) 488-7963 or foa5@cdc.gov

CDC's Clinical Standardization Programs (CDC CSP): Ensuring the Accuracy and Reliability of Chronic Disease Biomarker Tests

Hubert W. Vesper, Ph.D.

Director, CDC Clinical Standardization Programs

Clinical Chemistry Branch

Division of Laboratory Sciences, NCEH

The analytical accuracy and reliability of biomarkers used in patient care and public health have raised concerns among stakeholders

IOM 2011

"A single individual might be deemed deficient or sufficient *[for vitamin D]* depending on the laboratory where the blood is tested."

Endocrine Society JCEM 2010;95:4541-48

"deficiencies in these *[testosterone]* assays limit their broad and effective implementation and threaten the health of those patients whose medical care relies upon its accurate measurement"

Endocrine Society JCEM 2013;98:1376-87

"Breast cancer, diseases of bone, cognitive dysfunction, and cardiovascular disease are among those that suffer from a limited ability to combine data from diverse studies because measurements and standards *[of estradiol]* are not uniform."

Variability in vitamin D measurements may cause incorrect patient classification

CAP Accuracy-based Vitamin D Survey – 2019

Method/Assay	Median (ng/mL)	Lowest reported Value (ng/mL)	Highest Reported Value (ng/mL)
Assay 1	29.8	26.1	32.0
Assay 2	30.6	26.0	33.3
Assay 3	32.0	24.0	37.1
Assay 4	28.0	26.8	40.7
Assay 5	32.3	26.0	37.5
Assay 6	30.0	25.3	39.1
Assay 7	37.8	26.6	46.0
Assay 8	32.6	28.5	38.0
Assay 9	31.4	24.9	38.4
Assay 10	34.0	26.0	45.4
Assay 11	30.9	26.0	41.9

Indicates insufficient Vitamin D status based on Endocrine Society Guideline

Reference Value 36.70

True value

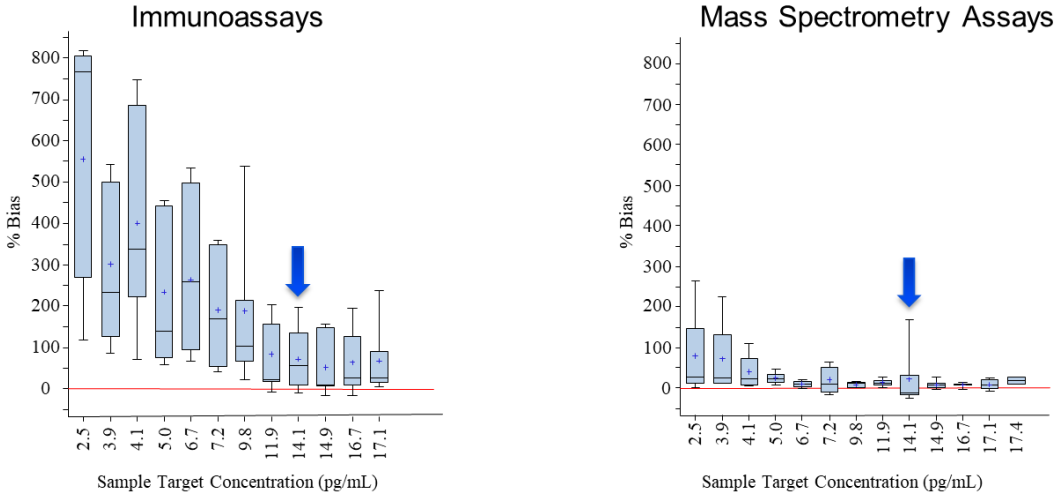
Sufficient Vitamin D status

Based on Endocrine Society Guideline

Variability in estradiol measurements prevent consistent diagnosis of patients

Example:
European Menopause and Andropause Society recommends a cut-off of 14 pg/mL to confirm diagnosis of premature ovarian failure

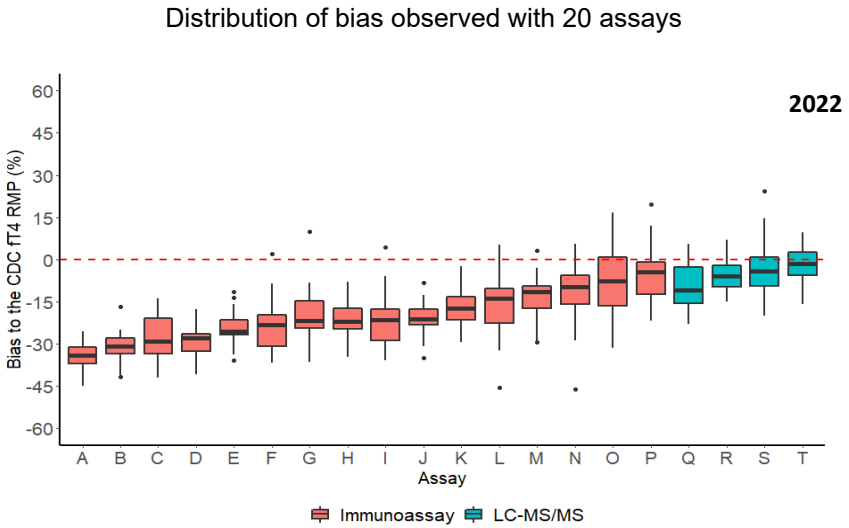
Bias distributions among assays for samples with reference values ranging between 2.8 – 17.4 pg/mL)



Values reported for a sample with a target value of 14.1 pg/mL ranged from 9.4 to 64.8 pg/mL

Vesper et al. Steroids 2014;82:7-13

Very high differences in analytical accuracy of FT4 assays may cause inconsistent diagnosis



2022 CDC Interlaboratory comparison study

- Data suggest inconsistent calibration being the main source of measurement bias among assays
- Alignment to the CDC/IFCC reference method can be achieved with immunoassays and mass spectrometry-based assays

Several tests in need of standardization are highly utilized in patient care

Several tests in need of improvements
are among top 20 based on Medicare payments

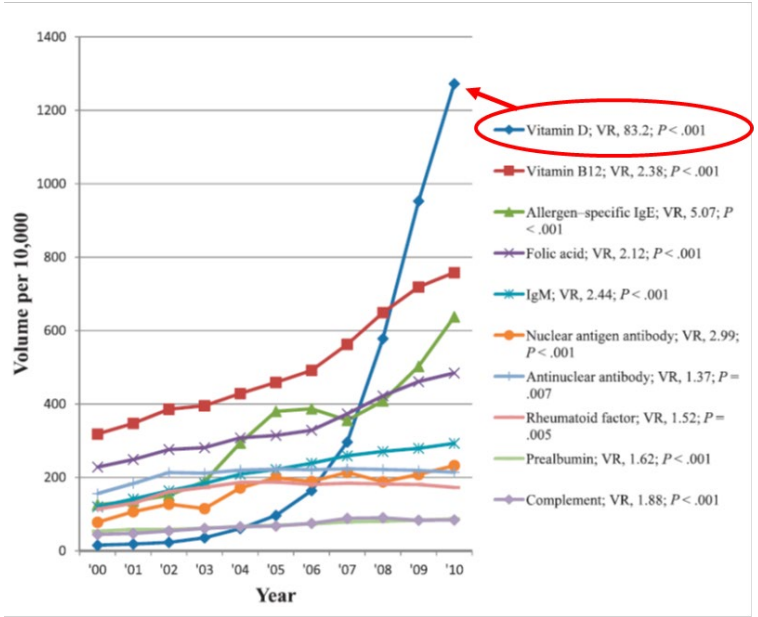
Top 20 lab tests based on Medicare Part B payments in 2016

	Test Description (Procedure Code)*	Number of Tests (Millions)	Medicare Payments (Millions)
1.	Blood test, thyroid-stimulating hormone (TSH) (84443)	21.5	$482
2.	Blood test, comprehensive group of blood chemicals (80053)	41.6	$470
3.	Complete blood cell count (red blood cells, white blood cells, platelets) and automated differential white blood cell count (85025)	42.0	$433
4.	Blood test, lipids (cholesterol and triglycerides) (80061)	29.0	$411
5.	Vitamin D_3 level (82306)	9.0	$350
6.	Hemoglobin A1C level (83036)	19.3	$250
7.	Drug test(s), definitive, per day, 22 or more drug class(es), including metabolite(s) if performed (G0483)	1.2	$241
8.	Drug test(s), presumptive, any number of drug classes, per date of service (G0479)	3.0	$221
9.	Blood test, basic group of blood chemicals (80048)	13.7	$133
10.	Drug test(s), definitive, per day, 15–21 drug class(es), including metabolite(s) if performed (G0482)	0.8	$127
11.	Parathormone (parathyroid hormone) level (83970)	2.2	$120
12.	Cyanocobalamin (vitamin B_{12}) level (82607)	5.6	$113
13.	Blood test, clotting time (85610)	19.6	$105
14.	PSA (prostate specific antigen) measurement (84153)	4.2	$103
15.	Thyroxine (thyroid chemical) measurement (84439)	7.1	$85
16.	Bacterial colony count, urine (87086)	7.6	$82
17.	Drug test(s), definitive, per day, 8–14 drug class(es), including metabolite(s) if performed (G0481)	0.6	$73
18.	Natriuretic peptide (heart and blood vessel protein) level (83880)	1.5	$69
19.	Drug test(s), definitive, per day, 1–7 drug class(es), including metabolite(s) if performed (G0480)	1.0	$69
20.	Ferritin (blood protein) level (82728)	3.7	$67

Analytes addressed in CDC CSP

Source: OEI-09-17-00140

The number of vitamin D tests reimbursed by Medicare increased over 80-fold between 2000 and 2010



Arch Pathol Lab Med. 2014;138:189–203

CDC CSP improve diagnosis, treatment, and prevention of selected diseases by standardizing clinical laboratory measurements

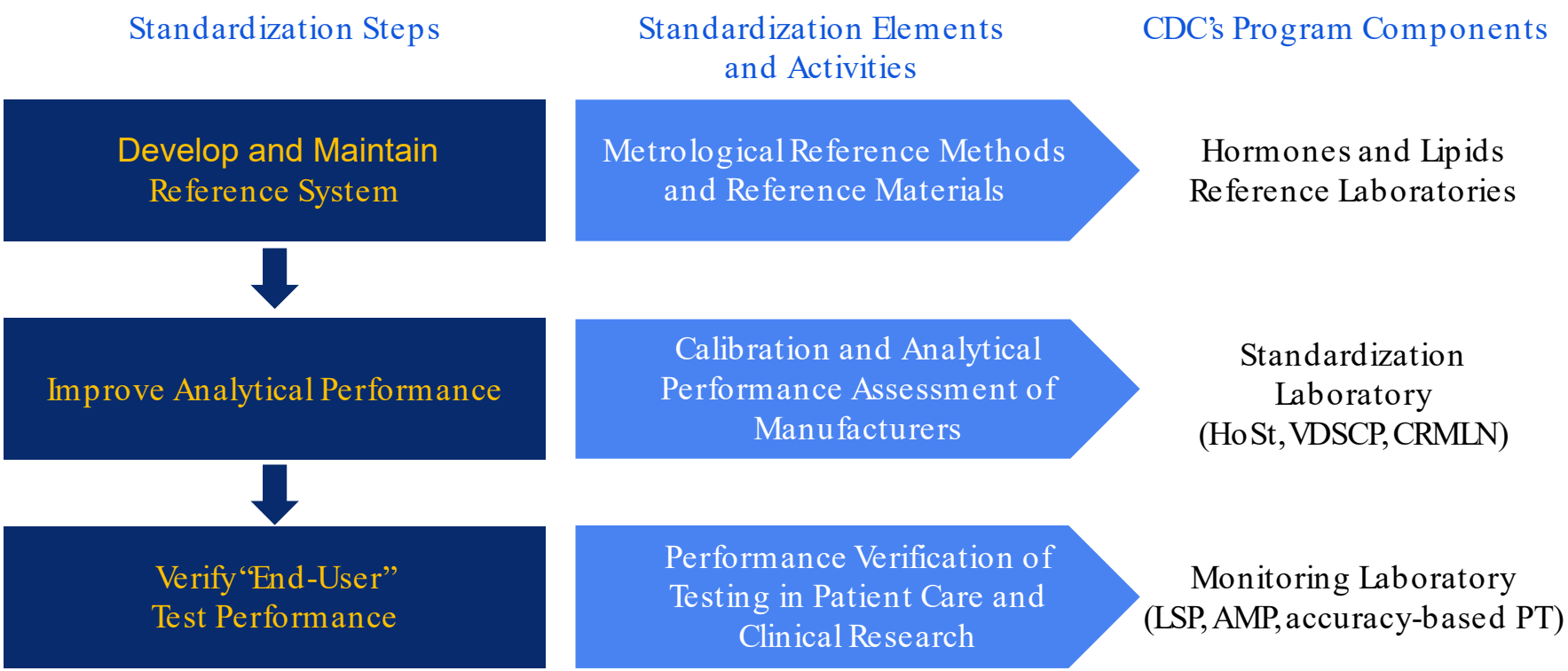
Objective

Create measurement results with measurement procedures of appropriate analytical performance that are traceable to one accuracy basis, and therefore are comparable across methods, location, and over time

CDC standardized laboratory test
has demonstrated through a thorough, independent assessment that its analytical performance meets relevant analytical performance goals derived from clinical needs

Standardization is an ongoing process
in which relevant analytical performance parameters of a laboratory test are improved and maintained to meet certain clinical needs

CDC's Clinical Standardization Programs provide unique services at every step in the standardization process



CDC's Clinical Reference Laboratories (CRL) continuously operate 10 reference methods

Reference Measurement Procedures operated at CDC CSP

Analyte	Method Principle	Performance Requirements Bias	Imprecision
Total Cholesterol	ID-GC-MS	± 1%	≤ 1%
	Spectrophotometry	± 1%	≤ 1%
Total Glycerides	ID-GC-MS	± 2.55 %	≤ 3.95%
HDL-C	Ultracentrifugation-Spectrophotometry	± 2%	≤ 1.5%
LDL-C	Ultracentrifugation-Spectrophotometry	± 1 mg/dL	≤ 1 mg/dL
Testosterone*	UPLC-MS/MS	±5.7 %	≤ 2.8 %
Estradiol*	UPLC-MS/MS	±5 %	≤ 2.1 %
25-OH-Vitamin D2* 25-OH-Vitamin D3*	UPLC-MS/MS	±5.7 %	≤ 2.8 %
Free Thyroxine*	Equilibrium Dialysis-UPLC/MS/MS	±2.5%	≤5%
Glucose*	GC-MS	±1%	≤ 2%

* CDC CSP is the only laboratory in the U.S. continuously operating these RMPs

- All RMPs were reviewed for compliance with relevant ISO standards (JCTLM)
- CDC CRL ISO 15195 (Calibration Laboratory) accredited
- CDC's CRL performs ~200 reference value assignments per year

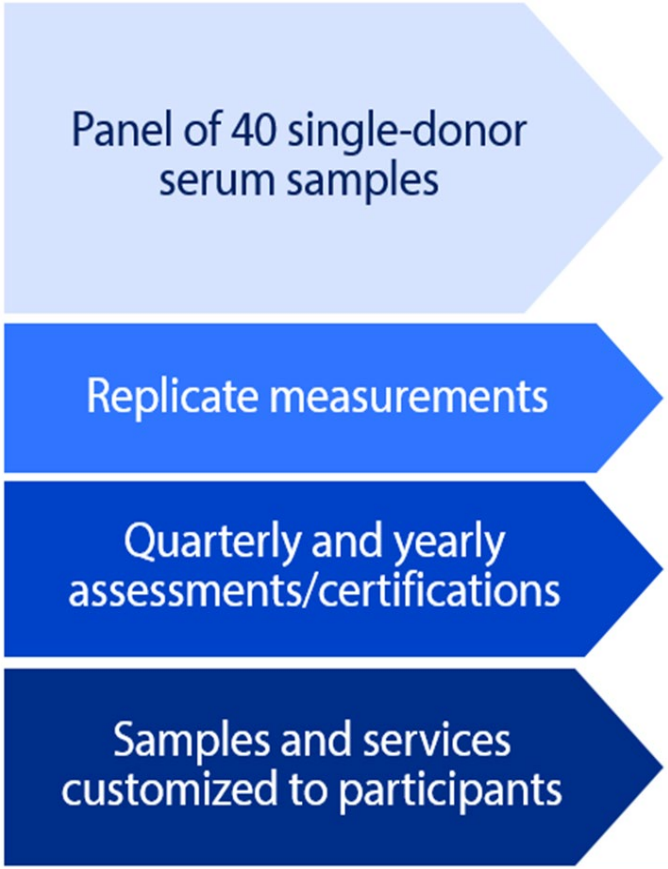
Reference measurement procedures in development

- Parathyroid Hormone by LC/MS/MS
- Lp(a) by LC/MS/MS
- Free testosterone by ED-LC/MS/MS

CDC CRL assists organizations with developing RMPs and with building reference laboratory capacity, for example:

- IFCC RMP development for Lp(a)
- Korea Disease Control and Prevention Agency reference lab development

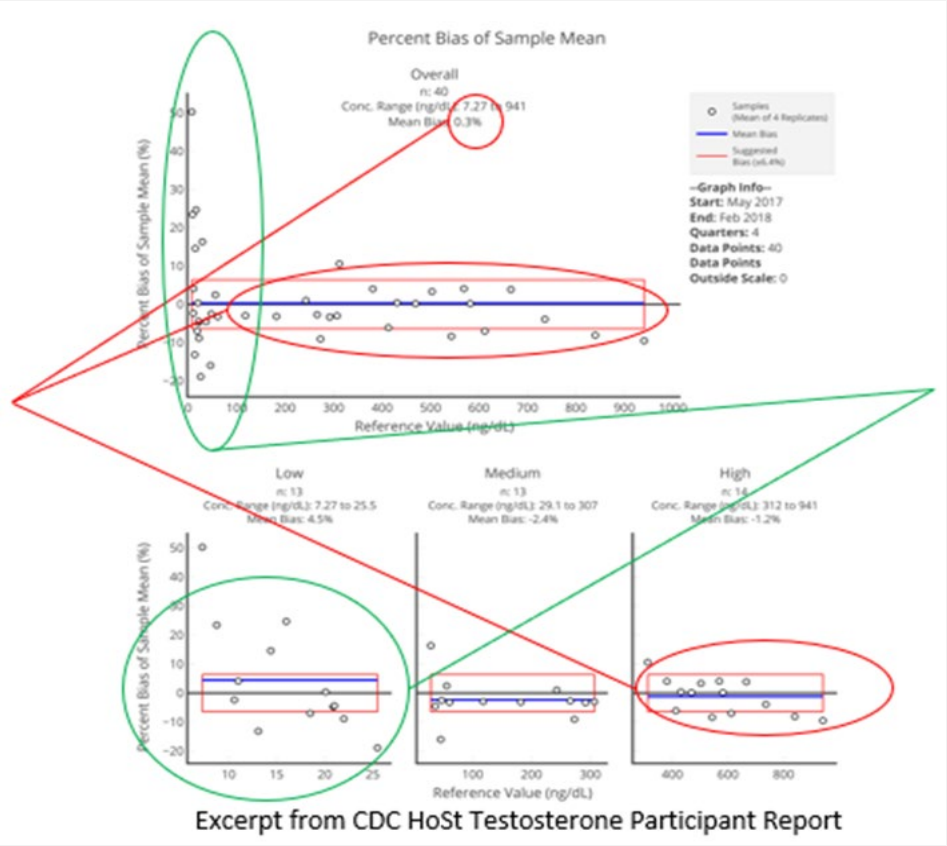
CDC CSP certification programs provide detailed information not available with other programs



- Enables thorough evaluation of measurement performance across relevant concentration ranges
- Allows for identification of sources of bias (i.e., calibration vs. non-specificity)
- Avoids potential problems related to commutability frequently observed in pooled/altered serum
- Provides information on imprecision in addition to bias
- Provides information about performance over time
- Allows timely detection of changes in accuracy
- Customization of sample concentration to cover reportable range
- Individual review of data to minimize non-analytical sources of error (i.e., clerical errors with data input)

CDC CSP provide detailed information to participants about the analytical performance across the analytical measurement range

Assay appears to be sufficiently well calibrated as indicated in the mean bias and bias patterns (especially at high analyte concentrations)



Excerpt from CDC HoSt Testosterone Participant Report

Assay appears to be affected by interfering compounds and analyte recovery, as indicated in bias patters at low analyte concentrations
(mainly samples from female donors)

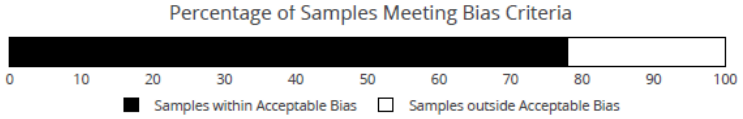
CDC's Clinical Standardization Programs provide detailed information about measurement performance to its participants and the public

Excerpt from CDC VDSCP Participant Report

Bias Evaluation by Concentration Range

	n	Conc. Range (nmol/L)	Bias (%)* Mean	SD	Median	95% CI	Min	Max	Percentage of Samples Meeting Bias Criteria
Reference Concentration Range									
Low	13	10.4 to 60.5	7.3	9.1	4.9	1.8 to 12.8	-1.1	34.0	54
Med	13	60.9 to 96.1	1.5	3.3	2.1	-0.5 to 3.5	-4.2	6.9	92
High	14	99.4 to 183	1.3	3.4	0.3	-0.6 to 3.3	-3.7	8.0	86
Total									
Overall	40	10.4 to 183	3.3	6.3	2.6	1.3 to 5.4	-4.2	34.0	78

* Evaluation was made using individual sample biases in each partition type



Excerpt from CDC Website

https://www.cdc.gov/labstandards/pdf/hs/CDC_Certified_Vitamin_D_Assays-508.pdf

Table 1: Currently Certified Assays

Participant	Measurement Principle	Assay Identifier	Assay Measurement Range (nmol/L)	Certification Measurement Range (nmol/L)	Certification Date *(active for 1 quarter)*	Individual Samples Pass Rate (%)	Participant's Contact Information

A certified assay meets the mean bias "calibration bias") criterion

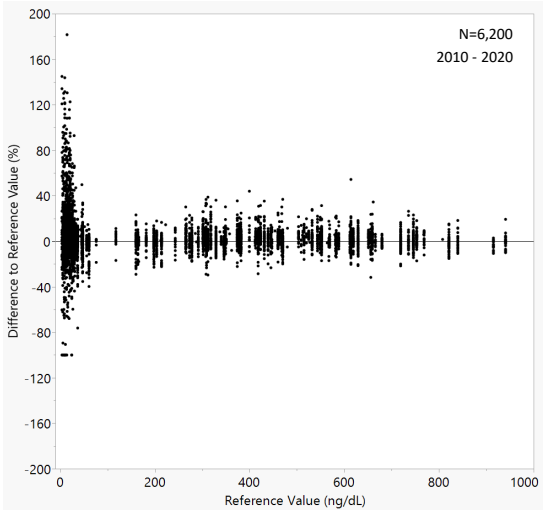
Mean bias calculated using 40 samples measured over 4 consecutive quarters

Proportion of individual samples meeting bias criterion ("reliability" of results obtained on individual samples)

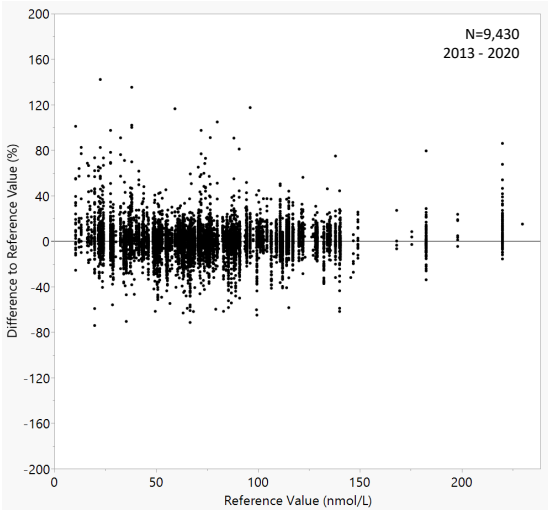
CDC's CSP data indicate consistent assay calibration is not always sufficient for improving the accuracy and reliability of measurement results

Bias patterns of individual donor samples for three key analytes obtained from CDC CSP participants (certified and non-certified)

Testosterone

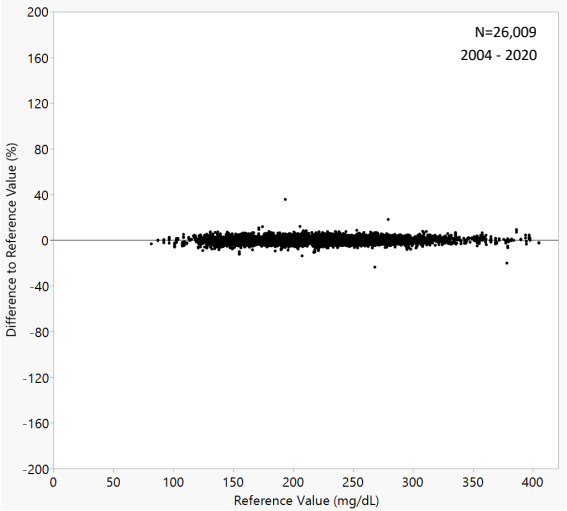


25-OH-Vitamin D



Each dot represents the mean of 4 measurements

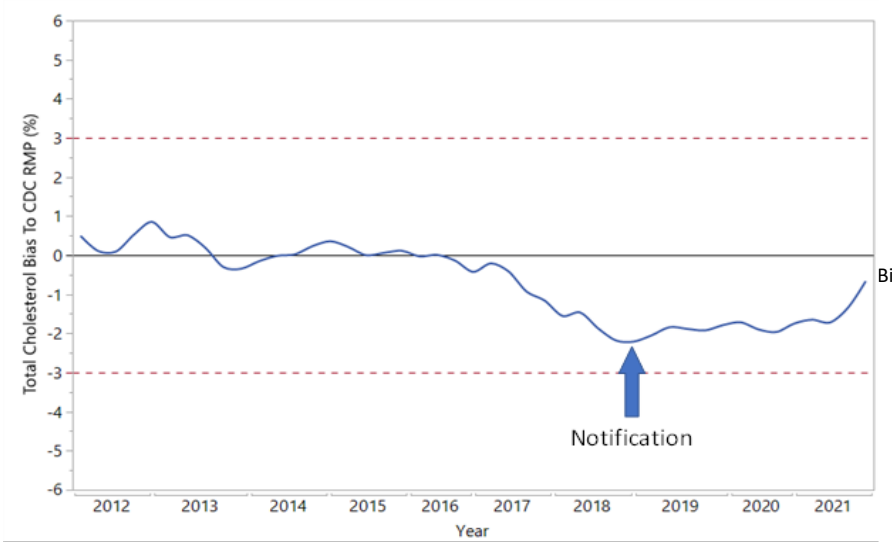
Total Cholesterol



Procedures and approaches to improve and maintain measurement accuracy and reliability need to extend beyond re-calibration activities.
These activities need to be customized for each analyte.

CDC CSP monitor analytical performance of its participants to detect and address trends in a timely manner

Total cholesterol bias to RMP observed with one manufacturer in the CDC LSP program

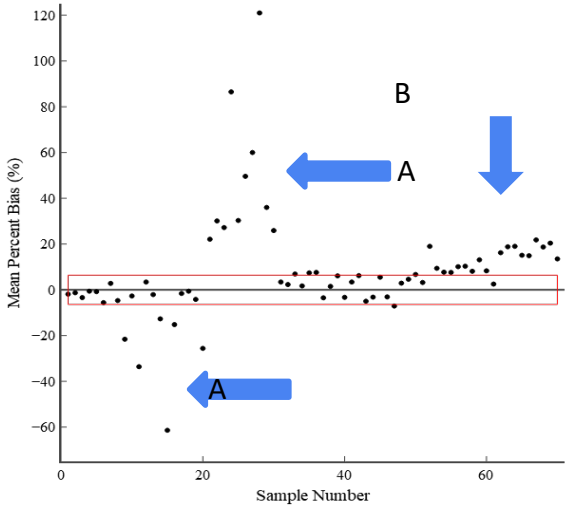


Manufacturer was notified which helped prevent bias to move outside limits

Line represents the mean bias from approx. 600 data points across a year collected from 50 laboratories

Bias Limits

Total testosterone bias to RMP observed with one CDC HoSt participant over 7 quarters

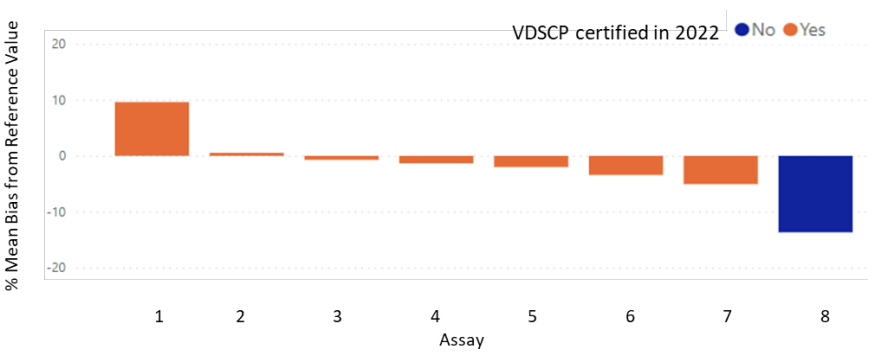


Quarterly reports helped participant identify problems with assay operation (A) and calibration (B)

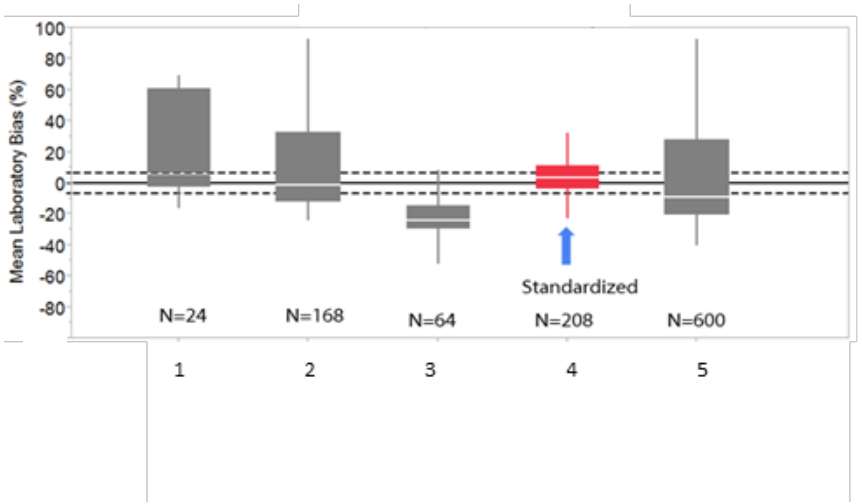
Each dot represents the mean of 4 replicate measurements

VDSCP certified assays show higher accuracy than non-certified assays

Peer group mean bias of 6 survey samples in the 2022 CAP Accuracy Based Vitamin D Survey

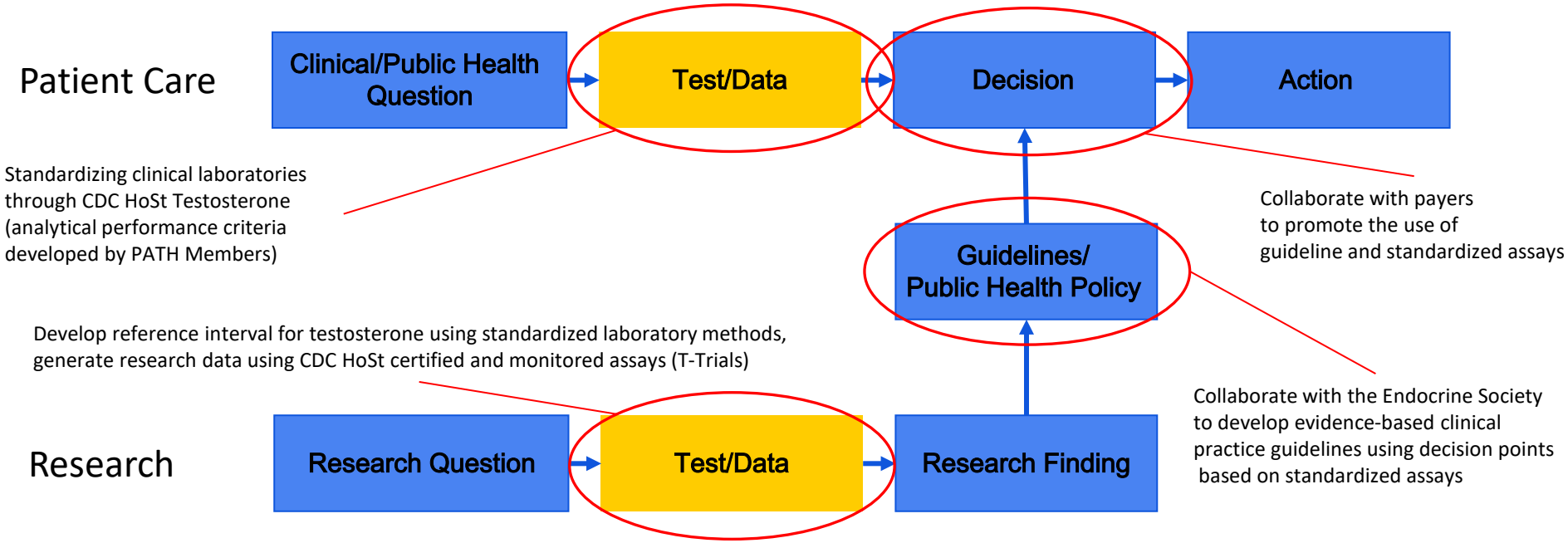


Bias distribution of samples used in the New York State Department of Health EQA/PT Survey



CDC CSPs participation is voluntary. Currently standardized and non-standardized tests are used in patient care and public health

CDC CSP collaborate with stakeholders to ensure quality in every step of the evidence-based decision-making process



Summary

- CDC Clinical Standardization Programs (CDC CSP) assist IVD manufacturers and laboratories with improving and monitoring analytical performance
- CDC CSP laboratories comply with international standards of metrology and use well-established evaluation protocols
- Establishing only correct assay calibration may not be sufficient to meet clinical needs, CDC CSP works with participants on improving all relevant performance parameters
- Certification programs and accuracy-based monitoring programs provide important, complementary information to IVD manufactures and laboratories
- Participation in CDC's clinical standardization programs is voluntary. Therefore, standardized and non-standardized assays are used in patient care without distinction. CDC CSP is collaborating with stakeholders to educate the laboratory communities about the importance of assay standardization.

Thank you!

For further information about CDC CSPs, please contact: standardization@cdc.gov

Hubert W. Vesper, PhD
Director, Clinical Standardization Programs
hvesper@cdc.gov

For more information, contact NCEH/ATSDR
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.atsdr.cdc.gov www.cdc.gov
Follow us on Twitter @CDCEnvironment

Clinical and Laboratory Standards Institute (CLSI)

Consensus Standards to Support Operational Excellence and Regulatory Compliance

CLIAC Meeting

Barb Jones, PhD | April 10, 2024

CLIA and CLSI Standards Clarification

(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 and standardized methods such as text book procedures), 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.

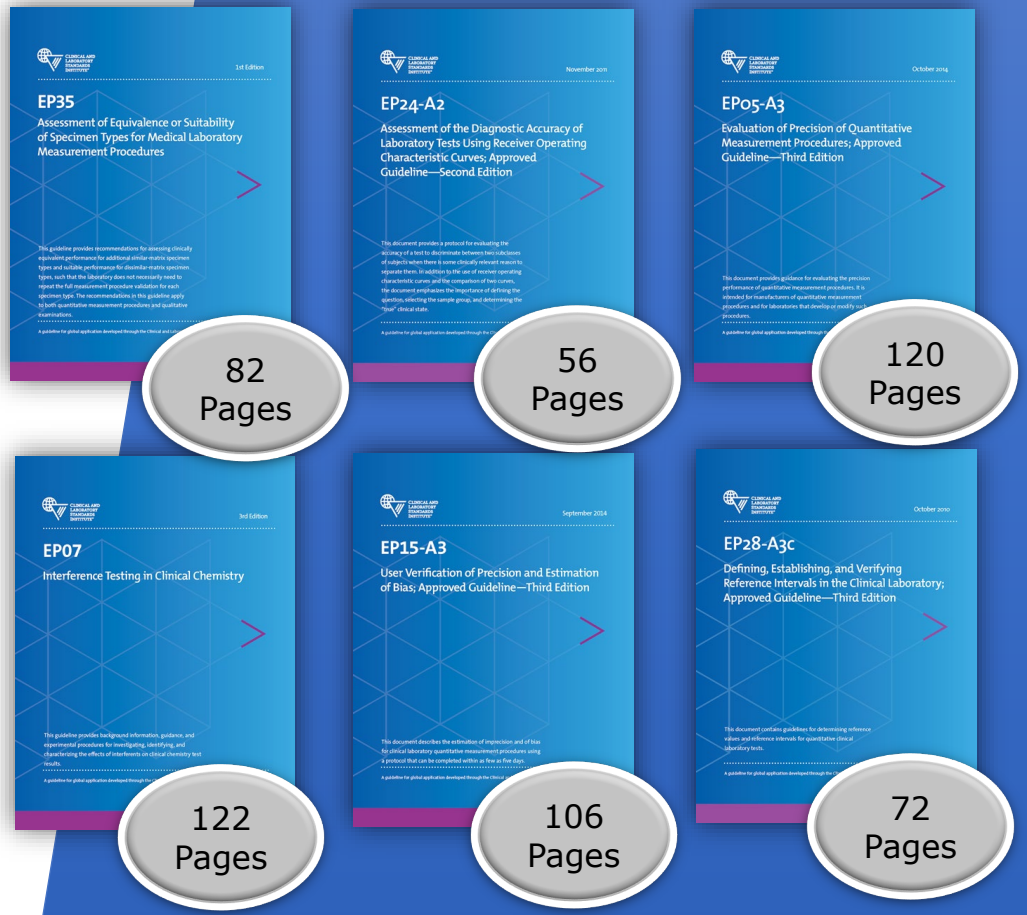
(iv) Analytical specificity to include interfering substances.

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

(vi) Reference intervals (normal values).

CLIA LDT Standard

Some Relevant CLSI Standards



CLSI Organization and Process

Accredited Standards Development Organization

Who Is CLSI?

The Global Leader in Setting Clinical Laboratory Standards

The Clinical and Laboratory Standards Institute (CLSI) is a not-for-profit organization that develops laboratory standards worldwide.

CLSI Role in the Diagnostics Ecosystem

- Founded in 1967 as NCCLS
  - 2 months before CLIA enacted
  - 20+ years before Amendments
- Created by members of 36 organizations
  - Department of Health Services (now CDC)
  - the College of American Pathologists (CAP)
  - the National Research Council (NRC)
  - the American Chemical Society (ACS)
  - the American Academy of Microbiology (now ASM)
  - National Bureau of Standards (now NIST)
- Accredited since 1977 by American National Standards Institute (ANSI) as a standards development organization (SDO)

"…advisory group for the improvement of standards in clinical laboratories and serve as a mechanism to achieve con-census on standards."

Requirements for SDO Accreditation

- Openness
- Lack of Dominance
- Balance
- Coordination and Harmonization
- Notification of Standards Development
- Consideration of Views and Objectives
- Consensus Vote
- Appeals
- Procedures
- Compliance with Normative ANSI Policies and Procedures

CLSI At-a-Glance

Globally recognized accredited not-for-profit standards development organization

Made up of 24,000+ individuals with membership access and 1,600+ active subject matter experts

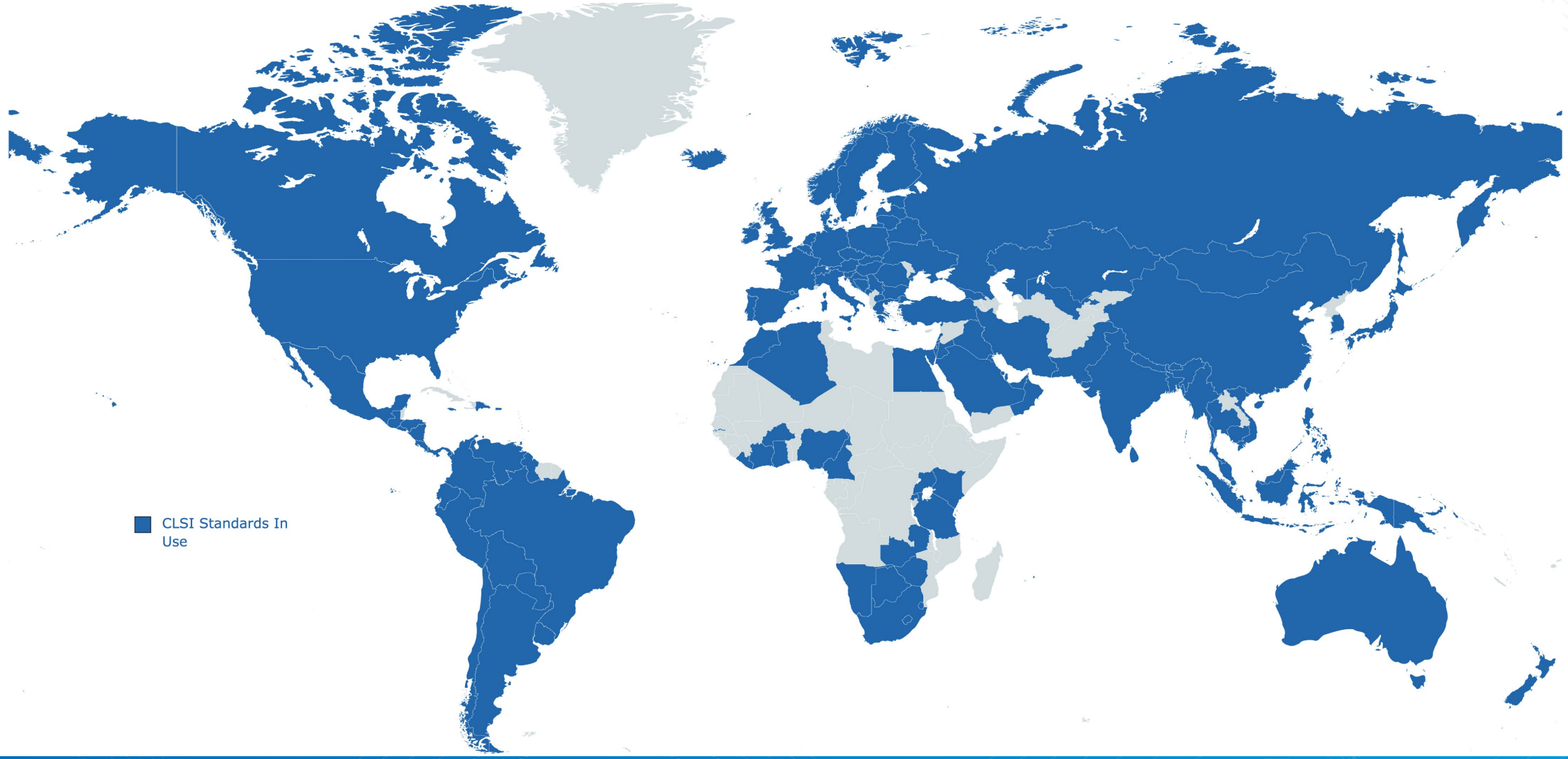
300 products:

standards, guidelines, educational resources, and more

Recognized by labs, accreditors, and government agencies as the best way to improve medical lab testing

Our products help improve testing outcomes, maintain accreditation, bring products to market faster, and navigate regulatory hurdles

CLSI Standards in Use Around the Globe



GLOBAL CONSENSUS-BASED STANDARDS

Bringing constituencies together through balanced, inclusive, and participatory processes

Professions

- Hospital & Clinical Laboratories
- Research & Reference Laboratories
- Colleges & Universities
- Pharmacies

Government

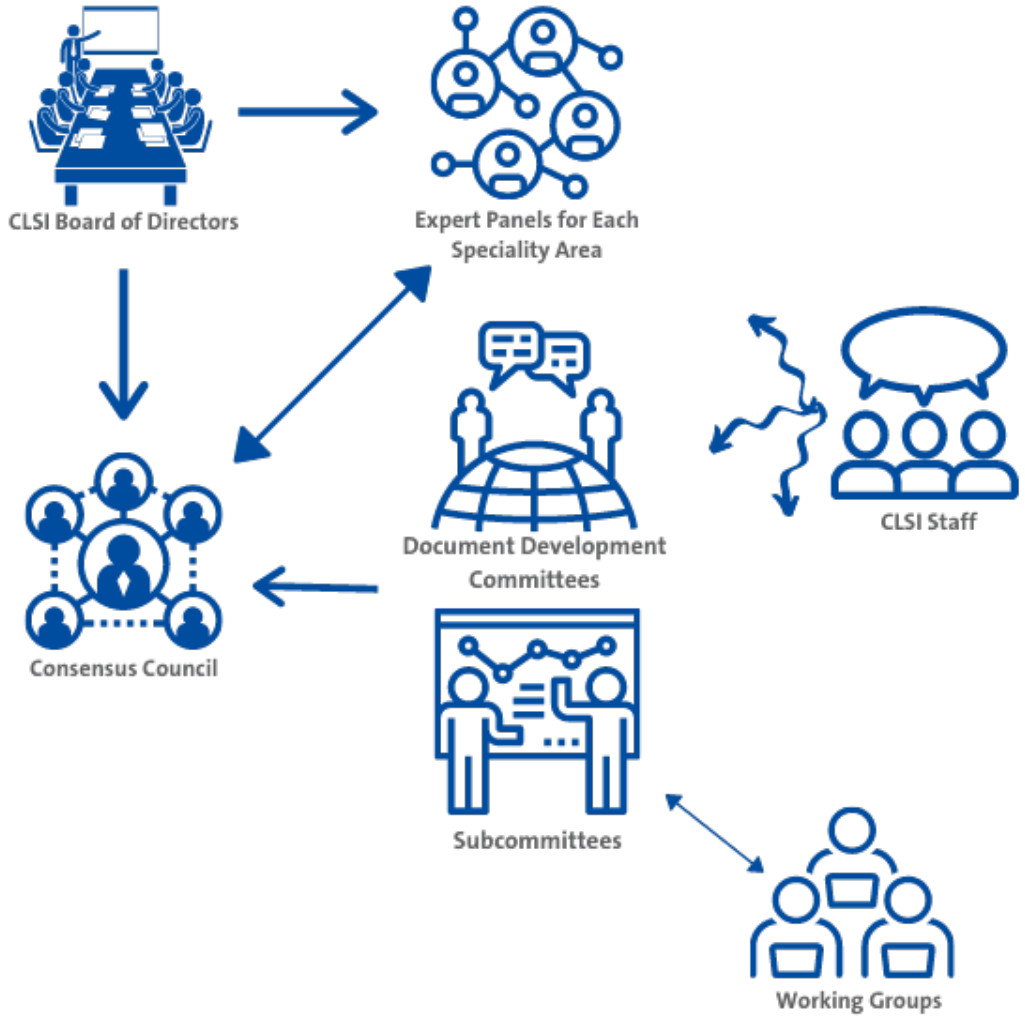
- Public Health Agencies
- Public Health Ministries
- Regulatory Bodies
- Accreditors

Industry

- *In Vitro* & Device Manufacturers
- Pharmaceutical Manufacturing
- Commercial & Clinical Trial Laboratories
- MedTech & Testing Companies

Members & Subject Matter Experts

How We Work



THE CLSI CONSENSUS PROCESS

11 Expert Panels

Automation and Informatics

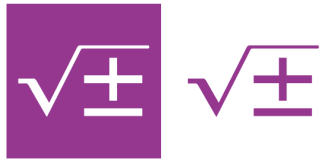
Clinical Chemistry and Toxicology

General Laboratory

Preexamination

Hematology

Immunology and Ligand Assay



Method Evaluation

Microbiology

Molecular Methods

Newborn Screening

Point-of-Care Testing

Quality Management Systems

Veterinary Medicine

More than 300 Clinical and Laboratory Standards

Automation and Informatics	18
Clinical Chemistry and Toxicology	57
IVD Development (Industry)	132
Emergency Response	5
Evaluation Protocols	62
General Laboratory & Lab Safety	36
Hematology and Immunology	36
Medical Office Practices	28
Microbiology	89
Molecular Diagnostics	28
Newborn Screening	42
Point-of-Care Testing	21
Preexamination Processes	9
Quality Management Systems	38
Specimen Collection & Handling	57
Veterinary Medicine	8

CLSI's Support of CLIA

Accreditation Crosswalks

190+ Documents provide guidance for accreditation requirements (CAP, JC)

Quality System Essentials

24 Documents and over **2800 pages** of guidance directly applied to CLIA quality regulations

CLIA Regulation (What must be done)	CLSI Quality System Essentials (How to do it)
Sub-part J: 493.1100-493.1101	Facilities and Safety Management
Sub-part K: 493.1200-.1239 / 493.1242-.1249 / 493.1282 / 493.1289 / 493.1299	Organization and Leadership
Sub-part M: 493.1351-.1495	Personnel Management
Sub-part K: 493.1252-.1255	Equipment Management
Sub-part K: 493.1252	Supplier and Inventory Management
Sub-part K: 493.1232 / 493.1240-.1242 / 493.1250-.1251 / 493.1256-.1282 / 493.1290	Process Management
Sub-part K: 493.1231 / 493.1291	Information Management
Sub-part J: 493.1101e / 493.1105 / Sub-part K: 493.1283	Documents and Records Management
Sub-part K: 493.1233-.1234 / 493.1291e / Sub-part M: 493.1407 / 493.1419	Customer Focus
Sub-part H: 493.801-.807 / Sub-part K: 493.1239 / 493.1249 / 493.1253-.1254 / 493.1289 / 493.1299	Assessments
Sub-part K: 493.1233-.1234 / 493.1282	Nonconforming Event Management
Sub-part K: 493.1236-.1239 / 493.1249 / 493.1289 / 493.1299	Continual Improvement

Federal Agency Use of Consensus Standards

Consensus Standard Use Requirements

- **National Technology Transfer and Advancement Act (NTTAA) (1996)**
  - Mandates that all federal agencies use technical standards developed and adopted by voluntary consensus standards bodies

- **Office of Management and Budget (OMB) Circular A-119,** *Federal Participation in the Development and Use of Voluntary Consensus Standards and in Conformity Assessment Activities*
  - Definition of "Standard" or "Technical Standard" including:
    - Guidelines or characteristics for products or related processes and production methods
    - related management systems practices
    - the definition of terms
    - test methods and sampling procedures
  - Considerations for standards selection, including:
    - the **costs and benefits** to the Federal government and the regulated public of the agency developing its own standard;
    - the **ongoing use of the standard by other agencies** for the same or a similar requirement, [to] increase consistency across the Federal government

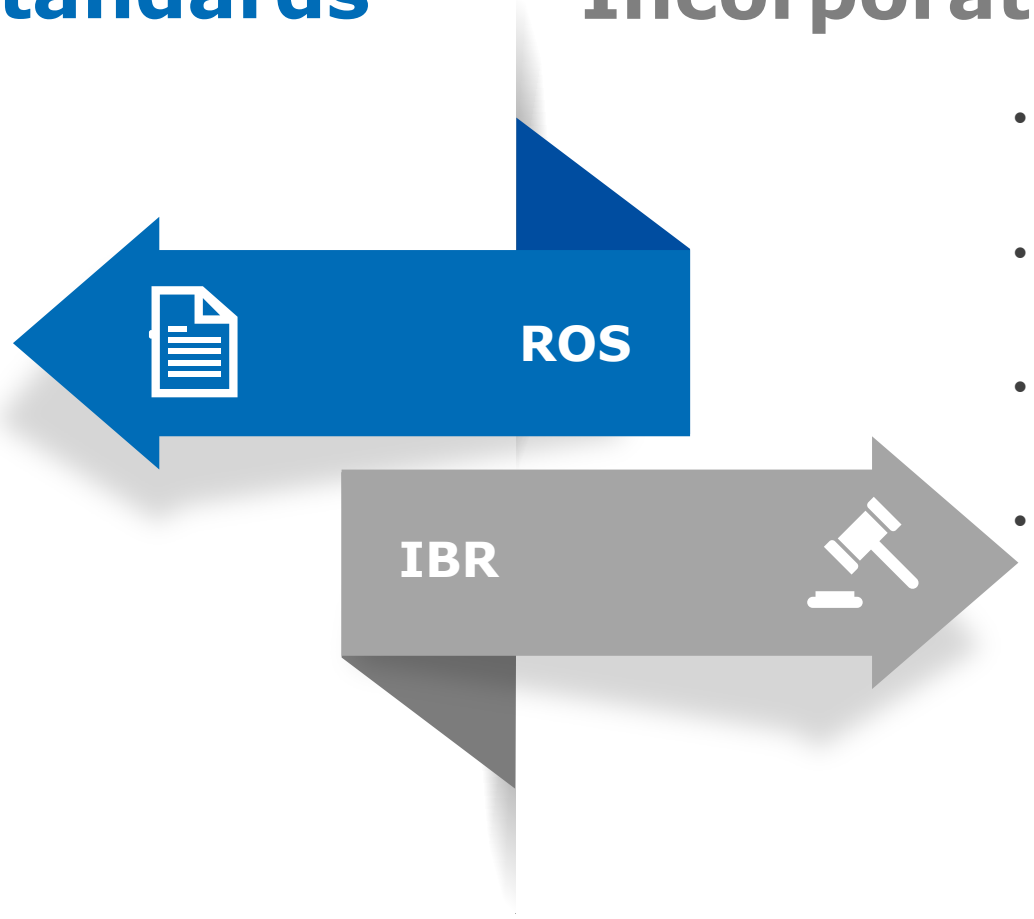
"[A]ll Federal agencies and departments shall use technical standards that are developed or adopted by voluntary consensus standards bodies, using such technical standards as a means to carry out policy objectives or activities determined by the agencies and departments."

-OMB Circular A-119

Federal Agency Vehicles for Consensus Standards

Recognition of Standards

- Use of standards is voluntary
- Agency has discretion to define process, procedure, requirements
- Can be partially recognized
- Not legally enforceable
- Revocation of recognition does not require lengthy rule change
- Can be easily modified as standards are revised



Incorporation by Reference

- Entire standard becomes part of rule (1 CFR part 51)
- Has the force and effect of law
- Rule change process must be followed to remove reference
- Example: FDA IBR of ISO 13485:2016 *Medical devices - Quality management systems - Requirements for regulatory purposes*

FDA Recognized Standards Program

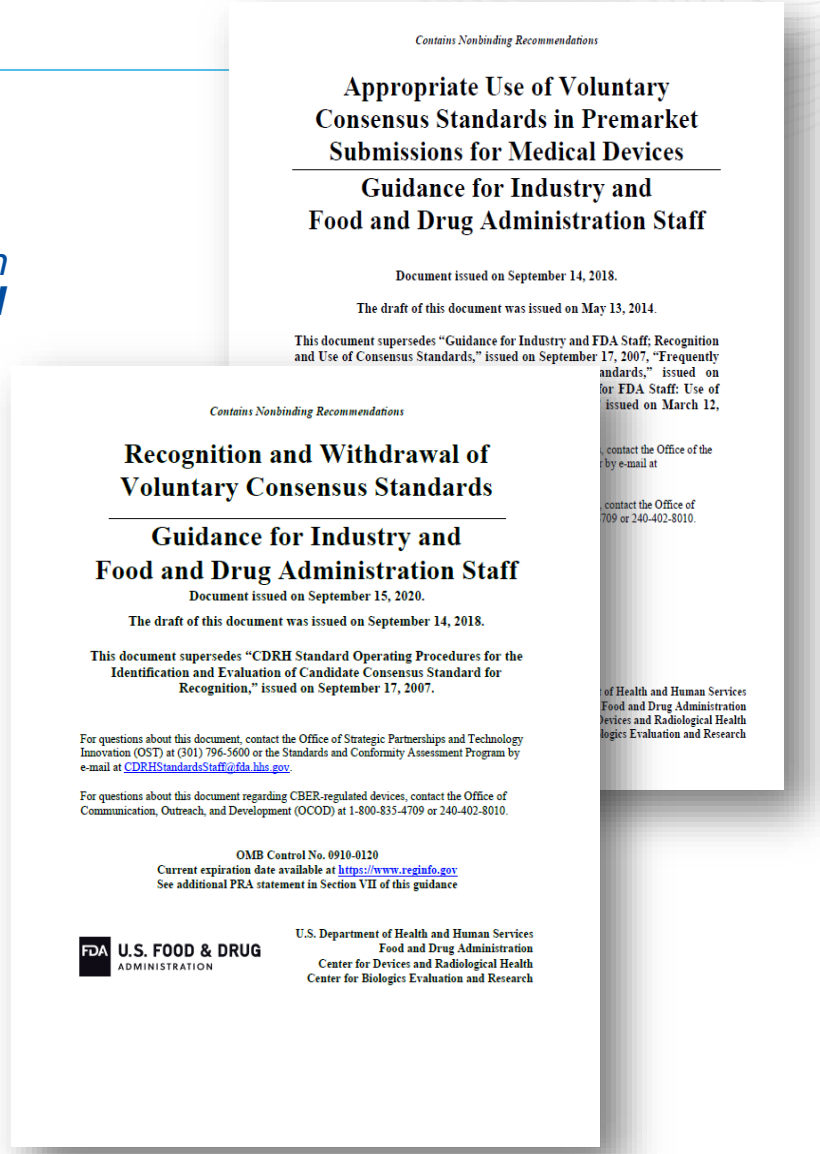
- FDA recognition is in FD&C Act

  *514(c)(1)(A) In addition to establishing a performance standard under this section, the Secretary shall, by publication in the Federal Register, recognize all or part of an appropriate standard **established by a nationally or internationally recognized standard development organization*** for which a person may submit a declaration of conformity in order to meet a premarket submission requirement or other requirement under this Act to which such standard is applicable.*

- FDA recognizes over 1400 standards from 32 SDOs

- Full or partial recognition of 132 CLSI Standards

- Clear process for recognition, withdrawal, and external request for recognition



Contains Nonbinding Recommendations

Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 14, 2018.

The draft of this document was issued on May 13, 2014.

This document supersedes "Guidance for Industry and FDA Staff; Recognition and Use of Consensus Standards," issued on September 17, 2007, "Frequently ...andards," issued on ...or FDA Staff: Use of ... issued on March 12, ...

... contact the Office of the ... by e-mail at ...

... contact the Office of ...709 or 240-402-8010.

... of Health and Human Services ... Food and Drug Administration ...evices and Radiological Health ...logics Evaluation and Research

Contains Nonbinding Recommendations

Recognition and Withdrawal of Voluntary Consensus Standards

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 15, 2020.

The draft of this document was issued on September 14, 2018.

This document supersedes "CDRH Standard Operating Procedures for the Identification and Evaluation of Candidate Consensus Standard for Recognition," issued on September 17, 2007.

For questions about this document, contact the Office of Strategic Partnerships and Technology Innovation (OST) at (301) 796-5600 or the Standards and Conformity Assessment Program by e-mail at CDRHStandardsStaff@fda.hhs.gov.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

OMB Control No. 0910-0120
Current expiration date available at https://www.reginfo.gov
See additional PRA statement in Section VII of this guidance

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

* Emphasis added

Recommendation for CLIAC

Recommendations for CLIAC Regarding Standards

1. CMS can and should provide CLIA certified labs with further guidance regarding “How to” meet regulation
2. CMS can and should develop a Recognized Standards Program (RSP)
3. FDA’s RSP can serve as a model for development
4. CMS has the discretion to develop a RSP without legislative authorization and should take steps towards implementation
5. CMS can compel accreditors to refer laboratories to recognized standards when applicable
6. CMS, FDA, and CDC can provide communication to CLIA certified laboratories about the RSP

Thank You

Barb Jones, PhD | bjones@clsi.org

COLLEGE of AMERICAN PATHOLOGISTS

Statement to the Clinical Laboratory Improvements Advisory Committee Meeting April 10, 2024

The use of clinical standards to improve laboratory quality

The College of American Pathologists (CAP) appreciates the opportunity to provide written comments to the Clinical Laboratory Improvement Advisory Committee (CLIAC). As previously stated, the CAP is the world's largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, whose mission is to foster and advocate excellence in the practice of pathology and laboratory medicine worldwide in service to our patients and members.

The CAP believes that clinical standards are an important tool to improve laboratory quality. Clinical standards and guidelines, such as CAP's Practice Guidelines, help define the current standard of care practice.

The ability of clinical guidelines and standards to improve quality is enhanced when used appropriately in tandem with regulations. Clinical guidelines and standards are developed in a consensus-based framework in which all relevant stakeholders are invited to participate, and they are regularly updated as technology and practices evolve and are applied to individuals. Regulations apply to entities and are meant to be comprehensive and broad to allow for flexibility in meeting their objectives of quality, safety, or other public health needs. Clinical guidelines and standards can fill in the gaps within regulations. Additionally, clinical guidelines can be revised and updated regularly and quickly to adapt to changing practices, needs, and technology. Regulations, meanwhile, take significantly longer to revise and update due to the necessary and valuable process of public comment periods, and thus relying solely on regulatory updates to account for changes and developments is not feasible.

The CAP uses clinical guidelines and standards in our accreditation and proficiency testing programs. These take the form of the CAP's Practice Guidelines, and the CAP Checklist.

The CAP's Practice Guidelines is a form of translational research that becomes increasing valuable as they facilitate the delivery of evidence-based care. Our practice guidelines provide standardized procedures, which when followed, produce more precise and useful test results. This is a win-win for both physicians and patients. This should entail a defined and transparent process for determining if a practice guideline, once complete, is appropriate for use in assessing performance or as an oversight mechanism.

The CAP's Checklists also provide current standard of care practice. CAP checklist requirements are complete and educational, with the goal of not simply identifying issues, but ensuring processes exist that prevent them from occurring in the first place. Because CAP checklists are updated annually, they reflect the latest requirements and most recent advances in best practices. The CAP also draws on the

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collective expertise of our scientific resource committees to introduce new checklists with detailed requirements to support advances in the modern laboratory.

Additionally, the CAP checklists incorporate various US regulations, such as:

- OSHA for employees' chemical and biological safety
- CDC and APHL for infection control
- Nuclear Regulatory Commission for radiation safety
- National Fire Protection Association for fire safety
- Environmental Protection Agency for hazardous chemical waste disposal
- US Department of Transportation for shipment of specimens to other laboratories AND
- FDA guidelines for blood banking and tissue practices

CAP checklists are based on guidelines and publications from nationally and internationally recognized standard setting organizations, such as:

- Clinical and Laboratory Standards Institute
- International Standards Organization – ISO
- World Health Organization
- Cystic Fibrosis Foundation
- American College of Medical Genetics and Genomics
- American College of Surgeons Commission on Cancer
- American Society of Clinical Oncology

CAP checklists also draw from CAP Q-Probes, Q-Tracks, and evidence-based guidelines developed by the CAP's Pathology and Laboratory Quality Center.

The result of this iterative and comprehensive effort are the CAP's 21 discipline-specific checklists which define the accreditation program requirements and reflect the most recent advances in best practices. For example, the CAP added next-generation sequencing requirements to the molecular pathology checklist in 2012 and continues to update them annually as advancements in the technology occur and as its use has expanded into different applications, such as inherited genetics, oncology, histocompatibility testing, pharmacogenetics and infectious disease testing.

The CAP welcomes the opportunity to discuss our concerns and recommendations for implementation at your earliest. Please contact Andrew Northup at anorthu@cap.org or 202.297.3726.

Closing,

The College of American Pathologists

College of American Pathologists
1001 G Street, NW, Suite 425W
Washington, DC 20001
202-354-7100

COLLEGE of AMERICAN PATHOLOGISTS

Appendix

The CAP has developed and contributed to work on checklists and clinical standards covering a wide variety of activity:

- The ASCO/CAP HER2 guideline is a good example for how we have incorporated these practices in the checklist to ensure the quality of breast cancer biomarkers used to determine patient treatment with companion diagnostics. As updated guidelines are released, we evaluate them and update the checklist requirements where needed to stay current with evidence-based practices.
- A CAP Center guideline update was recently released, Principles of Analytic Validation of Immunohistochemistry Assays. We incorporated key concepts when this was first published in 2014 and will be including newer updates for our 2024 checklist edition to ensure that IHC assays used for patient testing ensure accuracy and reduce variation in IHC laboratory practices. This includes content on recommendations for the numbers and type of samples to be used for validation or predictive and nonpredictive assays, criteria for validating laboratory-developed assays, concordance rates between the new assay and comparator assay, and processes to evaluate changes to the assay.
- CAP Cancer protocols provide guidelines for collecting essential data elements for complete reporting of malignant tumors and optimal patient care. The CAP checklist require laboratories to use these protocols for synoptic reporting and have processes to implement changes to their reporting templates in response to required data element changes in updated protocols.
- The American Cancer Society recently changed its guidelines for HPV screening for cervical cancer to promote the use of the primary HPV screening test, over co-testing involving an HPV test with a PAP test, to promote availability of testing to all patients and early detection abnormal cervical cell changes (pre-cancers) to treat patients earlier of cervical cancer. This is a newer type of testing that is not widely used in laboratories, as only one instrument has received FDA-approval. The CAP will be modifying its checklist requirements for the 2024 checklist edition to ensure that the appropriate quality measures are in place for laboratories that begin performing this testing and to educate physicians on the limitations of these tests.
- The ISO 15189 Standard is an international standard for quality and competence in medical laboratories. The CAP has incorporated concepts from the standard in the CAP checklists for addressing risks and opportunities for improvement, with the goal of increasing the effectiveness of quality management systems, decreasing the probability of invalid results, and reducing potential harm to patients, laboratory personnel, the public, and the environment. For example, the CAP has requirements for root cause analysis for certain types of non-conformances that serve to identify the source of the problem and prevent recurrence. Another example would be requirements that require a risk assessment process for laboratories to proactively identify problem areas and develop mitigation strategies to reduce risk, such as with

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pretransfusion sample misidentification and other causes of mistransfusion or evaluation of safe work practices to identify hazards and implement mitigation strategies to prevent laboratory incidents and accidents.

- The Cystic Fibrosis Foundation has published guidelines on sweat testing that are periodically updated for the screening and diagnosis of Cystic Fibrosis for newborns and adults. The CAP has incorporated concepts from these guidelines into the checklist requirements on sweat testing to ensure that the results provided by the laboratory produce accurate, reliable results using methods, collection techniques, and reference ranges appropriate for the testing.

THE CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE (CLIAC)

Virtual Zoom Webinar

April 10, 2024

Time (ET)	Topic		Speaker/Moderator
10:00	Call to Order/Welcome		Dr. Reynolds Salerno Dr. Jordan Laser
	Recognition of Outgoing Members: • Dr. Mary Edgerton • Dr. Nirali Patel • Dr. Michael Pentella • Dr. Chip Watkins Recognition of New FDA Ex Officio: • Dr. Courtney Lias	**1**	
10:15	Introductions/Conflict of Interest		Dr. Jordan Laser
10:25	CDC Update	**2**	Dr. Collette Fitzgerald
10:40	CMS Update	**3**	Mr. Gregg Brandush
10:55	FDA Update	**4**	Dr. Courtney Lias
11:10	Clinical Laboratory Improvement Amendments of 1988 (CLIA) Fees; Histocompatibility, Personnel, and Alternative Sanctions for Certificate of Waiver Laboratories Final Rule Presentation	**5**	Ms. Penny Keller
	The Applicability of CLIA Personnel Requirements to Preanalytic Testing		
11:30	Introduction to Topic	**6**	Mr. Gregg Brandush Dr. Courtney Lias Ms. Tamara Pinkney
11:50	Public Comments		
11:55	Committee Discussion		Dr. Jordan Laser
1:00	**BREAK (one hour)**		
	The Role of Artificial Intelligence and Machine Learning in the Clinical Laboratory		
2:00	Introduction to Topic	**7**	Ms. Heather Stang Dr. Courtney Lias
2:10	The Basics of Artificial Intelligence and Machine Learning	**8**	Dr. Alexis Carter
2:45	Public Comments		
2:50	Committee Discussion		Dr. Jordan Laser
3:45	**BREAK (30 minutes)**		

THE CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE

Virtual Zoom Webinar

April 10, 2024

The Use of Clinical Standards to Improve Laboratory Quality

4:15	Introduction to Topic	**9**	Dr. Víctor R. De Jesús
4:20	CDC's Clinical Standardization Programs: Ensuring the Accuracy and Reliability of Chronic Disease Biomarker Tests	**10**	Dr. Hubert Vesper
4:40	Clinical and Laboratory Standards Institute (CLSI): Consensus Standards to Support Operational Excellence and Regulatory Compliance	**11**	Dr. Barb Jones
5:00	Public Comments		
5:05	Committee Discussion		Dr. Jordan Laser
6:00	Adjourn		Dr. Jordan Laser

Clinical **L**aboratory **I**mprovement **A**dvisory **C**ommittee

Meeting Transcript

April 10, 2024

Atlanta, Georgia

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

April 10, 2024

❖ Call to Order and Committee Member Introductions

CLIAC DFO: Good Morning and Welcome to the spring meeting of the Clinical Laboratory Improvement Advisory Committee or CLIAC. My name is Ren Salerno. I'm the Acting Associate Director for Laboratory Science and Safety, the Acting Director of the Office of Laboratory Science and Safety, and the Acting Director of the Center for Laboratory Systems and Response at the Centers for Disease Control and Prevention. I'm also the designated federal officer of CLIAC. CDC manages CLIAC and provides scientific and technical advice and guidance to the Department of Health and Human Services. CLIAC provides advice and guidance to HHS that focuses on improvement in clinical laboratory quality and the practice of laboratory medicine. In addition, the committee provides advice and guidance on specific questions related to possible revision of the CLIA standards. Because this is a federal advisory committee meeting, the Zoom chat and Q&A functions have been disabled for the online audience members. If you are experiencing Zoom difficulties, please get in touch with CLIAC at cliac@cdc.gov.

CLIAC CHAIR: Yes, good morning, everyone. Just a note to the members regarding quorum. We're reminded of the importance of attending the entire meeting and returning promptly from breaks to ensure a quorum is maintained until all matters before the committee are addressed and the meeting is adjourned. I believe we're tight regarding quorum today, so it's especially important to return to the meeting promptly after each break. I'm also going to briefly talk through some of the process for the official recommendations. Official recommendations or those related to an item on the meeting agenda that is put forward as a motion, seconded as by another CLIAC member, and voted on by CLIAC and obtained a majority vote. A reminder that all CLIAC discussions and deliberations must be available to the public. As a result, the chat function is not available for public viewing. CLIAC members online should refrain from engaging in topic discussions offline through the chat. Please use the chat only to notify me of your desire to comment during the discussions or ask the question of a speaker. An email to Heather Stang is another option for submitting draft recommendations. And again, now that we're using Zoom, please feel free to just raise your virtual hand. It actually lines you up quite nice for us to be able to engage in a discussion. The CLIAC recommendations table is available on the meeting website and contains a list of all past CLIAC recommendations, including information on their implementation status.

CLIAC CHAIR: Thanks, [CLIAC CHAIR]. It is now time for us to recognize our Spring 2024 outgoing CLIAC members. Although these members' terms officially end in June, they will have the opportunity to extend their term an additional 180 days.

OK, next slide, please. Dr. Mary Edgerton. Dr. Edgerton's experience in anatomic and clinical pathology and clinical informatics, including research in data mining, bioinformatics, and mathematical modeling, provided the physician informatician perspective on various committee discussions. Dr. Edgerton was instrumental in drafting recommendations on many topics, including laboratory data exchange and harmonization, remote selection, interpretation and reporting of patient results, and standardization of test result communication. We thank Dr. Edgerton for her service to the committee.

Nirali Patel. Dr. Patel's experience as a board certified molecular geneticist, anatomic and clinical pathologist, and laboratory director provided a diverse perspective to many CLIAC discussions. Her experience leading and providing compliance oversight within multiple regulatory frameworks led to CLIAC recommendations on many topics, including remote selection, interpretation, and reporting of patient results, the laboratory workforce, and the role of the laboratory in diagnostic and antimicrobial stewardship. She is currently serving as the chair of the next generation sequencing workgroup. We thank Dr. Patel for her commitment to CLIAC.

Michael Pentella. Dr. Pentella's experience as a board certified medical microbiologist and his expertise in biosafety and clinical and public health laboratories were both very beneficial to many CLIAC topic discussions. He was instrumental in leading recommendations related to the partnership between clinical

and public health laboratories, laboratory data exchange, laboratory workforce, and laboratory training and education. He's currently serving as the chair of the biosafety workgroup for CLIAC. We thank Dr. Pentella for his commitment to the committee.

And finally, Chip Watkins. Great. Dr. Watkins' experience as a physician and laboratory director, including his diverse clinical experience spanning academics, corporate, and private practice medicine, has provided the physician perspective on numerous CLIAC topics. He was instrumental in discussions to develop recommendations related to the laboratory workforce training and education, the role of the laboratory in diagnostic and antimicrobial stewardship, and efforts to address the CLIA top 10 deficiencies. We thank Dr. Watkins for his commitment to CLIAC.

I'd now like to take this moment to recognize Dr. Tim Stenzel. Dr. Stenzel was appointed to CLIAC as the FDA ex-officio member in 2020. He provided the committee with seven FDA update presentations. During his tenure as the FDA ex-officio, there have been 64 CLIAC recommendations and two CLIAC workgroups, many of which benefited significantly from Dr. Stenzel's contributions and recommendations. We sincerely thank Dr. Stenzel for his service and his commitment not just to CLIAC but to FDA and the US government. We welcome Dr. Courtney Lias to CLIAC as the new FDA ex-officio.

OK, it is now time for committee members to acknowledge their presence and their conflicts of interest. I will call out your name and then ask you to indicate that you are present and reveal your conflicts of interest. We will start with our CLIAC chair, Dr. Jordan Laser.

JORDAN LASER: Good morning, everyone, Jordan Laser. Obviously, I'm here. Pathologist by training, sub-specializing in molecular genetic pathology, currently the Senior Director for Clinical and Medical Affairs at Bio-Techne. And my conflicts of interest include both employment and stock in Bio-Techne and the Chair of the Personalized Health Care Committee for the College of American Pathologists.

CLIAC DFO: Thank you. Dr. Esther Babady?

DR. ESTHER BABADY: Hello, everyone. I'm here. I'm the Service Chief for Microbiology at Sloan Kettering Cancer Center. And in terms of conflict of interest, I'm President of the Pan-American Society for Clinical Virology. I chair a subcommittee on evidence based guidelines for the American Society of Microbiology. And I have consulting fees and research funding from GenMark Roche and Bio-Rad and Copan Diagnostics

CLIAC DFO: Thank you, Esther. Mr. Michael Black?

MR. MICHAEL BLACK: Thank you. Good morning to everybody. Mike Black here. I'm currently the Vice President of Laboratory Services at Ochsner Health. And I have no conflicts of interest.

REN SALERNO: Thank you. Dr. Chester Brown?

DR. CHESTER BROWN: Hi, Chester Brown, present, obviously. Chief of Genetics at Le Bonheur Children's Hospital, University of Tennessee Health Science Center. I have no conflicts. I'm a medical geneticist.

CLIAC DFO: Thank you. Dr. Kimberle Chapin?

DR. KIMBERLE CHAPIN: Morning, everyone. My name is Kim Chapin. I am currently the Chief Medical Officer for a startup company called Deepull and a professor at Alpert Brown Medical School in Pathology and Lab Medicine. No conflicts.

CLIAC DFO: Thank you. Dr. James Crawford?

DR. JAMES CRAWFORD: Hello, I am Jim Crawford, Professor and Chair Emeritus Department of Pathology and Laboratory Medicine at Northwell Health. My three conflicts of interest-- I'm Chair of the

Board of Directors of the Project Santa Fe Foundation, a nonprofit educational foundation. I'm a non-voting board member of Clearpath, and President of the Northwell Health Genomics Alliance.

CLIAC DFO: Thank you. Miss Heather Duncan?

CLIAC EXECUTIVE SECRETARY: She is online in the audience. I'm having trouble moving her over. So we're working on that.

CLIAC DFO: OK. Dr. Mary Edgerton.

DR. MARY EDGERTON: Hi, I am Mary Edgerton, present. As far as conflicts of interest go, I am employed by the University of Nebraska Medical Center and Nebraska Medicine. I receive funding through a contract from the FDA for the SHIELD Initiative. I am an advisor to the College of American Pathologists, Pathology Electronic Reporting Committee. And I am a candidate for the College of American Pathologists Board of Governors. That's it.

CLIAC DFO: Thank you, Mary. Dr. Tanner Hagelstrom.

DR. TANNER HAGELSTROM: Hello, Tanner Hagelstrom. I'm the Senior Lab Director of Oncology at Natera. I'm employed there and own stock. I also consult for a laboratory called Skyline Diagnostics. And I'm co-owner and founder of a company called Expecting Diagnostics. I also serve on the Association for Molecular Pathology Economic Affairs Committee. Thank you.

CLIAC DFO: Thank you. Dr. Yael Heher.

DR. YAEL HEHER: Hello. I'm Yael Heher. And I'm a renal pathologist. My clinical work is at Boston Children's Hospital. I currently oversee the laboratories for the Beth Israel Lahey Health system. And I'm the Chief Quality Officer for that system. I sit on a few committees-- the SCAP Foundation Committee, and I don't have many conflicts of interest aside from that.

CLIAC DFO: Thank you. Dr. David Koch.

DR. DAVID KOCH: Yeah, good morning, Ren, and good morning, everybody. This is Dave Koch. I'm a clinical chemist, pathology and laboratory medicine professor at Emory University and Director of Chemistry at Grady Memorial Hospital. My current only conflict of interest, I'm an advisory board member for Roche in their blood gas and electrolytes instruments.

CLIAC DFO: Thank you. Dr. Hung Luu.

DR. HUNG LUU: Good morning. I'm an Associate Professor of Pathology at UT Southwestern Medical Center and Director of Clinical Pathology for Children's Health. My conflicts of interest include employment. I receive salary support from FDA grants for the SHIELD Initiative. And I am also a member of the Clinical Advisory Committee for Health Gorilla.

CLIAC DFO: Great. Thank you. Dr. Nirali Patel.

NIRALI PATEL: Good morning. I'm Vice President and Lab Director at Tempus AI. And in addition to that, I'm a member of the COLA Board of Directors.

CLIAC DFO: Thank you. Dr. Michael Pentella.

DR. MICHAEL PENTELLA: Good morning. I'm Mike Pentella. I'm the Director of the State Hygienic Laboratory in Iowa. And I'm a clinical professor at the University of Iowa. I'm also a member of the Board of Directors of the Association of Public Health Laboratories. I have no conflicts of interest.

CLIAC DFO: Thank you. Dr. Mark Tuthill.

DR. MARK TUTHILL: Yes, good morning, everybody. My name is Mark Tuthill. I am the Division Head of Pathology Informatics at Henry Ford Health System. I am a member of the API Governing Council, which is really not a conflict, but I have no direct financial conflicts of interest to report.

CLIAC DFO: Thank you. Dr. Chip Watkins.

DR. CHIP WATKINS: Hey, good morning. Chip Watkins. I'm Chief Medical Officer Laboratory Director of a small lab here in Asheville, North Carolina. I'm also an AAFP, American Academy of Family Physicians, appointed member of the COLA board. And I do want to thank the committee for allowing me to participate over the past, I think, four years. It's been a great pleasure and honor to serve, and I appreciate everyone's patience with me. And hopefully, 30 years in the field as a family doc have helped bring a little different perspective. But I appreciate everyone's work and brains.

CLIAC DFO: Thanks, Chip. Miss April Veoukas.

MS. APRIL VEOUKAS: Good morning. My name is April Veoukas. And I'm the AdvaMed liaison representing the medical device industry. So in terms of conflicts, I am employed by Abbott Laboratories and have employment and financial interests, as well as being the representative for the Medical Device Trade Association AdvaMed.

CLIAC DFO: Thank you. Dr. Colette Fitzgerald.

DR. COLLETTE FITZGERALD: Good morning, everyone. This is Colette Fitzgerald. I'm currently the Acting Associate Director for Science in the Center for Laboratory Systems and Response at CDC. I'm the CDC ex-officio for CLIAC. I'm on the Board of Directors at the Clinical and Laboratory Standards Institute and have no conflicts to report.

CLIAC DFO: Thank you. Mr. Gregg Brandush.

MR. GREGG BRANDUSH: Thank you, Ren. My name is Greg Brandush. I'm the Director of the CMS Division of Clinical Laboratory Improvement and Quality. And I have no conflicts of interest.

CLIAC DFO: Dr. Courtney Lias.

DR. COURTNEY LIAS: Hi, I'm Courtney Lias. I am the Acting Director of the Office of In Vitro Diagnostic Devices at the Food and Drug Administration. And I have no conflicts.

CLIAC DFO: Thank you, and Miss Heather Stang.

MS. HEATHER STANG: Good morning, everyone. Heather Stang. I'm the Senior Advisor for Clinical Laboratories in the Division of Laboratory Systems here at CDC. I also serve as the CLIAC Executive Secretary, and no conflicts for me.

CLIAC DFO: Great. Thank you. And I should also acknowledge that I am Ren Salerno at CDC, and I do not have any conflicts of interest. I'll now turn it over to Jordan.

CLIAC CHAIR: Wonderful. Thank you, [CLIAC DFO]. And again, thank you everyone for joining us today. We have a good lineup for the rest of the day. Just a little few housekeeping items in terms of public comments. During the period that's dedicated to the committee discussion, participation is limited to CLIAC members only. CLIAC can only accept public comments that directly relate to the topics announced in the Federal Register Notice of the CLIAC Meeting and as related to the topics. So as I mentioned, we have a good agenda for the meeting today. The committee will discuss and deliberate on the applicability of CLIA personnel requirements to pre-analytic testing, the role of artificial intelligence and machine learning in the clinical laboratory, and the use of clinical standards to improve laboratory quality. Public comment periods are scheduled at the end of each topic area for today. And today, public comments will be limited to a total time of five minutes per individual or group. So if anyone in the

audience wishes to address the committee, the public comment portion of the meeting is the proper forum. A little bit of logistics. Copies of the PowerPoint presentations and other meeting materials are posted on the CLIAC website. Again, that's cdc.gov/cliac. This meeting is being webcast via Zoom webinar. We welcome everyone online. And links to access the webinar are provided on the CLIAC website as well. The meeting is also recorded to assist in preparing an accurate written summary of the proceedings. So today, as usual, we're going to be starting with agency updates from the CDC, CMS, and FDA. Following the agency updates, there will be a final presentation on Clinical Laboratory Improvement Amendments of 1988, specifically fees, histocompatibility, personnel, and alternative sanctions for certificate of waiver laboratories final rule. We'll likely have some time for some clarifying questions and hopefully be able to squeeze in a bio break before we move on to the other sessions.
So with that, we are slightly ahead of schedule. And why don't we move on to our first update from the CDC with Dr. Colette Fitzgerald?

CLIAC DFO: Hey, [CLIAC CHAIR], if I could just jump in real quickly. I believe—

CLIAC CHAIR: Sure.

CLIAC DFO: --Heather is now online and has joined us. Heather, could you quickly introduce yourself and acknowledge your conflicts of interest, if any?

MS. HEATHER DUNCAN: Sure. I'm Heather Duncan, the Director of Laboratory Services at ECU Health. And I have no conflicts to declare today. Thank you.

CLIAC DFO: OK, thank you. OK, back to you, Jordan. Sorry about that.

CLIAC CHAIR: Yeah, no worries, perfect. Thank you. Yeah, I'm going to turn it right over to Dr. Collette Fitzgerald.

❖ Agency Updates and Committee Discussion

Centers for Disease Control and Prevention (CDC) Update
Collette Fitzgerald, PhD, CDC EX OFFICIO

DR. COLLETTE FITZGERALD: Thank you, Jordan. Good morning, everyone. Thank you for the opportunity to share updates this morning on our work in the Division of Laboratory Systems in the Center for Laboratory Systems and Response at CDC. I'll refer to our division as DLS for the remainder of the presentation. Next slide, please.

As described in the CLIAC charter, the CLIAC committee provides scientific and technical advice and guidance to the Secretary and Assistant Secretary for Health at the Department of Health and Human Services or HHS, the Director at CDC, the Commissioner at the FDA, and the Administrator at CMS. The CLIAC committee does this by providing recommendations to the tri-agencies of the CLIA programs at CDC, CMS, and FDA. These recommendations, made by CLIAC, are then utilized by the tri-agencies of the CLIA program to guide a variety of our activities. So CLIAC recommendations from the committee are very important. A list of all CLIAC recommendations and their current status can be found in the CLIAC Recommendations Table available at the link on this slide.

This morning, I will share recent highlights from six DLS initiatives aligning with categories and recommendations from previous CLIAC meetings as shown in the table on this slide. This includes updates on a CLIAC Biosafety Workgroup, the ECHO Biosafety Program, a CLIAC Next Generation Sequencing Workgroup, the Forum on Adoption of Standards for Laboratory Data Exchange, updates on the OneLab Initiative, and the upcoming Clinical Laboratory Partners Forum Meeting. Next slide, please.
During the April 2016 CLIAC meeting, committee members raised the matter of biosafety in clinical laboratories as an urgent unmet national need. CLIAC recommended that CDC convene a multidisciplinary task force to develop a biosafety strategy for clinical laboratories that would include

partners from all areas of clinical and public health laboratories, industry, other relevant federal agencies, clinicians, and patient representatives. At CDC, we have made significant progress on this recommendation and have periodically updated the committee on our activities during previous CLIAC meetings. This included hosting a June 2022 town hall with clinical and public health laboratory partners and industry manufacturers. The purpose of the town hall was to provide an overview and discussion on laboratory biosafety when using laboratory instruments to test human specimens. The discussions during the town hall led CDC, CMS, and FDA to convene a CLIAC workgroup to address the issues raised. CLIAC member Dr. Michael Pentella chairs the CLIAC Biosafety Workgroup. Ms. Heather Duncan is our CLIAC member representative on the workgroup and the designated federal official or DFO, and ex-officio members are listed on the right hand side of this slide.

The Biosafety Workgroup is charged with providing input to CLIAC for consideration in making recommendations to HHS on potential additions to the CLIA regulations and the need for solutions that will provide a safe working environment for the nation's clinical and public health laboratories. The workgroup had an introductory meeting on January 10, 2024. And at its next meeting, which was held on February 12, 2024, it discussed how interested parties can better address biosafety for already established IVD instruments and IVD instruments currently under development. It also addressed how interested parties can ensure appropriate biosafety activities where end users are established, effectively provided, communicated, and followed. You can find more information on this CLIAC workgroup at the link at the bottom of this slide. We thank all of the workgroup members for sharing their time and expertise with the workgroup. The workgroup will continue to meet through 2024, and we look forward to sharing updates on their activities at a future CLIAC meeting. Next slide, please.

The ECHO Biosafety Program, launched by DLS in January 2023, responds to the same 2016 CLIAC recommendation on laboratory safety. The initiative's goal is to develop and engage a biosafety community of practice to address biosafety challenges in clinical and public health laboratories. The ECHO Biosafety sessions brings together laboratory biosafety professionals to bridge gaps, share experiences, and enhance biosafety. The main feature of the sessions is the discussion of solutions to address biosafety challenges. We have held 14 sessions since the start of last year, and we're continuing with monthly sessions in 2024. Upcoming topics of discussion include planning, developing, and achieving biorisk management objectives on April 30th. Support resources, competence, and awareness on May 28. And support communication and documented information on June 25, 2024. For a complete list of upcoming ECHO Biosafety sessions and to access a link to connect and register to attend the upcoming ECHO Biosafety sessions free of charge and to see resources from previous sessions, please visit the link at the bottom of this slide. Next slide, please.

Moving next to updates on the CLIAC Next Generation Sequencing Workgroup. During the November 2021 CLIAC meeting, the CLIAC committee heard presentations and deliberations on the role of next generation sequencing in clinical and public health laboratories. CLIAC recommended that CDC, CMS, and FDA convene a workgroup to define the scope of practice and the requisite clear qualifications for personnel performing bioinformatic data analysis and interpretation to produce test results that inform clinical decision making. In 2022 and 2023, the CLIA Regulations Assessment Workgroup met to provide input to CLIAC for deliberation on how CLIA might specifically be updated as related to the total test process, data as a specimen, histopathology, analytical testing specifications, and digital pathology. This workgroup also had discussion elements related to the next generation sequencing testing process and personnel performing data analysis. This workgroup presented its final report to CLIAC in November 2023. And this information will be used by the newly established CLIAC Next Generation Sequencing Workgroup. Also, as Miss Penny Keller will present later this morning, CMS and CDC work to publish the CLIA Fees, Histocompatibility, Personnel, and Alternative Sanctions for Certificate of Waiver laboratories proposed rule in July 2022 and the final rule in December 2023. The final rule includes changes to high-complexity testing personnel qualification pathways that may impact the ways that individuals performing bioinformatic analysis for NGS can qualify. The CLIAC Next Generation Sequencing Workgroup is using the final rule as the basis to determine if there are any additional education, training, experience, and competencies that CLIA should require to qualify personnel performing next generation sequencing bioinformatic data analysis and interpretation. The NGS Workgroup held its first meeting on March 15, 2024. The workgroup is chaired by CLIAC member Dr. Nirali Patel. Other CLIAC members on the

workgroup include Dr. Chester Brown and Dr. Tanner Hagelstrom. Workgroup topics will focus on the current regulatory requirements, guidelines, and practices related to the role of bioinformatics in clinical and public health laboratories performing NGS, a harmonization of definitions of bioinformatic roles, and a discussion on education, training, experience, and competencies for various bioinformatic levels. The CLIAC Next Generation Sequencing Workgroup will continue to meet through 2024. And you can find more information on this CLIAC workgroup at the link at the bottom of this slide. We thank all of the workgroup members for sharing their time and expertise on this workgroup and look forward to sharing additional updates on their work at a future CLIAC meeting. Next slide, please.

Moving next to updates on the Forum on Adoption of Standards for Laboratory Data Exchange. In November 2021, CLIAC developed a recommendation related to the Systematic Harmonization Interoperability Enhancement of Laboratory Data or SHIELD Initiative to improve the implementation of laboratory data exchange standards. The CDC leveraged our involvement with SHIELD to identify interested parties, including federal agencies, IT vendors, professional groups, and industry partners to create the Forum on Adoption of Standards. The forum facilitates discussion about challenges to adopting standards and allows organizations to brainstorm solutions to standardize laboratory data exchange between laboratories, clinical providers, and public health departments. The forum members committed to holding meetings every other month in 2023. Across those six meetings last year, participants presented on various challenges related to adopting laboratory data exchange standards. These included challenges related to frequently updated versions of standards, financial burdens on laboratories, and knowledge gaps and limited access to educational resources for end users. Forum participants provided feedback to address the challenges presented at each meeting. Suggestions included increasing informatics expertise within laboratories and availability of resources to implement simplified updates. Creating incentive programs that provide funding for laboratories to implement informatics standards. And developing educational resources on how laboratory data exchange standards are connected. Using the Office of the National Coordinator for Health Information Technology, or ONC's Interoperability Standards Advisory and expertise from forum participants, the group developed an educational resource depicting how laboratory data exchange standards work together to promote interoperability. The resource defines several factors associated with each standard and clearly identifies the interactions between them for a laboratory audience. By providing this resource through the SHIELD network, it will help address the educational burden associated with standards adoption and improve understanding of how standards work together to promote interoperability. Next slide, please.

Moving next to OneLab Initiative updates. DLS developed the OneLab Initiative to bridge, train, and sustain a capacity building community among laboratory professionals and testers to collectively support rapid large-scale responses to public health emergencies. Several 2019 CLIAC recommendations related to the laboratory workforce guided the creation of OneLab. And more recent CLIAC recommendations have shaped OneLab's evolution. OneLab has experienced 83% membership growth since November 2023 and has recently passed a major milestone. As of March 2024, we have over 22,000 unique members across all our OneLab elements. This slide highlights some six-month metrics for our OneLab resources and members. We chose to focus on growth since the last CLIAC meeting. Since the start of fiscal year 2024, we have attracted 168,000 registrations for our OneLab training materials, nearly matching the FY23 total of 171 registrations in half the time. Releasing new courses and job aids is essential to OneLab's continued growth. We recently released a new centrifuge safety practice scenario on OneLab VR and launched a new e-learning course on fundamentals of handling compressed gas cylinders safely in November 2023. The total number of learners and new members for OneLab REACH, the OneLab Network, and OneLab TEST are broken out on the right-hand side of this slide. Upcoming priorities for OneLab include adding new features to OneLab REACH and piloting live site specific training on OneLab VR. For more information on OneLab, you can please visit the link at the bottom of this slide. Next slide, please.

The second ever OneLab Summit will be held next week on April 16th through the 18th. OneLab Summit is a three-day virtual summit that connects laboratory professionals in real-time to support a unified response to laboratory training needs. The theme of the meeting this year is "Thrive-- People, Planning, and Preparedness." The summit includes hands-on experiences designed to help attendees improve their skills through training and technologies, learning and development tools and practices. The collaborative

environment connects peers in laboratory education and training to each other and to CDC. OneLab's summit content is most relevant to those who have education or training responsibilities for clinical public health and academic laboratories. Registration is free and now open and can be accessed through the QR code on this slide. Next slide, please.

DLS will hold will host the next Clinical Laboratory Partners Forum meeting on May 22, 2024. The spring meeting will focus on early diagnosis of chronic kidney disease or CKD, and how clinical laboratories play a vital role in identifying patients at risk for CKD. I won't read out the topics, but you can see the topics that will be discussed at the meeting listed on the bottom half of this slide. This meeting is responsive to the CLIAC recommendation on the laboratory's role in advancing health equity from the April 2023 CLIAC meeting. To learn more about the forum, please visit the link at the bottom of this slide or email dlsinquiries@cdc.gov. Next slide, please.

To close out, I'd like to remind everyone that Medical Laboratory Professionals Week, also known as Lab Week, is next week. Every year at DLS, we use the occasion of Lab Week to honor laboratory professionals for their contributions to public health and patient care. Join us as we celebrate the 49th Lab Week on April 14th through the 20th. And this year's theme is the "Future is Lab." Please join us in celebrating Lab Week by showing your appreciation to a laboratory professional, participating in DLS's Lab Week activities, or accessing our digital tool kit to increase awareness of the significant contributions of laboratory professionals by sharing social media hashtags, key messages, and digital graphics with your colleagues.

And lastly-- next slide, please-- I'd just like to close by taking the time to first thank our partners through the clinical and public health laboratory and testing community for your hard work, collaboration, and support. And also, importantly, want to thank and acknowledge my DLS colleagues whose work I have highlighted for you this morning. In conjunction with many other CDC colleagues, their work is instrumental to our division, center, and agency's mission. Thank you.

CLIAC CHAIR: Thank you. Yeah, I appreciate the update. It's really great to see the programs and how they are progressing and the accomplishments they're doing. Incredibly, the OneLab growth is really remarkable. We have a couple of minutes. Are there any clarifying questions from CLIAC members? Again, not necessarily a discussion, just any clarifying questions for Dr. Fitzgerald?

CLIAC MEMBER: I would.

CLIAC CHAIR: OK. Go ahead.

CLIAC MEMBER: Sorry. I was wondering-- thank you for that presentation. And forgive me if I missed it. But what is the relationship with the CLIAC members and that CKD workgroup? And would it be possible for those of us interested in kidney care to participate at all?

DR. COLLETTE FITZGERALD: Yeah, so I can reach out to the quality and safety systems branch and others in DLS who coordinate the Clinical Laboratories Partners Forum. And we can connect you and see if it's an option for you to be able to listen in to that meeting.

CLIAC MEMBER: Thank you so much. Really important work.

CLIAC MEMBER: Yeah, hi, Collette.

CLIAC MEMBER: My question was maybe one of ignorance, so I apologize, but I'll ask anyway. And that is I'm wondering about the funding that supports this. Because you've just done amazing stuff. It would be really sad to see it fall apart because the lack of money. I'm interested in just your budget, how you get funding. Are you getting adequate funding? How well are you supported?

DR. COLLETTE FITZGERALD: Ooh, funding questions. I might punt that to [CLIAC DFO]. Is this the appropriate forum to discuss funding?

CLIAC DFO: Yeah, so just at a high-level, we at CDC are part of the federal tri-agency CLIA program. And we receive funding from CMS that comes from the CLIA laboratory fees to support some of this work, not all of this work. We also receive some funding through congressional allocations to CDC. But you know, I think every federal government official would say this. We think this work is extremely important, and we have limited resources to do all the things that we would like to do. But we do appreciate your interest in this work. Thank you.

CLIAC MEMBER: Yeah, thank you. I just wanted to say it's really just really impactful boots-on-the-ground kind of work. So great job.

DR. COLLETTE FITZGERALD: Thanks.

CLIAC CHAIR: Excellent. Thank you. All right, let's go on to the next update. This is a CMS update from Mr. Gregg Brandush.

Centers for Medicare & Medicaid Services (CMS) Update
Gregg S. Brandush, RN, JD, CMS EX OFFICIO

MR. GREGG BRANDUSH: Thank you, [CLIAC CHAIR]. And you can see my screen, correct? OK.

CLIAC CHAIR: Sure can.

MR. GREGG BRANDUSH: I always follow Colette on this, and she's so smooth and professional and sets the bar so high. So it actually takes the pressure off because you all know I'm not going to present like that. So I'm Gregg Brandush. I represent the Division of Clinical Laboratory Improvement and Quality with CMS. I'm going to give the updates that have occurred since our last meeting.

So this is the standard disclaimer. I'm not going to read this to you. But basically, it says that nothing in this presentation should be taken as official guidance, and that any mistakes that are in this presentation are mine and not representative of CMS.

So the big news internally to CMS is that we've had a reorganization since the last meeting. So previously, we had two policy branches and three operations branches that all had overlapping responsibilities. And it's really hard to create consistency in a program when you have two and three leaders of the program. There's different sort of opinions and how things should be enacted and administrated. And in order to develop some improvements in our internal efficiency and consistency, we restructured our division along what's really the five primary product lines.

So we have a survey branch. And this branch is responsible for our federal monitoring surveys, our validation surveys, and our federal jurisdictional surveys, so those that we have direct responsibility for completing.

We have an enforcement branch now. And that branch is responsible for all the enforcement action across the nation. So this is any instance in which a lab has, I call it, condition plus noncompliance. So if a lab has a condition out. They're not able to make that correction. They have an immediate jeopardy as well, or if they have standard noncompliance that's persistent across 12 months, the enforcement branch is responsible for proposing and imposing enforcement action and promoting a return to compliance if possible.

Our logistics branch is the jack-of-all-trades branch. They are responsible-- I was told once that they're like-- in a wheel, they're the spokes in the wheel. They support all the other branches. They possess and monitor and update our data systems. They're responsible for FOIA. They're responsible for the state budget process. And they're our primary spoke for communication with the outside world.

Our regulations and clearance branch, this is the one that is most germane to all of you. This is the branch that's responsible for identifying, drafting new regulations proposing, statutory change, drafting new interpretive guidance related to new regulations, and then navigating us through the clearance process for any new public issuance that we may pursue.

And then the fifth branch is the state oversight branch. This is a really state and AO oversight branch. And they work with ensuring that our state agencies are administering the CLIA program according to regulatory requirements, policy requirements. They monitor the various data systems to ensure consistency. They work with the accrediting organizations to make sure that they are clear and understand CMS expectations.

The screen is the leadership. So it's an organizational chart that shows the leadership of each area. The five people directly under me, these are our technical advisors. So each branch has a technical advisor. Elysse Lessner is the technical advisor for the enforcement branch. Scott Stacy is the technical advisor for the logistics branch. Karen Sutterer is the technical advisor for the survey branch, Penny Keller for regulations and clearance, and then Cheryl Dobbe for the state oversight branch. The managers of each branch. Daniel Hesselgesser is the manager of the survey branch. Latoya Laing out of Philadelphia is the manager of the enforcement branch. Karen Fuller out in San Francisco is the manager of the logistics branch. Angie Daubert here in Chicago is the manager of regulations and clearance. And Raelene Perfetto in Baltimore is the manager of the state oversight branch. And one of the things that I really like about this reorganization is we aren't-- so Baltimore focused independent. It's really a national organization now, where any of our staff can be located in any one of the 10 regional offices within CMS or in Baltimore.

This is a slide that I give every year. A few people are just really interested in how the numbers look for laboratories. So we've got 317,000 labs, roughly. 14,000 of them are in our exempt states-- New York and Washington. The number of labs with a certificate of compliance is about almost just under 18,000. The certificate of accreditation a little bit less than that, around 16,000. The certificate of waiver, as we all know, it's the largest group, there's 257,000 of those. And PPM about 20, just under 27,000 of that. The next slide is just a visual breakdown. Again, this is the same information. It's just how it looks. This is what we would expect with the blue certificate of waiver occupying the largest percentage of the pie. Compliance and accreditation about the same. Microscopy slightly larger.

All right, I shared this slide last year at this time last year. Because I went through some goals for the agency. So the things that are marked in yellow are things that we accomplished. The things that aren't highlighted, either we didn't accomplish them, or they're evergreen, and we're always going to be looking at those things. So the first one, improved processes, I would hope that I never yellow that one out and say, OK, we're done. We can't make any improvements. That's going to be an ongoing forever goal. But we most definitely improved our data systems significantly to help us out identify outliers in terms of survey findings, time spent on survey, survey team size. And we've been using this data to develop action plans to make sure that we are creating a survey process that's consistent and fair for all laboratories. With respect to adherence to enforcement timelines, just partially highlighted that. That's still a goal in progress. We've made a lot of progress towards this. There's more work to do. We're not quite there yet. But what we do have is we're very close to having a data system that's going to identify all the instances where there is condition noncompliance with laboratories and help us ensure that state agencies are notifying us of this condition in a timely manner so that we can take enforcement action with the ultimate goal of promoting compliance by the lab. That's still a work in progress. We enhanced our state oversight activity. We made revisions to our SAFER process, which is the formal evaluation of our state agencies. That one really is kind of an evergreen, where we will be looking at evaluating that to make sure that it's the most effective means of assessing states that it can be. Modernizing CLIA. We're always looking to modernize CLIA. We issued the new proficiency testing rule. We issued electronic certificates. That was a big change in the past year. And we work closely with modernizing CLIA with everyone on this meeting to ensure that the regulatory requirements really are in lockstep with the times. The next section there during the PHE, I'll talk about what we did with this a little bit in a couple of slides. But we reviewed all the ways that we used enforcement discretion and flexibility during PHE. And those are six examples under

that. Just to see what lessons were learned, and what we can do that really reflected an improvement, or would make our response more timely and effective should there be another public health emergency. And then the stakeholder engagements, we want to continue this regularly. We've participated in meetings with COLA, with CAP, the Joint Commission. We've got an ongoing dialogue with APHL that's been really valuable. And one of the things that we've changed that I'm really proud of is we've been more open to people that have differing views with us. And there are people that, when a new regulation comes out or a new interpretation of the regulation, they are not happy. And they're never pleasant or easy conversations, but it's important to me to make sure that people are heard, especially those that don't agree with us. So we've had several meetings with people where they gave us an earful. And we may not agree, but we do need to be able to at least explain why we've made a particular decision.
Some additional accomplishments in FY23. I mentioned the electronic certificates and QCOR links. We've improved our data exchange with the CDC to hopefully help the CDC be quicker in their response with the data that they need from us. I wrote the fee rule there. That was really lazy. This was really way more than just the fee rule. It was the fee rule, the histocompatibility, the personnel, the enforcement action against certificate. You could see what I was focused on that. I'm not going to go into that in too much detail because Penny is giving an overview on that in a little bit. We issued an RFI, request for information, related to histopathology, cytology, and clinical cytogenetic regulations. We significantly improved our budget process. So prior to the reorganization, we had each fiefdom making determinations of what the state allocation should be to implement the CLIA program. We've moved to a national model now. Saw that there was inconsistency in the way we were addressing and awarding funds and made the first steps to level that field and make sure that the allocations are fair. The backlog plan was also a really innovative thing that the team came up with. As a result of survey suspensions during the public health emergency, we had a number of labs that didn't receive a timely survey. And it created a backlog.
And when we were looking at the limitations related to when we can conduct a survey and the size of the backlog, it would be upwards of five or six years before we could get caught up on this backlog. So we developed a plan that basically used the surveys that we have already conducted and moved the labs compliance date to a current state so that we wouldn't have to go back and try to do surveys from two, four, six years ago to establish compliance. It's a move forward type of measure. And I think it's going to be a tremendous cost savings to the program. It's going to increase efficiency for our state agencies.
And then, finally, the dashboards. We have lots of use of data in all the various branches to support our activity.

I mentioned the review of the public health emergency flexibilities that we use. One of the major things to come of that is we submitted an A-19, which is just the name of the OMB flyer. And that's how you make a recommendation to Congress to change statutory authority. So under the PHSA, we do not have authority to waive any of the CLIA regulations if there's a public health emergency. So we submitted this request that would mirror the authority in section 1135 of the Social Security Act that allows CMS to waive regulatory requirements that are not statutory in order to have a more prompt response to allow access to testing. Our current mechanism for this is really use of enforcement discretion. That makes everybody who's subject to federal regulations really uncomfortable because this is really literally us saying, hey, we're from the government, and we're here to help. Trust us that this is going to be OK. This is much better because you get an actual piece of paper that says this requirement is waived. You don't have to follow it. Hopefully, Congress will support us in allowing this authority.

We talked about this a couple meetings ago. This was always just interesting. So from 2019 to 2021, this is the top 10 deficiency list. I'm not going to go through all of this. I'm going to go to the next two-year branch then. So from 2021 October to September 30, 2023, the list is exactly the same. The only difference is the highlight in the middle. Those are flipped, but otherwise it's the same thing.

And then on pace for this year, the middle there, 6033 and 2000 should have been flipped again. You could see by the numbers. But we're still on track for the exact same top 10 deficiencies. So the question that all of you very legitimately can have is, all right, yeah, here, that's what you got, but what are you doing about it? One of the things that Cheryl Dobbe, who is our technical advisor for the state oversight branch, is working on-- she's working very closely with the CDC on it that I'm really excited about-- is the creation of Lab Director University. And this is going to be a free online educational portal. It will allow laboratories to get the-- at least it's proposed-- to get the CME requirements under the new rule that will

be expected of them. And it's really going to focus on what is essential for a lab director to know to function in that capacity and give some real specific guidance related to each of these things. We hope that this educational opportunity is going to allow lab directors to proactively be in compliance in these areas. And hopefully, we'll see a change down the road.

Our goals for 2024. I've got one, three, and five-year here. So CLIA certificates by next year, 50% will be on-- or by the end of this year, 50% will be electronic and available online. A year from now, we're going to be pretty much everyone. We're going to issue the interpretive guidance on the rule that Penny will be talking about. Initiate our action plan related to the data inconsistencies we've identified. I mentioned enforcement tracking. And in the next six months or so, we plan to make a certificate of compliance survey findings available on QCOR. So if people have specific questions about specific non-compliance, they'll be able to identify it there. Our year three goals are the Lab Director University, making our enforcement letters more readable. They're really hard to read. They're complex, difficult. And then do an assessment of these state budget allocations and presumptions that we use to ensure that the funding that states are given is fair. Year five, we want to expand on the Lab Director University concept, and expand it to technical supervisors, technical consultants, and others. And then, what I'd really like to be able to do is develop a standardized survey process that's objective, consistent, and computer-assisted to help ensure that everyone gets the same survey. That you aren't subject to regional difference or individual surveyor preferences.

This is the new guidance. I'm not going to go over this because I'm a little over time. I mentioned the final rule a million times that Penny's going to talk about. We issued two admin memos to give guidance on when to conduct an onsite/offsite revisit and to properly fill out the 670 form. That is my presentation. So [CLIAC CHAIR], I will turn it back to you.

CLIAC CHAIR: Excellent. Thank you for the update. It's really interesting to hear about the reorganization and, of course, all the 2023 accomplishments. And hopefully, I'll hear positive news back from Congress in terms of the emergency waiver authority and would really streamline things. That'd be wonderful. Looking at the time, let's hold off on question-- oh, I see one question. All right, [CLIAC MEMBER], yeah, if you want to ask a quick question, then we'll go on to the FDA.

CLIAC MEMBER: Yeah, sorry. For some reason, my video doesn't seem to be working. I emailed [CLIAC EXECUTIVE SECRETARY], but-- and I don't know if you can see me or not. But anyway, thanks, Gregg. My question is about the Director University. And my question is, are people qualified but they're just like because they're doctoral level people but don't have the right training? And I'm just wondering where this compares to people who are actually certified by either ABMM or ADLM certification, that kind of thing. And just wondering about that sort of erosion of that level.

MR. GREGG BRANDUSH: Yeah, so it's really-- it's two things. It's a response to a consistent repeated noncompliance that we see and new regulatory requirements that require 20 CMEs for new lab directors that are coming in. Anybody currently in a position is going to be grandfathered in. When we were talking about the CME requirement, it seemed a little unfair to us that we would have a requirement like that but not make a free way to get that available. So there are all kinds of the AOs and consultants, there's all kinds of for pay training that's available. This is really a free one to make sure that everybody really has no excuse for not being in compliance with the regulations.

CLIAC MEMBER: OK, so this is more lab specific then? Because you can get lots of free CME, but if it's relevant or not. OK. Thank you so much.

MR. GREGG BRANDUSH: Yeah.

CLIAC CHAIR: OK, let's take one last question, [CLIAC MEMBER]. And then we'll move on to the FDA update.

CLIAC MEMBER: Yeah, Gregg, there was a bullet point on one of your middle slides, like slide eight, I think. It said university non-CLIA COVID testing. What did that have to do-- I'm wondering what you were trying to convey there?

MR. GREGG BRANDUSH: Yeah, it was just a flexibility that we allowed universities to test students during the public health emergency without having to follow all the rigorous requirements to get a CLIA certificate.

CLIAC MEMBER: All right. Thank you.

CLIAC CHAIR: Excellent. So yeah, let's go on to the FDA update. We have an update from Dr. Courtney Lias.

Food and Drug Administration (FDA) Update
Courtney H. Lias, PhD, FDA EX OFFICIO

DR. COURTNEY LIAS: All right, thank you very much. My screen look OK?

CLIAC CHAIR: Sure does.

DR. COURTNEY LIAS: Powerpoint's doing a little weird thing on my end. But hopefully, everyone can see it. So first of all, it's a real pleasure to join the group here. Thank you to Ren and Heather for really getting me back up to speed on the great work of CLIAC. And today, I'm here to provide an update. Once again, I'm Courtney Lias. I'm the Acting Director of the In Vitro Diagnostics Devices Office at FDA. And when Tim Stenzel retired at the end of December, I took over. So I've been back in the Office of In Vitro Diagnostics for about three months now. So with that, I will go ahead with our update.

So many of you may be aware of a lot of the activities we do in our office from previous updates. But in case you aren't, really quickly, our office really does everything with respect to FDA regulation of In Vitro diagnostic devices. So we work with companies or test developers in advance of tests being offered on the market to talk about what requirements might apply if they need to do analytical or clinical evaluations. We talk to them about the least burdensome way to get the information to show analytical and clinical validity. And we review, once they have that, the information to demonstrate that test can go on the market and is good for patients. And it's our mission to both promote and protect. So we're not only looking for analytical and clinical validity, but we're looking for opportunities to make sure that tests that can help patients reach them in an appropriate manner. And that includes promoting the availability of tests for unmet needs. We also look at tests once they are on the market. What we want to do there is we want to make sure that those tests continue to work the way that they are supposed to work. And we do that through surveillance of adverse events, working with companies to make sure that their manufacturing is going OK. If there are recalls, we assist the companies in making sure those recalls are effective. And that laboratories and patients and health care providers are notified when they need to take action to prevent a problem from a malfunctioning device. We also do external engagement and outreach. We certainly-- and I'll talk about this a little bit more later-- work on emergency use issues or emerging countermeasures issues. We provide guidance. And certainly, we are part of the government, so we have a lot of other sort of activities that we fulfill.

So some of the ones I want to highlight today are going to follow. So first, I'd like to highlight something that we recently announced. Our center director, Dr. Shuren, announced at the end of January, beginning of February, formally that we are in the process of reclassifying most of our high risk tests in the IVD land. So many of you know we have different sort of classifications for tests. High risk tests have the more complicated method of getting to market. Most of our tests are in what we call the 510(k) pathway, which are class II products. And it's a little bit more streamlined. So what's happened is we've had these high risk tests out there in a lot of cases for enough time to enable us to understand the aspects of those tests that provide risk.

So for example, through our surveillance activities, looking at adverse events, working with companies, understanding where the tests fail and where they don't fail. We are able to create strategies to mitigate those risks and not put some of the regulatory burden in areas where risks don't exist for those tests. And the outcome of that is that we can take those tests from the more complicated regulatory pathway to a more straightforward one so that these tests can reach patients faster. A lot of the tests that we're done classifying are in the microbiology area, where we've learned a lot from those. We are in the process of down classifying, for example, hepatitis B, parvovirus, and tuberculosis. We've previously done classified hepatitis C and other tests. In addition, we have announced that we are planning to put into class II, sort of that more streamlined pathway, all companion diagnostic assays. This will, hopefully, make companion diagnostic devices analytically and clinically valid and more smoothly available for people who need it because companion diagnostic devices are becoming increasingly relied upon. And we want to make sure that patients have access to those good tests.

Another area related to companion diagnostics is our pilot program. I'm sure that Tim presented this in the past. But just a quick overview here, we have, since last summer, been piloting a new approach to try to assure the availability of effective companion diagnostic tests for oncology drug treatment decisions. So this pilot process provides sort of a pathway by which multiple tests can be validated for the same companion use, instead of just a single test that was used in the drug trial, for example. And because of some of our paperwork requirements in the government, we are limited at this time to nine drug sponsors. And it's got certain criteria. The test has to be a companion diagnostic. It has to be a novel type where there aren't other alternatives. It has to be something that one could bridge performance on. Is there a reference standard material? Is there something by which laboratories can look at analytical validity in a straightforward and effective way, et cetera? And to do that, what we're going to do is request performance information from the drug companies on the tests that are used to enroll patients in the clinical trial for the drug. Then, we can publish that test performance on our website to show people that tests with this type of performance would be good options to use to select therapy for this particular drug product. And then health care professionals and laboratories can use that information to choose which companion diagnostic tests they'd like to use. So we're trying this out. At this stage, we don't know whether or not this is a good way of doing this. Whether or not it will achieve the goals of making more tests available for laboratories, health care providers, and patients, but we are seeking to provide transparency around what types of tests work well for drug products.

I think you all also realize we work very closely with CDC, in particular, and also CMS to address public health emergencies. And we're still doing that. We have, over the course of the last few years, been authorizing tests for COVID, including molecular diagnostic tests, including serology tests, and antigen diagnostic tests. And I know you all are acutely aware of this. So this slide is mainly a summary. But we have about 299 authorized molecular tests and 69 authorized antigen tests for COVID, including 33 over-the-counter antigen tests and five over-the-counter molecular tests. And this push toward sort of home use and point-of-care testing for infectious disease or common infectious disease has really helped us move in this area and a lot of areas, so not only for COVID but also for other infectious diseases, such as flu. We have eight multi-analyte COVID, flu, and, in one case, RSV tests that are either point-of-care or over-the-counter now available to help the public identify those conditions more quickly. We also work on other situations, outbreaks, including mpox, where we have eight authorized mpox tests and other notified laboratory developed tests for mpox to enable responses in the areas that have the highest need for mpox testing still. And when new issues arise, we mobilize forces to make sure tests are available.

So currently, there is concern about H5N1 outbreaks in Texas. And we are working with our colleagues at CDC and HHS and others to make sure that tests are available. And I can give good news that, in general, our flu A diagnostics, both molecular and antigen, will be able to pick up this particular strain of H5N1, so that's encouraging.

But we don't want to remain in emergency use land forever for COVID. And so we have announced, through a couple of guidance documents, our plans to transition from doing EUAs for COVID to business as usual, making sure enough tests are available, like we do for flu each year. And I'll let you know in the rest of our device center, other devices used during COVID where there were sort of extenuating policies put in place or EUAs accepted, for example, for masks and ventilators, those have ended. So we have

transitioned away from those being allowed to be marketed through alternative pathways as of about November. However, we are accepting certain EUAs still for COVID and, of course, other products like mpox. However, we are working toward transition away from EUAs so that we have a more predictable, steady, and transparent supply of COVID tests for the US. And to do that, we're working with test developers to transition their emergency authorized devices to forever authorized devices. And here, denote DN stands for de novo, which is one pathway 510(k) is another, but they basically result in the same thing. So far, we have about 20, a little over 20 molecular tests that have a permanent authorization and about a little over five antigen tests with permanent authorization as well. And we are working with other test developers to increase that share. So we're looking forward to doing that.

One area that's been very helpful is that we've been working with NIH and their RADx program on ITAP, which many of you may be familiar with, but it's been a very successful program. Basically, ITAP selects well-positioned test developers to develop things for unmet needs. In a lot of cases, they have been point-of-care and home use tests. For example, there was interest in having multi-analyte point-of-care and over-the-counter tests, as I mentioned, for COVID, flu, and RSV to look at being able to triage, diagnose differentially assess respiratory viruses at home, in doctor's offices, et cetera. And we have authorized several that have come out of the ITAP program, including the one on the screen, which was the first one authorized on February 29th. But the ITAP program isn't just working on COVID. They're also helping us on a very interesting effort run through CMS, through NIH, through CDC to increase the availability of a test-to-treat paradigm for hepatitis C. So it's a very interesting scenario where the idea is that if we can have accurate and reliable point-of-care tests that can detect hepatitis C virus, that potentially some of the under-served populations that may be hard to treat can be treated at the same visit where they are diagnosed to try to increase the eradication of hepatitis C in the US. So it's a very exciting effort.

And ITAP is working with one test developer, Cepheid, who is positioned to have a point-of-care hepatitis C test. And so, hopefully, soon we'll understand how that's going, but the ITAP program has been extremely helpful there. And the advantages, as I mentioned, we want to diagnose individuals who might not normally go to a doctor, at drug clinics, for example, or homeless shelters, and then treat them on the same visit to minimize loss to follow-up.

So we've also-- I just wanted to give some updates on some recent authorizations. We have a session later where we're going to be talking about artificial intelligence. It's been in the news frequently lately. You know, how will the government assess artificial intelligence in things like medical devices? And it is a big topic. But we are authorizing devices that include or were developed using AI. And we have been for several years. Recently, our office authorized the Hologic Genius Digital Diagnostic Systems with a Genius Surgical AI Algorithm. And this is, basically, image analysis software to help pathologists evaluate cervical cancer for screening. And so these types of devices exist in other imaging modalities, such as colonoscopy, where AI is used to narrow down the frames that a GI physician will have to review in a colonoscopy. And here, AI is being used to try to target pathologists' attention to the particular slides or parts of slides that are of most interest.

We've also recently granted marketing re-authorization for a first-of-a-kind test for ADAMTS13 activity. This is used in conjunction with other lab findings, but it's intended to aid in the diagnosis of TTP in patients with TMA. And it is measured on microplate readers, so a lot of laboratories have access to this. And hopefully, it will be beneficial for this patient population.

In addition, we have several authorized devices meant to assess risk of traumatic brain injury. So the clinical problem here is that somebody presents with a head injury, maybe to the emergency department, and they have to understand how severe that injury is. They need to decide whether or not a CT scan is necessary. These types of tests generally have been useful in ruling out a more severe type of TBI. For example, if you had a test that was positive, you might identify that this person may have a more severe type of TBI. But if it was negative, you'd have a little bit more confidence, along with other clinical symptoms, to potentially think that they may have mild TBI and may not need a CT scan right away. Of course, those patients would still be monitored.

Recently, our recent re-authorization included the first point-of-care cartridge for the i-STAT handheld analyzer. And this will enable this type of assessment in a more point-of-care environment, maybe the emergency department or in some cases other types of urgent care facilities, et cetera.

And then, finally, I wanted to highlight something that isn't specifically used in a clinical laboratory but I think indirectly will impact all of us in the clinical laboratory environment. And that is that we have just authorized the first continuous glucose sensor for over-the-counter use. So, of course, you all know that blood glucose meters have been over-the-counter for many, many, many years. And people with diabetes use them, can buy them at the drugstore, et cetera. This would enable CGMs to be bought that way too without a prescription. This is interesting, I think, in general to us as Americans, but is also potentially going to impact how people and doctors can interact to provide, hopefully, earlier detection of dysglycemia or other things that should be looked at. So it's, I think, going to be a very beneficial thing, not only for people with things like type 2 diabetes, but other people who are interested in learning more about their glucose values.

So with that, I'll leave you with a summary that we're always available for interaction. Our slides here have a few links. You can interact with us and get information on our general web page, but also just pick up the phone. Give us a call. We're always available to have a chat and/or talk to you about any questions that you may have. And with that, I will hand it back over. Thank you.

CLIAC CHAIR: Excellent. Thank you so much. I really appreciated the updates on the down classification. The oncology drug product pilot program, I'm really excited to see the output of that and the tour of some of the notable recent approvals. I'll ask the group-- I know we're a little bit over on time, which is OK. We'll make it up somewhere else. Just, again, a question or two from the group if one is present. Otherwise, we can move on to the next talk. All right, I see [ADVAMED LIAISON], You're up first. And then [CLIAC MEMBER], and then we'll move on.

ADVAMED LIAISON: Sure. And Thank you, Dr. Lias, for your presentation. In regards to the classification of the products in terms of companion diagnostics, if you could just clarify a little more about that. What are the agency's thoughts on the down classification of companion diagnostics, like just generally or in specific therapeutic areas?

DR. COURTNEY LIAS: We mean it to be for most companion diagnostics. You know, obviously, most of the diagnostics that have been approved so far have been in oncology and not all of them. But we are open to hearing if you have a new product with a new intended use, we really encourage you to come in thinking about special controls that might be appropriate for that. I know you understand that, [ADVAMED LIAISON], some of you may not. So that we can de novo classify that into class II. [CMS EX OFFICIO] mentioned earlier the certain processes that are in place for things like regulatory change. Actual down classification of things that have already been approved does take some time. We are looking to see if there are streamlined ways to provide options to industry to make sure that's smooth and fair. So we are working that out. But if you have a new product, a new companion diagnostics, you should definitely talk to us about potential pathways toward class II classification.

ADVAMED LIAISON: Thank you.

DR. COURTNEY LIAS: You're welcome.

CLIAC CHAIR: Great. [CLIAC MEMBER]?

CLIAC MEMBER: Yes, that was really great presentation. Thank you. I also had a question about reclassification. Do you also look beyond class III to class II to classifying things that may be currently moderate to something low risk? And again, when I think of infectious disease, a lot of the newer sort of simple in and out tests that are class II seems that there could be even waived. So how is that considered sometime?

DR. COURTNEY LIAS: We do we can down classify something from class II to exempt, either class II exempt or class I exempt if we want to. And we have done that in certain cases. I would like to distinguish, though, waived compared to classification. They are two completely different things. So you could have a high risk class III product that is waived. And you could have a class I product that's high complexity. So they are different things. But yes, it is possible. I will tell you it is difficult. So it's notice and comment rulemaking to take something from class II and class I. So it is worth doing when it's worth doing, but sometimes we can find alternate pathways, especially as the device's technology evolves. We might be able to create a new pathway for it. But also, we might be able to adjust what would be necessary for class II for that product in the meantime, if we were in agreement that the bar isn't very high because the risk is mitigated by a lot of other things. Pre-market data review isn't always the thing that mitigates the risk for something. And we should always talk about ways to make it make sense.

CLIAC CHAIR: Excellent. Thank you very much. Let's go on to our last presentation for this section. It's clinical laboratory improvement amendments CLIA 88-- fees, histocompatibility, personnel, and alternative sanctions for certificate of waiver of laboratories. Final rule presentation presented by Miss Penny Keller.

Clinical Laboratory Improvement Amendments of 1988 (CLIA) Fees; Histocompatibility, Personnel, and Alternative Sanctions for Certificate of Waiver Laboratories Final Rule
Penny Keller, BS, MB(ASCP)

MS. PENNY KELLER: Thank you, Dr. Laser. My name is Penny Keller. I'm one of the technical advisors under Gregg Brandush. And I am the technical advisor for our new regulations and clearance branch. Next slide.

This is the standard disclaimer for CMS that Gregg went over. Basically, the information in this presentation is for information purposes only and should not be used for the regulatory requirements themselves. And as he mentioned, any errors or missing information that's in this presentation is my own and not representative of CMS.

So I will be discussing the two effective dates that are in this new final rule. And the final rule applies to the CLIA regulation updates for the following four sections-- the CLIA fees, the histocompatibility test specialty, the personnel requirements, and the alternative sanctions for the Certificate of Waiver Laboratories. The CLIA Fees, Histocompatibility, Personnel, Alternative Sanctions Final Rule was published in the Federal Register on December 28, 2023.

In this slide, we are providing the links to the general Federal Register where you can find all notices that are published on the Federal Register, including the proposed and final rule related to this. We are also providing the direct link to the CMS-3326 final rule itself, if you have not looked at it. The final rule announcement did go out through the CMS CLIA listserves to our laboratory stakeholders as well as our partners. Another venue that we use was the QSO memo QSO-24-03 CLIA, which had the announcement for the final rule. The other links that are provided here are two correction notices that was posted. The first correction notice was published on February the 2nd. And that correction notice addressed a typo in the cross-reference to regulation 493.1423(b)(7)(i), which was related to the testing personnel moderate complexity blood gas. The cross-reference to five and six was omitted-- four, five and six was omitted in the final rule. Also, the effective dates were also corrected in the correction notice. The second correction notice was published on March 5, 2024. And that correction notice corrected typos in three tables-- table four, table 18, and table 17. And they are related to the CLIA fees.

Moving on to the next slide. So the first effective date in the rule was January 27, 2024. And the applicable sections in the final rule that applied was CLIA fees updates and the alternative sanction regulation related to the laboratories that have a Certificate of Waiver. Also effective January 27th was the new definitions for replacement certificate and revised certificate.

The second effective date in the final is December 28, 2024, which is the end of this year. The sections that are applicable on December 28 or effective December 28 is the histocompatibility and personnel regulations. Also effective December 28 are the new definitions that are related to the updates to the personnel regulations. And those include the following-- continuing education credit hours, doctoral degree, experience directing or supervising, laboratory training or experience, and mid-level practitioner.

Starting with the CLIA fees. It's located in Subpart F General Administration of the CLIA regulations. And this is the regulations that are affected. As I mentioned, there are two new definitions related to the CLIA fees in the final rule. The first one is the replacement certificate. The replacement certificate means an active CLIA certificate that a laboratory holds. And it is reissued with no changes made. A revised certificate would mean an active CLIA certificate that is reissued that has changes made to it in one or more fields displayed on the certificate, such as the laboratory's name, the address, the laboratory director name, approved specialty or sub-specialty changes. And for purposes of this part, revised certificates do not include the issuance renewal change and certificate type or reinstatement of a terminated certificate with a gap in service.

In the final rule, we establish new but currently authorized fees that have not been previously assessed over the years. The fees will be assessed when the following activities are performed. The first one is when we perform follow-up surveys to confirm correction of deficiencies. The next one is review and approval of testing when a laboratory adds a new specialty or sub-specialty of testing. Fees will also be assessed when complete surveys are performed where findings are substantiated. Also, the desk reviews involving unsuccessful performance proficiency testing would now be assessed. Fees are also assessed for issuing revised or replacement certificates.

There is also an 18% across the board increase to the current fees. There's also in the final rule a $25 certificate fee increase for the Certificatea of Waiver Laboratories. And this is to recover the cost of categorizing the waived tests by the FDA. The final rule also states that we apply a formula to assess user fees every two years to account for the inflation, if needed, to meet the program obligations.
This is a table six from the final rule, which has the cost of the revised certificate-- issuance of the revised certificate for the five different CLIA certificate types. Also included on this slide is the link to the CLIA certificate fee schedule, which is currently available on the CLIA website. It was updated on January 27, 2024 and has the different types of CLIA certificates.

Moving on to the histocompatibility test specialty that's located in Subpart K Quality Systems and is at the regulation site 493.1278. For histocompatibility in the final rule, we state that we remove the histocompatibility specific requirements that are already addressed by the general requirements which require the laboratory to have laboratory test procedures and quality control procedures for all the test systems that they perform. We also revised the name at 1278(d) from Antibody Screening to Antibody Screening and Identification for clarification as both processes apply to the histocompatibility testing.
We also revised the words transfusion and transfuse to infusion and infuse, respectively, which reflects the current practices. We also removed three requirements regarding the laboratory having cross-match procedures and controls. These are, again, already addressed by the general requirements for all test systems at the following regulation sites. We also modified the following terminologies to reflect current practices, again. Here, we replaced cadaver donor with deceased donor. We replaced transfused with infused. And we replaced combined with paired. We also updated the World Health Organization committee name for the HLA nomenclature committee. It now reflects Nomenclature Committee for Factors of the HLA System in the regulatory text. We also added the requirement to obtain a recipient specimen prior to transportation for cross-match on the day of the transplant, if possible.

Moving on to personnel. It's located in Subpart M. And these are the regulations that were updated in the final rule. There are five new definitions in the final rule related to the personnel requirements. The first one is mid-level practitioner. The definition was amended to add nurse anesthetist and the clinical nurse specialist. Currently, the definition only includes nurse midwife, nurse practitioner, or physician assistant.
We also added the definition for continuing education credit hours, which means either the continuing medical education or continuing education units. The 20 continuing education units must be obtained before qualifying as a laboratory director.

The definition of doctoral degree is added, which means an earned post-baccalaureate degree with at least three years of graduate level study that includes research related to the clinical laboratory testing or advanced study in clinical laboratory science or medical technology. Doctoral degrees would not include doctors of medicine, doctors of osteopathy, doctors of podiatry, doctors of veterinary medicine, or honorary degrees. The doctoral degree of clinical laboratory science would be included as an acceptable doctoral degree. The definition of laboratory training or experience means that the training or the experience must be obtained in a facility that meets the definition of a laboratory as stated under 493.2, and it's not exempted from the CLIA oversight under 493.3(b), such as, for example, forensic testing. The definition for experience directing or supervising means that the director or supervisor experience must be obtained in a facility that meets the definition of a laboratory under 493.2 and is not one of those exempted under 483.3(b).

Moving on to the PPM or the provider performed microscopy laboratory director responsibility. We modified the PPM laboratory director's responsibility to now include the competency assessment requirements. So they must perform the competency assessment at intervals as stated at 493.1413(b)(8) and at 493.1451(b)(8).

Moving on to the laboratory director qualifications and responsibilities for modern high complexity we're just summarizing here. We removed the language "or possess qualifications that are equivalent to those required for such certification" which is the language related to the American Board of Pathology and American Osteopathic Board of Pathology. We also now include 20 continuing education units to the modern high complexity laboratory director qualifications. We added the phrase or language "directing and supervising experience" to the high complexity laboratory directors doctoral degree qualification requirements. We removed the residency provision. However, please note that relevant experience that is obtained through a residency or fellowship program could continue to be acceptable experience and training for qualifying individuals. Under the regulations addressing laboratory director responsibilities, we now require the laboratory to be on-site at the laboratory at least once every six months with at least a four-month interval between the two on-site visits. We also updated the language of the regulations to address laboratory director qualifications and specify that an individual qualifying under the doctoral degree algorithm must have an earned doctoral degree.

Moving on to the technical supervisor qualifications. We combined the provisions with identical technical supervisor requirements into a combined requirement. So, for example, at 493.1449(c), you'll see that we combined the specialty of bacteriology, microbiology, mycology, parasitology, and virology requirements for the technical supervisor at that one regulatory citation. We also updated the immunohematology test specialty requirement to allow individuals with doctoral, master's, and bachelor's degree with the appropriate training and experience to qualify as a technical supervisor for immunohematology.
And I think I missed the second bullet, which is to remove the reference to the American Society of Cytology as it has not provided certification for cytology since 1998. I apologize for omitting that.

Moving on to this general supervisor qualifications and responsibilities, we revised the language to allow the delegation of the competency assessment, both semiannual and annual, to the general supervisor now. Moving on to the cytotechnologist qualification, we simply removed the CAHEA acronym with the current CAAHEP, which stands for the Commission on Accreditation of Allied Health Education Programs. We also removed the phrase "or other organizations approved by HHS" in the introductory regular text as it has not been applicable over the years.

Moving on to the testing personnel for modern high complexity testing, we added the nursing degree for testing personnel for the moderate complexity testing personnel regulations at 493.1423. However, for the 493.1489, the high complexity testing personnel, a nursing degree itself does not automatically meet the high complexity testing personnel qualifications. We also added the blood gas testing personnel for moderate complexity. We also moved the military provisions out of the grandfather clause related to the April 24, 1995 provisions for high complexity and made it as made it a separate mechanisms in which an individual will be able to qualify for high complexity testing personnel. We also moved the Department of Health Education and Welfare acronym HEW that you may be familiar with to qualify individuals under 493.1489.

So you'll note in the final rules regarding degrees that we added an educational algorithm qualification option now for both the moderate and high complexity testing for the equivalent bachelor's, master's, and doctoral degrees. We also removed the references to a physical science degree from Subpart M, as that has not been an applicable qualifying pathway over the years. We also added an approved thesis in research for the educational options.

We also removed all the current grandfathering provisions at the following regulatory sites that's listed here. Instead, we added a new grandfathering provisions for all the currently qualified individuals that are employed in their given personnel positions before the date of the effective rule for this final rule. However, we intend to require all individuals who become employed by laboratory or change assignments within a laboratory after the final rule's effective date to qualify under the new personnel provisions. And this is a slide where the conforming amendments just refer to the updated regulatory cross references at the other regulatory citations in relation to the personnel regulations that were updated. And the next three slides is just a listing of the personnel regulatory sites for the qualification and responsibilities. And you can see that all of the clear regulatory positions were affected at the staff or the clinical consultant position. And this lists the grandfathering provisions that were removed for your awareness.

Then moving on to the alternative sanctions for Subpart R Enforcement Procedures. The update was at 493.1804(c)(1). That is the update to allow CMS to impose alternative sanctions on Certificate of Waiver laboratories as appropriate. Currently, we are only allowed to apply principle sanctions. In summary, the Clinical Laboratory Improvement of 1988 CLIA the Histocompatibility Personnel and Alternative Sanctions final rule, also known as CMS 3326-F was published in the Federal Register on December 28, 2023. The final rule updates the following four sections of the CLIA regulations-- the CLIA Fees, Histocompatibility, Personnel, and the Alternative Sanctions specifically for the Certificate of Waiver laboratories.

There are two effective dates for the CMS 3326 final rule. The first one already went into effect January 27, 2024 related to the CLIA fee updates and the alternative sanctions for the Certificate of Waiver laboratories. The second effective date December 28, 2024 at the end of this year will affect the updates for the histocompatibility and the personnel qualifications and responsibilities. And again, there's a general link to the Federal Register where you can look at the posting for this final rule.

And this slide is just the general resource slide for your awareness. There is a general email address for the public to send their questions, inquiries, comments, and that's the lab excellence mailbox at cms.hhs.gov. And if you're not aware, on the CLIA website, you can find some updates that we've made over the years. As Gregg has mentioned, we have the online payment option now. We also have the CLIA laboratory lookup feature, which if you opt to sign up for electronic notification, you can receive your certificates electronically. And you can find that also on the QCOR CLIA laboratory lookup as well. And then we also have the CLIA communication listserv where you can get announcements such as the final rule. And that concludes my presentation. I thank you for the opportunity to share the news of the final rule. I'll turn it back over to you, Dr. Laser.

CLIAC CHAIR: Yeah, thank you so much. Tons of updates and what seemed like very logical and consistent clarifications in fees, histocompatibility, and personnel, as well as the alternate sanctions. Any quick questions from the committee members? Otherwise, we'll move on to our first topic for the day. OK, seeing none, let's move on. I know we're trying to squeeze in a bio break for us. I failed in that objective. Obviously, do what you got to do. But we'll move on to our first topic for the day, which is the applicability of CLIA personnel requirements to pre-analytic testing. We're going to start with an introduction to the topic by Mr. Gregg Brandush, Dr. Courtney Lias, and Miss Tamara Pinkney. After the introduction, we'll have some time for public comments and, of course, a committee discussion. So I don't know who's starting off. Gregg, if you are, take it away.

❖ Presentations and Committee Discussion

The Applicability of CLIA Personnel Requirements to Preanalytic Testing

Introduction to the Topic
Gregg S. Brandush, RN, JD
Courtney H. Lias, PhD
Tamara Pinkney

MR. GREGG BRANDUSH: All right. Thank you. I really want to express my appreciation to CLIAC for taking on this subject. This is something that we're really struggling with because, as regulators, we want to strike a balance between what is really essential for patient safety, while also promoting reduced costs and efficiency. And when we're looking at this issue of whether we should have a strict application of the high complexity personnel requirements to all aspects of high complexity testing, there are some nuances to that that we really appreciate and are thankful for any view and opinions that this group can share. So some of the considerations with this is at the pre-analytic stage of testing, many of the tests just require loading, a simple loading. And we have many laboratories that do not use high complexity personnel for that function. Additionally, additional considerations are do we need to apply those requirements when there's no manipulation of the sample, beyond just centrifuging and storage? There's no calculation that's needed, no precision pipetting. There's no specific skills related to specimen rejection or the requirements that require individual assessment or the modular systems. So how do we apply this where specific modules can be taken offline if quality issues are encountered? So those are all of the primary issues that we're wrestling with. Like I said, I really appreciate any guidance and feedback all of you can provide. And I will turn it over to Courtney for the FDA aspect of this.

DR. COURTNEY LIAS: Thanks, Gregg. Yeah, we are happy to help. I just want to set the stage of what FDA does in this environment. Many of you know this, but FDA has designated authority to categorize the tests themselves. And CMS, CLIAC, CDC relate to the personnel requirement piece. So I think this question of how they intersect is an interesting one. I'll hand it over to Tamara to talk a little bit more about how we do that complexity assessment, and then maybe we can discuss some of the nuances here. Tamara?

MS. TAMARA PINKNEY: So yeah, thanks, Gregg and Courtney, for the intro. And CMS and FDA have had some discussions about this and just want to probably just give you guys an idea of what we do when we categorize a test system. So as some of you may be aware, when we do a CLIA categorization, it follows clearance or approval of a test or a test that may be already legally marketed. If it happens to be exempt for laboratory test, of course, and they come in, they're cleared or approved. When we perform the categorization, it's based on the seven criteria, seven CLIA categorization criteria. And the review division, who has cleared the device, basically is looking at the package inserts, the instrument manuals, seeing how the test is performed, the entire test procedure, and all that it includes. And that is inclusive from the time the sample goes on the instrument until the results come out, so everything that encompasses that. So for each of the seven criteria, we assign a score of one to three. Of course, one being the lowest level of complexity and three the highest level. And then we add those scores together. So a final score or a total score of 12 or lower will give you a moderate complexity test, or 13 or higher we'll give you a high complexity test. So we do want to be clear that FDA does consider pre-analytical steps when we are using these criterion. Three of them, in particular, really focus on pre-analytical steps, including the knowledge, training, and experience, as well as interpretation and judgment. These are all part of the seven criteria that we take into consideration. But we don't sparse that apart. So we just want to be clear that we can't take just this pre-analytical step and say, oh, well, this should be high complexity, or this should be moderate complexity. It's the overall score that determines the complexity of the test. So with that, yeah, that's how we categorize the test.

DR. COURTNEY LIAS: One thing I'd like to add, just to make sure it's clear, is that loading a specimen would never alone lead to a high complexity determination, right? If pre-analytical steps were contributing to a moderate or high complexity assessment, they would be pretty complicated. There would be something about them that led to that. It's not going to be that led to the complexity determination if it's something like loading.

MS. TAMARA PINKNEY: Right.

DR. COURTNEY LIAS: The question of personnel and who does it I think is separate from the FDA complexity determination when that's the case.

CLIAC CHAIR: That's a good point. Just for clarification's sake, Tamara, did you have anything else to mention?

MS. TAMARA PINKNEY: No, just cosigning on what Courtney said. The handling, if it's-- the loading would not be a thing. If we're looking into pre-analytical steps that would potentially make that test more high complexity, it would be things like if the test-- we have to do visual inspections for like lipemia or icterus, or you're checking sample volume or something. If there's pipetting or any kind of pre-analytical steps, dilutions, or anything like that. So those are the kind of things that are considered with the categorization that would potentially make some of those criteria a three versus a one or two. But simply putting a sample on an instrument would not throw it into high complexity.

CLIAC CHAIR: Excellent. Thank you. OK, so we'll enter our public comment time point here in this topic. We do have one written comment from the National Society of Histotechnology. That written comment is available online if anyone would like to read it. And we do have one verbal comment from the College of American Pathologists that will be given by Dr. Diana Cardona.

Public Comments

DR. DIANA CARDONA: Thank you for having me this morning. The College of American Pathologists appreciates the opportunity to provide written comments to the Clinical Laboratory Improvement Advisory Committee. As the world's largest organization of board certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, the CAP serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide. As such, the CAP recommends that the current scope of CLIA be maintained and that personnel requirements related to the pre-analytics of testing remain outside the scope of CLIA regulations. At the November 2023 CLIAC meeting, CLIAC approved a recommendation to include histology under CLIA. The CAP disagreed with this recommendation, as through our own monitoring and oversight of laboratories, we have not detected quality issues.

Furthermore, the study cited during the last meeting was from overseas, so not necessarily reflective of laboratories in the US, but was also focused on the impact of digital pathology implementation and not necessarily a pathologist's ability to render a high quality diagnosis. Therefore, increasing the scope of CLIA regulations is not needed. And there is no consensus supporting the assertion that there are quality issues that would warrant such an expansion. Thus, more discussion and further study of US laboratories should take place before expanding CLIA oversight to new areas.

The CAP provides oversight for over 8,000 laboratories, providing a firsthand view into how they operate. While issues do arise during the pre-analytical phase of testing, they are not the result of personnel being unqualified. Typically, the pre-analytical steps that can compromise the quality of analysis are associated with the time to stabilization of tissue and time to processing the sample. This indicates that the laboratory and personnel could benefit from process improvements, not increased qualifications. And our concern is that increased regulation will not solve these issues but could likely exacerbate them. Some pre-analytical activities are appropriately within the purview of CLIA, such as test requests, specimen submission, handling, and the laboratory systems quality assessment. However, instituting CLIA oversight of pre-

analytical testing personnel would mean increased regulatory burden for laboratories while reducing the flexibilities available to laboratory directors who must make decisions on laboratory workflow based on the best interests of the patient balanced with the realities of constricting financial resources. And I can attest to the fact that if this requirement had existed now for histotechnologists, for example, as a medical director with a large histology laboratory, this would have compounded the ongoing staffing challenges we face.

So as laboratories continue to adapt to workforce challenges and with the automation rapidly changing within the field of laboratory medicine, it may be premature to develop regulations as practices remain in flux and issues with quality have yet to be identified. The CAP does support increased consistency of application and interpretation of existing CLIA regulations and requirements. CLIA is appropriate and needed to regulate testing, which can be defined as producing a test result. We would support and encourage efforts to make interpretation of regulations more consistent. For example, guidance documents to address laboratory questions and consistency of surveyor interpretation from state to state on pre-analytic duties that may be performed by laboratory assistants as defined as individuals that help perform testing versus those requiring further knowledge and judgment that must be performed by qualified testing personnel. This would help laboratories remain compliant with clear requirements, while also allowing for the use of laboratory assistance to meet workforce needs. However, regulations regulating personnel qualifications for individuals involved in pre-analytic testing would be a challenge from a functional standpoint and unnecessary. The CAP and I thank you for this opportunity to discuss our concerns and recommendations and welcome the opportunity for further dialogue. Thank you.

CLIAC CHAIR: Thank you. [CLIAC EXECUTIVE SECRETARY], is there any other public comments that snuck in since we last connected?

CLIAC EXECUTIVE SECRETARY: No, we do not have any additional comments.

Committee Discussion

CLIAC CHAIR: No? OK, perfect. And also, do we have questions to guide our next section? Yeah, if you could put them up on the screen. So yeah, so now we'll be entering the committee discussion portion. Feel free just, again, to raise your hand virtually. It actually puts you in a beautiful order for me to keep track. And to help frame the conversation, we do have some questions. Again, these are questions that are being asked of us, the members of CLIAC, in order to be able to comment and help refine. So [CLIAC MEMBER], it looks like you want to kick us off, so feel free to go ahead.

CLIAC MEMBER: Yeah, so, Tamara, thank you for your presentation. I had a question just to clarify. You said there were seven criteria that you used. Can we see what those-- can you give us a list of what those seven criteria are? Even if it's just a written thing at some point. I'm just curious to that.

MS. TAMARA PINKNEY: It's actually-- I'm sorry. I was just going to say it's actually accessible on one of our FDA web pages. I'll be happy to drop a link.

CLIAC MEMBER: OK. Well, there's a lot of FDA web pages, but I'm looking for the easy way out, Tamara.

MS. TAMARA PINKNEY: OK. I mean, I can quickly run them down for you, but also want you to know that it is accessible on one of our--

CLIAC MEMBER: OK, great. If you could provide me that link, that'd be great. Then, the other question I have, because you said there was like a rating of 12, it was moderate complexity, 13 or above, it was high complexity. And so my question is if something is really simple all the way through, but the interpretation of the test might be very high complexity, that might get a score of three. Where does that put the test overall in complexity? Because I'm kind of worried about this very simple sample to result but the result is really critical. So just wondering about that.

MS. TAMARA PINKNEY: Yeah, so, again, we consider-- the final categorization is based off of the total score. So even if, say, the interpretation and judgment, which is one of the criteria, may be a three, that's the highest score you can get for any of these criteria, may be a three. But if other portions of the other criteria may be a two or one, the overall score is what's going to make the difference between moderate or high complexity. So where you may have two categories that may be a three. If the others have ones and twos, if the overall score is a 12 or lower, it's still going to be moderate complexity versus high. So that's what was trying to convey when I said we can't kind of sparse it apart, you know, to say--

CLIAC MEMBER: Right, right, right, right.

MS. TAMARA PINKNEY: --oh, this part is this and this part is that. It's the overall score to give you that.

CLIAC MEMBER: Yeah, I am worried medically about the ramification of something that requires some really kind of high level interpretation, potentially. And that may affect, say, a manufacturer about how they report a result where it literally has a bigger comment or something like that along that line. But I'm still worried about if somebody has-- it could literally be a waived test if it got a really low score. And that's what I'm concerned about. And what the risk to a patient might be.

MS. TAMARA PINKNEY: Well, let me also just clarify here as well, when we do categorizations, it's more so to categorize the tests for moderate versus high complexity.

CLIAC MEMBER: OK, OK.

MS. TAMARA PINKNEY: Tests are going to be waived automatically either by regulation or if they are--

CLIAC MEMBER: Yeah, OK.

MS. TAMARA PINKNEY: --cleared for home use.

CLIAC MEMBER: OK. All right. Thank you. That helps because that makes me feel a little better. Thanks.

CLIAC CHAIR: So it looks like we have a question or comment from Courtney.

DR. COURTNEY LIAS: Yeah, I actually just wanted to clarify-- this may not have been what you meant, but I want to make sure it's clear that if the interpretation of a test result clinically is complicated, that's not really what we're looking at either. We are looking at whether or not interpretation of the test result and what it is, if that has complexity to it. So even for a very clinically complicated decision, if the test itself is easy to interpret, that may not lead to a higher complexity determination. So I want to make that distinction too because there still is a physician involved in most of these cases at the end of the day. So that's it.

CLIAC CHAIR: Great. Thank you. [CLIAC MEMBER]?

CLIAC MEMBER: Yes, thank you. So just to clarify, this is only related to high complexity tests? We're not talking about any other pre-analytical involvement for moderate or waived testing, correct?

CMS EX OFFICIO: Yeah, that's correct. That's the biggest concern. The high complexity personnel requirements are a little more strenuous and rigorous. And we want to make sure that we are applying them in a way that is consistent and makes sense and works for everybody. And really, there's a lot of questions about the FDA categorization. The categorization of the FDA, for the purposes of this conversation, they are what they are. So it's really do we apply those personnel requirements?

CLIAC MEMBER: Yeah, and my first instinct is to say no, right? Like, I think there is something to be said about the fact that there is such a variety of processes depending on the test. Some of them, particularly pre-analytical, that are not so complicated that you would require a technologist to do this testing where a technician or even a lab assistant could be helping. And similar to something that CAP said, you know, it's

already challenging enough to have the very high-- what's the word I'm looking. Like, the person with the highest requirement involved in this. That if spinning or recognizing hemolysis is something I can easily train a lab assistant or a technician to do as pre-analytical processes, that's definitely something that I would think shouldn't be under this particular personnel requirement. To add to this, I think in New York State, there is even like additional challenges. Even when you think of the pre-analytical, we have technologist license. We have a technician's license. And technician have particular things they may or may not be able to do. But there is some flexibility from the laboratory depending on the test to assign or figure out what is something that would require that level of knowledge to make sure that the test is performed adequately. And what would be simple tasks that can be assigned to personnel that may be easier to recruit because there's not like that need for licensing and so on. So I want to say that this is something I'm thinking should really be reviewed by the lab director to make sure that, depending on the test, you can assign who may qualify to do this as opposed to a general rule like this. I think this would be really challenging to implement.

CMS EX OFFICIO: Yeah, that's interesting that you brought that up because that is one thing that we've discussed is tying the responsibility to the lab director to make those staffing assessments.

CLIAC MEMBER: Yeah.

CLIAC CHAIR: Yeah, thank you. So, again, to frame the conversation for everyone, this is we have a test that is classified or categorized as high complexity. We're recognizing that there are parts, particularly we're focusing on the pre-analytical steps, that may be-- I won't use the term low complexity because that'll be confusing-- simple, right? Simple parts of the process that-- and the question that we are being asked to give advice on is should the high complexity personnel requirements apply to those simple pre-analytical steps? So we've heard a couple of no's so far. Would love if anyone has a dissenting viewpoint to speak up as well. And then, I think we'll start to see how we could potentially solution this and give a recommendation. [CLIAC MEMBER]?

CLIAC MEMBER: Thank you. You asked for dissenting opinion after I raised my hand. I do not have a dissenting opinion. But as I listen to the discussion of what constitutes what might be called specimen handling versus potentially important specimen pre-analytical work, I'm wondering if redefining where the starting point for a test may be helpful. Because receiving a test in the loading dock and accessioning is not performance of the test. And if we were to say, yes, and picking up the specimen and putting it into a machine is also not performance of the test, we're not so much calibrating the personnel who hold the specimen. We're actually, quite specifically, asking the manufacturer and the regulatory bodies to say where does the actual performance of a test begin. And if there is an operational step in the pre-analytical stage that enters into yes, we're now actually beginning to perform the test, a spin, for example, that may be a way to reframe the personnel who are handling a test and the qualifications required for that personnel.

CLIAC CHAIR: Thank you. Any other thoughts or comments? So I'll ask the group-- is the quietness because everyone's in agreement, or is it quiet dissension? I just want to get a sense of that-- of where we're all leaning. Anyone want to chime in? OK, well, not here. [CLIAC MEMBER], you put your hand back up, or is it--

CLIAC MEMBER: Yeah, you're asking for a reaction.

CLIAC MEMBER: Yeah, no. Yeah. Yeah. One of the things I just want to clarify because we just did this whole previous year of what's the total testing process. And so I'm just wondering. Now it sounds like we're taking it apart again. So I just want to make sure that we're clear on how we present something like this going forward. I completely agree that there's these processes, like [CLIAC MEMBER] said, a lab director can make the assessment along with the rest of the management team about who's qualified to be able to do these simple steps up front. I don't have any issue with that kind of thing. I just think it might be confusing if we start pulling it apart without being really, really clear going forward about what those pieces are.

CLIAC MEMBER: [CLIAC CHAIR], I'll—

[INTERPOSING VOICES]

CLIAC CHAIR: Go ahead.

CLIAC MEMBER: [CLIAC MEMBER] and [CLIAC MEMBER] sounds the same. I'm looking at the top line question. And I focus in on all aspects. I don't disagree with what [CLIAC MEMBER] said, which is picking something apart that's already been discussed for the past year is not necessarily the right way to go. But all aspects-- you're asking us to respond to a global statement. All aspects of a high complexity test, including the handling of a specimen by a non-certified personnel and one who arguably is not subject to proficiency testing and the documentation thereof. I think that's part of the question you're asking is does CLIA apply to the entirety of the sequence or a portion of the sequence? That's why I'm parsing it out just a little bit, which might be different than what [CLIAC MEMBER] is saying. And I would invite discussion of what, quote, "all aspects," unquote, means.

[INTERPOSING VOICES]

CLIAC CHAIR: Yeah, to be clear, right, I want to make sure that we're not redefining where the test begins or ends to [CLIAC MEMBER] point. But it's really are those pre-analytical processes, the simple ones, do we need to hold those folks to the high complexity personnel requirements? [CLIAC MEMBER]?

CLIAC MEMBER: Thank you. I think this is a real important issue because of the workforce shortages and everything in the lab space. However, I agree with [CLIAC MEMBER] point because it's very difficult without knowing the situation in every step in the process to determine exactly where something is going to make an impact on the result of that test and something is not. So I really think you have to rely on the laboratory director to make that decision for the situation that they have. But that also assumes they're taking responsibility and accountability for that decision.

CLIAC CHAIR: Excellent point. [CLIAC MEMBER], I saw your hand up. You pulled it down. Just want to make sure you didn't pull it down by accident.

CLIAC MEMBER: No, I actually had it put down for me by the system.

CLIAC CHAIR: Oh. OK. Did you want to comment on something?

CLIAC MEMBER: I guess I might have missed the conversation, but when I hear pre-analytical, that includes part of the process of collection, right? And so to me this feels like a slippery slope. Where does it end in terms of what about phlebotomists? They are some of the hardest to hold on to because they're not higher paid, and so they're easily-- they move around very quickly. And so there's significant turnover. And so I think that we should proceed with caution because I feel like there's a lot of unintended consequences that this could produce. It could literally bring laboratory testing to its knees if it's done in a manner that's not sensitive to the reality of the job market.

CLIAC CHAIR: Yeah, good point and a good warning to us as well. So again, reflecting back what we're hearing so far and to put something on an initial stab at on the recommendation board, I mean, it sounds like all the comments so far the answer to the question that's at the top of the screen right now, what we're really saying is no, right? No, these high complexity personnel requirements should not necessarily apply to all aspects of high complexity testing, again, with that focus on pre-analytic. So given that no, right, we're also hearing some ways of potentially operationalizing that. High complexity testing is, of course, complex. And some of these processes could be potentially unique to a single assay. Some may be shared across multiple tests and multiple laboratories. So with the initial response of no, it sounds like we're starting to go towards a direction of the decision of applying those requirements to the pre-analytical phase should fall onto the lab director. And if it falls onto the lab director, I would also recommend or propose that that process be documented in some kind of a risk assessment, right? So it's a risk assessment and/or mitigation, saying that, OK, I've analyzed this step. This is simple enough to not be

run by high complexity personnel requirements. And so at least the thought process is documented. There's some mitigating steps that could be identified on the form as well. And then, it's a document that can be discussed during a survey. I think that would best blend quality and flexibility, particularly with workforce shortages that we've all experienced that have been talking about. So as a reflection back to the group, how does that make everyone feel? [CLIAC MEMBER], I see your hand up.

CLIAC MEMBER: [CLIAC CHAIR], I think you've captured the spirit of the moment. And yes, I do think this is an elegant clean way of answering the top line question. What I would reflect back is the non-uniformity of application of that principle. And I don't know whether CLIAC is the place to ask for the package insert to provide guidance on this. But I do think that guidance would be helpful in informing the laboratory director and making this determination, wherever that might come.

CLIAC CHAIR: Yeah, I think it's a really good point. And again, as we really did focus last CLIAC meeting when we want to make sure that we capture the spirit of the recommendation. And then we could put down things to consider or points. And so we don't get caught into a word-smithing thing, not that I think we're doing that now, but I think in addition to making that recommendation of putting it to the lab director and having that documented, your point of could we also provide some rules or guidance, a guidance document to just help create some structure, maybe some boundaries for those lab directors as they navigate this decision process.

CLIAC MEMBER: Right. And so there are generic guidance rules, which could come from call it CLIAC, CLIA, whatever the appropriate agency is. And then, the specifics, if they were in a package insert, it would then be incumbent upon the laboratory director to document very clearly variation from such guidance. And that would be transparent subject to inspection, subject to quality review.

CLIAC CHAIR: Excellent. [CLIAC MEMBER]?

CLIAC MEMBER: I would also ask that practice setting be taken into account as well because the vast majority of adult chemistry and hematology specimens are literally you just load it onto the instrument. But you have to remember that for pediatric practice settings, that's the reverse. Practically every single one of the pediatric specimens have to undergo aliquoting and some kind of processing that would be above and beyond just loading on an instrument. And so my fear is that this would be crippling for pediatric facilities because of the fact that practically everything would qualify as something above just loading it onto an instrument.

CLIAC CHAIR: And if this is a fair reflection, I think that's highlighting the advantage of putting it on the lab director as making that decision so they can respect those local differences and challenges. But again, with the form or the risk assessment being completed, again, those mitigating measures in case there are some special circumstances in any given laboratory. [ADVAMED LIAISON]?

ADVAMED LIAISON: Hi. I just wanted to clarify-- in terms of the additional points to consider, I thought I heard package insert or other type of guidance to guide the laboratory but didn't see it presented that way. So just a point of clarification.

CLIAC CHAIR: OK. So yeah, I think there are two points there, right? One is the package insert review, certainly about the lab director but maybe more centrally. But then also the generation of a guidance document for lab directors, again, for those to provide some relative boundaries as to what-- when this kind of exception could be made, right? One thing that I would personally struggle with that has been mentioned so far would be like precision pipetting or pipetting, right? Like, where do you draw the line between precision pipetting or routine pipetting? And I would love a guidance document along those lines of what would we consider truly in the flexibility or outside the flexibility. [CLIAC MEMBER], is your hand back up or—

CLIAC MEMBER: It is back up, yes.

CLIAC CHAIR: OK. Go ahead.

CLIAC MEMBER: And it's to respond to [ADVAMED LIAISON] request for clarification. Yes, I had indeed made a second point, which is what I would call generic principles. And whether that came from CLIAC recommendations, whether it came from a regulatory agency, a deemed entity, for example, as to the general principles that a laboratory director should take into consideration, including specific examples such as the one that [CLIAC CHAIR] mentioned. Having said that, the generic is irregardless of any particular package insert. But then the working relationship between the manufacturer of the package insert and the site-based laboratory director is a second form of guidance. And given what [FDA EX OFFICIO] has mentioned, generic guidance could also include examples of circumstances that would merit consideration of variation. I think there's a lot of opportunity for informed input to help guide the laboratory director. I concur with what appears to be the strong consensus that the laboratory director carrying this responsibility is an appropriate recommendation.

CLIAC CHAIR: OK. [CLIAC MEMBER]?

CLIAC MEMBER: Yeah, I wanted to follow up on a comment I put in the chat. When we say package insert, it's just for the director to get a sense of the complexity of the various tasks? Because I'm not aware that you'll get guidance for which personnel may or may not be able to do a particular task. Yeah, OK, cool. Thanks.

CLIAC MEMBER: For the record, I am nodding my head. It's guiding—

CLIAC MEMBER: Yes, yes.

CLIAC MEMBER: Its guidance to the laboratory director about how complex a specific task is, not a recommendation for who does it.

CLIAC CHAIR: So using the microwave popcorn method, it sounds like the comments are starting to slow down, which means we're probably aligning on a recommendation. So I know I always mess up these rules. And [CLIAC MEMBER] always keeps me on track. But is there a motion for this recommendation?

CLIAC MEMBER: Motion.

CLIAC MEMBER: Second.

CLIAC MEMBER: Second.

[INTERPOSING VOICES]

CLIAC MEMBER: Yeah, that's where I jump on you.

[INTERPOSING VOICES]

CLIAC CHAIR: I remember that part.

CLIAC MEMBER: And my recommendation is that the word-smithing can be done during off hours, and we could bring something back.

CLIAC CHAIR: Yeah. OK, so we have a motion and a second. A little bit of time for discussion. Should we go for a vote? All those in favor, if you could please just put up your virtual hand, and we'll count them.

CLIAC MEMBER: Are we looking at—

CLIAC CHAIR: Yeah, don't do the reaction. Do the-- like, actually raise your hand so we could count.

CLIAC MEMBER: [CLIAC MEMBER], are we looking at recommendation one or two or both?

CLIAC CHAIR: Oh, I'm sorry. I didn't realize that there were two.

CLIAC MEMBER: Two maybe?

CLIAC CHAIR: Let's start with—

CLIAC MEMBER: Two is the one that was in the chat, so maybe that's the one that we're looking at.

CLIAC MEMBER: [CLIAC CHAIR], if I may, I think we're talking about recommendation one.

CLIAC MEMBER: OK. Perfect.

CLIAC MEMBER: Yeah, this is [CLIAC CHAIR]. I put the second recommendation in the chat, but I would say that recommendation one is basically the spirit of what I suggested. And it's cleaner.

CLIAC CHAIR: OK, so for clarity's sake, we are voting on recommendation one. Sorry. I'm trying to put my hand up. [CLIAC EXECUTIVE SECRETARY], you're keeping track somehow? I just messed up my whole screen.

CLIAC EXECUTIVE SECRETARY: We are good, and we have a majority vote.

CLIAC CHAIR: Excellent.

CLIAC EXECUTIVE SECRETARY: 100% vote. So yes, we are good.

CLIAC CHAIR: Excellent. OK, now we can all lower our hands. Excellent. So [CLIAC MEMBER], I think that was you who put in that second one. Just to double-check, do you agree with removing draft recommendation two because it's fully encompassed in draft recommendation one?

CLIAC MEMBER: Absolutely. I don't think we—

CLIAC CHAIR: OK, just wanted to make sure.

CLIAC MEMBER: Yep, thank you.

CLIAC CHAIR: And so we have some additional points to consider, right? We don't necessarily have to approve them or debate upon them. I recognize-- and again, I don't know how I just messed up my screen, so I got to find my notes. But I believe we have-- so in essence, we've accomplished the goal and the question that was posed to us from CMS. We do have a reasonable amount of time left in this particular session, so I would love to take a little bit of time for at least maybe we can list out some of the-- we don't necessarily have to define the boundaries, but should we at least try to list out some of the components that should be considered? The processes that should be considered in a guidance document for lab directors of allowing non-high complex personnel to perform simple actions of a high complexity testing process. I think this would just be helpful in case we end up creating it in the future. So I'll leave that open to the group to just, again, name some of those characteristics or components. And I see, [CLIAC MEMBER], your hand is up?

CLIAC MEMBER: I actually just don't know how to put it down. Sorry. I'm going to work on that. I'm going to work on that.

CLIAC CHAIR: If you click on Reactions, you should—

CLIAC MEMBER: It still says Raise Hand as an option.

CLIAC MEMBER: It's a toggle.

CLIAC MEMBER: Lower hand. OK, sorry.

CLIAC CHAIR: OK, you're good now. Yeah. [CLIAC MEMBER], your hands up. Is that—
[INTERPOSING VOICES]

CLIAC MEMBER: OK. If [CLIAC EXECUTIVE SECRETARY] will screen just to the top, I do notice something in the recommendation that we have passed. There's a subtle difference between determination of the competency of personnel, which is proficiency, and determination of the required competency, which is I think the guidance that we were talking about. First, you have to determine the required competency. And then, you have to figure out who's going to do it, and whether they are competent to do it. So I call that word-smithing, but I think it is important from the standpoint of guidance that might be provided. Because, again, I'm intentionally being broad-minded into where such generic guidance and specific guidance-- generic being general principles, specific being specific to the test-- where that can come from. Although, I think there are some logical choices. So I'll stop right there. I may have some other thoughts, but I just wanted to make that point in terms of the syntax of the recommendation we just passed.

CLIAC CHAIR: Very good point. I appreciate that. To kick us off in some of the components of the guidance, and I think in some of the questions or the sub-questions or sub-comments of the question that was posed to us should be included. And some of my recommendations are included there, which would be, obviously, the receipt and the rejection criteria or determining whether a sample is rejected. Is that-- again, we don't have to answer the question, but just something to consider in the guidance document. Can a non-high complex personnel requirement individual make that call of a rejection? Centrifugation differentiating, say, transfer pipetting from high precision pipetting. If there's any temperature changes related to the specimen prior to processing-- heating, cooling, whatever. Transfer pipetting, I would even differentiate from is it transfer pipetting off of spun cells or a gel top. What would be the risk or ability to have cellular contamination of the sample? [CLIAC MEMBER], I see your hand up. Any things you were going to say?

CLIAC MEMBER: No, I mean, I think you captured it with sample receipt rejection criteria. My first question would be appropriate-- are they able to know the appropriateness of the specimen for the test requested?

CLIAC CHAIR: Mm-hmm. And also just to call out something that I have been missing. I've been very liquid sample focused. Let's also make sure we try and include tissue sample as well. [CLIAC MEMBER], your hand's up?

CLIAC MEMBER: Yes, and this does get into the turtles all the way down. How far do we want to go on these sorts of things? The laboratory director makes the determination of the required competency. Hopefully, the assessment of that competency can be pushed down to immediate supervisors.
And the reason I bring that up is that as we go through these generic guidance, hopefully, the assessment of the actual competency of an individual, including just to keep track of the label on a specimen and put it in the right machine, is something that could be immediate supervisor. I think it will help in how guidance is framed. It does get to a laboratory workforce thing in terms of management and supervisors for bench personnel.

CLIAC CHAIR: Excellent. Any other questions, comments, modifications, additions? OK, hearing none.

CLIAC MEMBER: Could I add one--

CLIAC CHAIR: Go back to the agencies. Yeah, of course.

CLIAC MEMBER: And that is assessment of the quality control of the specimen coming in. And I think of temperature requirements. It's one thing to hold a specimen up and see whether it's hemolyzed. It's another thing to check the log of the specimen coming in because you may receive a specimen, think it's perfectly fine, but the temperature control was not checked. And that's just one example.

But we've had this discussion before at CLIAC, which is, is the laboratory responsible for specimen chain of custody defects prior to receipt in the lab? Well, that's the checkpoint for assessing those potential defects. And that is, ultimately, a laboratory director's responsibility to make sure that those checkpoints are observed. It's not part of performing the test, but it is part of verifying that the test can be performed on a quality specimen.

CLIAC MEMBER: I just want to echo that comment. I think there's too much siloing of pre-analytics. And we just can't afford to do that.

CLIAC MEMBER: And then, CLIAC, this committee has intentionally tried not to reach up to the point of collection. And yet, this is the handoff. Is the most important part of verifying that the chain of custody was successfully accomplished.

CLIAC CHAIR: Excellent. So I want to just make sure that the agencies feel that they're getting at least the answer to the question, which was posed to us. If we're missing anything, please let us know. And I also want to make like a boundary clarification statement. And if I'm incorrect, please challenge me. That we're really focusing on the pre-analytic phase here. That's what the root of this question is. And the challenging it to make sure that we're not talking about any other phase of the testing process where it would still be considered, quote, unquote, "a simple activity." Is that correct? And again, that question is probably for the agencies. Yeah?

CLIAC MEMBER: I'll start with a response. So one thing that makes me crazy is always the slippery slope argument. And I hate myself now because I'm going to use it. The conversation that we're having makes complete sense to look at the complexity of the pre-analytic stage, have the lab director make that assessment. Hold the lab director accountable for assigning staff with the right qualifications based on that flexibility. The regulations don't specifically say that. They talk about test systems, which is pretty broad. And we do have a number of people that are doing kind of just this pretty simple high complexity test, high complexity personnel, not making these kind of more fine-tuned distinctions between that, whether that's completely necessary. I do have this concern that it evolves and morphs into the more actual testing phase of things. And lab directors making the argument, well, in this particular test that we don't need high complexity personnel to do that. What I don't want is to create a CLIA regulatory expectation that really it circumvents the FDA's role and the FDA making this determination that this is a high complexity test and high complexity personnel are required. So we already have existing regulations that we can morph these requirements into that cover the lab director. But I am wondering if we need a regulatory authority that really limits this to pre-analytic because I am afraid of the encroachment.

CLIAC CHAIR: Yeah, that's exactly why I wanted to call it out to make sure that what we are talking about and what our guidance, we are restricting it to the pre-analytic phase, which was the root of the question. So I want to make sure that we're respecting the boundaries of the question and our guidance. [FDA EX OFFICIO]?

FDA EX OFFICIO: Sure. This is very interesting. I mean, I'm sure we're very interested in hearing the recommendations and if CMS is planning to provide guidance to laboratories on personnel requirements. With respect to pre-analytic, I think that term is very broad, I think as [CMS EX OFFICIO] mentioned. So if you're going to make recommendations, I really recommend that you define what you're talking about there because pre-analytic for some test systems can include the actual collection device. I mean, it wouldn't usually include normal blood collection tubes. But sometimes there are proprietary collection methods associated with the product or a device in question. Sometimes there are steps that are specified for that particular test and things like that. So I think it'd be useful to think about the scope of whatever recommendation you would like to make so that we can understand what you're most concerned about addressing.

CLIAC MEMBER: Yep.

CLIAC CHAIR: Yeah, thank you, and I see we're documenting it on the page as well. [CLIAC MEMBER]?

CLIAC MEMBER: Yeah, and actually, that was the point that I was trying to get at initially in the [CLIAC MEMBER] moment, which was there are steps in the chain of custody for a specimen, including the time of collection, that are critical to having a successful outcome. And at bedside, we're not asking the laboratory director to be at the bedside, nor to do proficiency on the person at the bedside. But there is a sequence of steps for any given test. And at the very least guidance for when a laboratory director needs to have line of sight is I think what both [FDA EX OFFICIO] and I are trying to get at. And that's why I brought up temperature. But clearly, just duration of specimen transit is another. And the examples abound, which is why we shouldn't be trying to micromanage it. The general principles I think are important.

CLIAC CHAIR: Yeah. And I think the rejection criteria at least covers a lot of those circumstances that you're mentioning, right? Each test will have different rejection criteria that could be temperature, time, whether it was pre-spawn, et cetera, different kinds of tubes and how they were handled. I think all of those or a lot of them could be adequately represented in rejection criteria. Any other questions or comments? It feels like we've generated a really good recommendation and depth of response to the questions posed to us. We already have a recommendation passed. Is there anything else you wanted to discuss on this particular topic? [CLIAC MEMBER]?

CLIAC MEMBER: Yeah, so we've got all these additional points. Who's going to define pre-analytic, for instance?

CLIAC CHAIR: Yeah, again, when we tried to-- we try not to get caught in a tremendous amount of word-smithing in the CLIAC meeting. It ends up getting refined on the back-end. And also, we're giving guidance or advice to the agencies. And so by these additional points, we're basically bringing these up that these are elements that we want to be considered and addressed in, say, a guidance document or something. But it's really going to be up to the agencies to be able to define everything and put more clarity to it. And we do that very purposely because they have a much broader viewpoint of laboratory medicine, how it's practiced, and a wide range of how different laboratories function and work. So we always like to give the agencies as much flexibility in that sense as possible.

CLIAC MEMBER: Fine. But my question was, who's going to have the charge to do that? And we all know about the total testing cycle. And pre-analytical phase starts with the ordering of the test by the doctor. Can go back that far.

CLIAC CHAIR: Yep.

CMS EX OFFICIO: If I could add-- there's a condition related to pre-analytic testing. So I think it's reasonable just to define pre-analytic testing as the standards that fall within that condition.

CLIAC MEMBER: And I would intentionally remain silent on the definition of pre-analytical. I think that's a compendium unto itself. And I will defer to the laboratory director. I think if we try to pin pre-analytical down, we actually create more problem.

CLIAC CHAIR: OK. So I think we did a great job. I think let's try and put this to rest for now. I do want to ask a question. And I may need some guidance. There's a comment in the chat that it's not directly related to this topic. I know we generally don't have a conversation. The discussion really should be limited to this particular topic. Is that correct?

CLIAC EXECUTIVE SECRETARY: Right. Yes. We have to announce all the topics.

CLIAC CHAIR: OK.

CLIAC DFO: So I think if this is a concern, perhaps that can be a talk line with the agencies, but we save the chat.

CLIAC CHAIR: Yeah, OK, all right. So then, right, it is Eastern 12:40. We're supposed to end at 1:00. I'm not hearing that we need to discuss, or we have another recommendation coming out of this. [CLIAC EXECUTIVE SECRETARY], some other question in terms of guidance is given that it is a public meeting, if we were to end-- break early now, we should probably maintain that 2:00 PM start point as opposed to just shifting the day over, just for everyone who may be joining externally.

CLIAC EXECUTIVE SECRETARY: Yes. Yeah. Our next sessions have the presenters already scheduled at a certain time. And so we'll just extend our break and return back at 2:00. I'm sure no one will argue with that.

CLIAC CHAIR: I was just going to ask. Anyone object to ending this morning's session early and going to lunch? OK, well, with that, let's break. Now, we'll start, reconvene at 2:00 PM Eastern. And again, for a quorum sake, please make sure you come back on time, again, at 2:00 PM Eastern, so we'll be ready to start our next topic, which is the role of artificial intelligence and machine learning in the clinical laboratory. So until then, enjoy your lunch and break.

The Role of Artificial Intelligence and Machine Learning in the Clinical Laboratory

Introduction to Topic
Heather L. Stang
Courtney H. Lias, PhD

CLIAC CHAIR: All righty. Everyone should be filing back in. [CLIAC EXECUTIVE SECRETARY], do you know, do we have a quorum yet? I don't know if we can tell with—

CLIAC EXECUTIVE SECRETARY: We are good to go.

CLIAC CHAIR: We're good to go? Excellent. OK, well, thank you everyone. Hopefully you enjoyed the break and/or your lunch. We'll move on to our second topic for the day, which is the role of artificial intelligence and machine learning in the clinical laboratory. We're going to start with an introduction from Miss Heather Stang and Dr. Courtney-- I don't know why I keep struggling with your last name, even though I've said it so many times today. Lias? Lias. I keep struggling. I don't know why. Followed by a presentation on artificial intelligence, machine learning, the anatomic and clinical pathology perspectives by Dr. Alexis Carter. After the presentations, we'll have some time for public comments and committee discussion. And with that, Heather, why don't you kick us off?

MS. HEATHER STANG: Sure. So I am very excited to announce the topic of the role of artificial intelligence and machine learning in the clinical laboratory. This is the first time that this topic has been included for CLIAC discussion. And I venture to say it's not going to be the last time.

So I'm just going to provide a very little bit of background. As you all know and have heard, in previous CLIAC meetings, we had a CLIA regulations assessment workgroup that was formed in 2022. This workgroup was formed to provide input to CLIAC on how the CLIA regulations might be updated. The charge was specifically providing advice to CLIAC for consideration and making recommendations to HHS on revising CLIA regulations. The workgroup provided its final report during the November 2023 CLIAC meeting. There were numerous topics during those workgroup discussions, ranging from data as a specimen to analytical testing specifications. And you can look at all the workgroup reports on the link provided on the slide. So during the total testing process evaluation topic of the CLIA regulations assessment workgroup, several questions were posed. How do the technologies that utilize artificial intelligence play a role in the total testing process? How does CLIA apply the use of these technologies? What requirements should be added or revised in CLIA to ensure testing quality when utilizing artificial intelligence?

So the workgroup started discussions on this topic, but they felt that they needed a little bit more information to help understand the challenges of utilizing AI and machine learning in the clinical laboratory. Luckily, we had Dr. Alexis Carter as a member of the workgroup, and she eagerly volunteered to provide a presentation on the topic to frame those discussions. During the workgroup discussions, members felt that it's essential to understand some of the basics of AI to help inform decisions and definition was needed to define AI as related to the clinical laboratory process. And this definition could potentially help determine CLIA applicability. Since the workgroup didn't delve too deep into the topic, we felt it was a good time to add this to the CLIAC agenda.

We are very happy to have Dr. Carter with us today to provide an overview of artificial intelligence and machine learning. Dr. Carter is a physician informaticist and molecular pathologist with expertise in anatomic and clinical pathology and informatics at Children's Healthcare of Atlanta. Before Alexis's presentation, Dr. Courtney Lias, the CLIAC FDA ex-officio, will provide a brief overview describing some AI machine learning FDA submissions and approvals. After the presentation, we will open CLIAC discussions to focus on these two questions. Thank you, and I will now turn it over to Courtney.

DR. COURTNEY LIAS: Thank you, Heather. And instead of focusing on clearances and approvals, I'm just going to give a little bit of an overview of AI/ML approaches at FDA Center for Devices and Radiological Health. So I know all of you have been following in the news that AI and the use of AI in medical devices has been a broadly discussed topic, including how will FDA approach the rational regulation of these types of devices? And so I want to give you a little bit of an overview of some of the things that we have going on. And then describe to you my perspective on the types of in vitro diagnostic or laboratory-related products that include AI/ML. So of course, AI/ML has tremendous potential in a lot of areas in what we do. And it's certainly going to move into the clinical laboratory space more and more, but we really need to understand what we're talking about here. So I second the idea that a reasonable and standardized definitions of AI/ML will be helpful. We are addressing this issue through a few ways. One is the creation of what we call the Digital Health Center of Excellence within our center at FDA. So the Digital Health Center of Excellence was created in 2020. And it empowers stakeholders to advance health care by fostering responsible and high quality digital health innovation. This group within our center connects and builds partnerships to accelerate digital health advancements. They share knowledge, and they innovate regulatory approaches, including developing approaches appropriate for AI/ML. And they publish some documents, which I'll get to in a minute.

In addition, we've been publishing white papers and guidances related to AI/ML. And the final thing that I'll emphasize is what we call PCCPs. PCCPs is a new authority that FDA received in 2022 where Congress gave us the authority to use what we call a predetermined change control plan within device submissions. Now, we call these PCCPs. That's the predetermined change control plan. So a PCCP is basically-- I'll give you an example. A device comes in. They get it approved. And then they want to make a modification to it later. They can come back and get that modification approved, but maybe a little bit easier and more agile development of devices would be using the PCCP approach. And that is that they would get sort of agreement from FDA on the process that they would use to validate the modified device. So it sort of spells out we're going to do this type of modification. This is how we're going to validate that it works. And if it does work, we can go ahead and do it without coming back to FDA. And so we've already been putting that in place in some devices' submissions. The PCCP process is particularly helpful in an AI/ML type environment because it allows for the types of software changes that may be needed when you develop AI/ML based software. So I'll provide Heather with some resources we have at FDA related to publications, draft guidances, et cetera, on AI/ML. And so she'll be able to share them with the group. But I want to close my comments with just a description of the types of devices we already see. So we don't typically yet see too many devices that are true machine learning AI devices in that they are providing things like diagnosis or clinical decision support through true machine learning. That's relatively rare. We certainly have conversations with entities wanting to develop that type of product.

But more common are two other approaches. One approach is the use of AI or ML in the development of a device. So, for example, in developing a multivariate algorithm that may be used to predict a complex disease, or the use of AI/ML in the algorithm itself, but then it's locked. So those algorithms are typically when they come in locked algorithms that are then evaluated for effectiveness. And then they may

change in the future, perhaps by AI/ML or perhaps by other mechanisms. And those things are often what we see listed as AI/ML type devices right now. So I thought that might be helpful for you to see. I acknowledge that there are definitely additional AI/ML related topics that the clinical laboratory is likely to need to grapple that aren't related to diagnostics or clinical decision support themselves. So I look forward to that particular discussion. So like I said, Heather, I'm going to send in the chat to you a set of links that you can send around to give people a little bit more information on FDA efforts in this area. So thank you, and I look forward to hearing from the committee.

CLIAC CHAIR: Excellent. Fantastic. All right, let's roll right into the presentation. Alexis?

The Basics of Artificial Intelligence and Machine Learning
Alexis B. Carter, MD

DR. ALEXIS CARTER: Hi, everybody. Just give me a few seconds to get my screen up and running. So can everybody see my screen?

CLIAC CHAIR: Yes.

DR. ALEXIS CARTER: OK, great. So thanks to everyone for inviting me to come talk to you today. I do want to preface this by saying this is really the barest of bare bones basics in artificial intelligence and machine learning. So people get PhDs in this stuff. This is really very much the tip of the iceberg, so be aware of that going into this.

Because this is a federal talk and generally speaking, I do give disclosures. I don't have any significant financial interest. But you should be aware I'm a paid faculty member of the AMIA Clinical Informatics Board Review Course. My spouse recently received some consulting fees from Sysmex, which were relatively minimal. I'm the immediate past Secretary/Treasurer for AMP, and I have my hands in a lot of cookie jars, so just be aware of all of that.

So for the goals and objectives, what I was asked to cover today was, again, a very high-level overview of AI and ML. We're going to describe a little bit about the current and future potential applications of AI and ML for both anatomic and clinical pathology. And really, what I hope you get at the end of this is to understand why it is absolutely critical for pathologists and laboratories to bring in data scientists to be able to use this technology in a safe, wise, cost-effective way. And those are huge challenges. We're going to talk about artificial intelligence, some of the definitions around that, its uses and benefits, challenges, as well as some published guidelines. We'll go into machine learning from a very high level forest view. Talk about some of the basic definitions that apply to all machine learning, as well as how you go about developing a model. What kind of quality metrics that you can put into place. And then how you would design, train, test, and deploy a model. We're not going to cover too much on the algorithms. We will cover a little bit about which algorithms do which kinds of things in which categories of machine learning. And we will touch on neural networks, but we won't be able to get much further than that due to time constraints.

So we're going to start with some definitions for artificial intelligence. Really, the bigger bucket, which artificial intelligence sits in, is called data science. And the way I think about data science is that it's the science of organizing and analyzing really massive amounts of data. In pathology, we've been using this term computational pathology in some areas. But really, your electronic health record, even a laboratory information system, this is a huge repository of big data that's constantly changing with many different types of data coming in and out. And so you really need to use a separate set of skills to be able to analyze that data effectively.

And so one of the big categories of tools that you can use in that space is artificial intelligence. Artificial intelligence, it means different things to different people. Generally speaking, the way that most people have defined it is that it's the ability of a computer or computer controlled robot, in some cases, to perform

tasks that are commonly associated with intelligent beings. And we'll talk a little bit more about that in a minute as to the variability that can come in there.

Machine learning is a set of algorithms within artificial intelligence, which allow computers to learn without explicit programming. And I'll give you some more detail on that. I'm sure many of you have heard this term of deep learning. Deep learning is a subset of machine learning tools, which are really designed to handle massive amounts of data. Neural networks are the most common example of this. So when you're talking about artificial intelligence, you'll hear this term narrow AI, general AI, and strong AI. Narrow AI basically means the machine. And this is really where you see most of the papers nowadays. The machine learning algorithm can perform usually a single task better than a human. So this would be like telling the difference between invasive ductal carcinoma and normal breast tissue, which sometimes I think my seven-year-old when he was-- he's now 12, but when my seven-year-old was seven, he could have done that to some extent when you're not throwing everything else in between. General AI is when you've got a machine that can perform any intellectual task with the same accuracy as a human. So this would be if you had developed a diagnostic algorithm and anatomic pathology that would really was able to consider the whole spectrum, for example, of breast diagnoses, anything from inflammatory conditions all the way from normal up to florid ductal hyperplasia, atypical ductal hyperplasia, ductal carcinoma in situ, and invasive ductal carcinoma or invasive lobular. Strong AI is really kind of-- if any of you have ever seen the movies in the Terminator series-- is where the machine can outperform humans in many tasks. And it's strong AI that we've started seeing a lot of news and publications about being concerned about AI being able to function in this capacity.

You should be aware of a couple of other terms. There's what's called the AI effect or Tesler's theorem. And this is people often don't think about artificial intelligence as whatever really hasn't been done yet. So it used to be at one point in time that optical character recognition and voice recognition were considered to be very fancy artificial intelligence, machine learning things. But because they are now in such common use, most people don't really think of them as being artificial intelligence. So that's what this term AI effect means. Automated pap smear machines are also very common in our laboratories, as well as peripheral blood smear readers. And bioinformatics pipelines, those that actually are using machine learning tools, which it's relatively uncommon but it's becoming more common, often people aren't really thinking of them as artificial intelligence anymore. There is a difference when you're talking about medicine between autonomous intelligence and augmented intelligence. So autonomous intelligence refers to machine learning algorithms that are set up to make decisions with no human in the loop. I don't think many or any of us are really comfortable with this idea because we've seen machine learning and artificial intelligence algorithms make some pretty significant blunders. And blunders really is a weak word considering some of the things I'll talk to you about in a minute.

Augmented intelligence, however, is a very interesting way to think about AI and ML. This is where you're using technologies really to augment or assist humans in their work, to make you faster, better, to help you not miss things that you need to not miss. And this really maintains that human in the loop, where the human is ultimately making the decisions, and the AI is just being used as an assistive technique.
So why is AI different from traditional programming? So in traditional programming, what you often end up seeing is where you have input data that is being analyzed. And a human has kind of already pre-analyzed the data and is developing rules to help analyze that data faster using known or suspected patterns that they already think is in the data to generate output. Machine learning is different because, especially if you're talking about a supervised algorithm, you're feeding both the input and the output data into the algorithm. And you're having the machine basically learn the patterns, or learn how to do pattern recognition in those patterns to generate your groups, your classifications, sometimes numbers and other things. We'll talk about unsupervised data in a minute. But really, when you set up these models, you don't have humans actually writing code to determine how to classify or how to rank these individual things. You're having the computer learn to do that for you.

So machine learning is also different from traditional statistics. And we've gotten to a point now where machine learning is really the way that we want to go. In traditional statistics, you were defining these explicit mathematical relationships between your inputs and outputs. You had to know things about your data to be able to help classify it. And you really didn't have very large sets of data that you could do this

on. It could not be terribly complex or multifactorial. That's why we all had to hire statisticians when we got that kind of data we were trying to analyze. But the real advantage in traditional statistics is that the output, the reasons why your output is generated the way it is is very clear and explainable usually. Machine learning is almost the opposite in all of these categories. Usually, there isn't an explicit mathematical relationship because of the way these models are trained. And then, you can't always make assumptions about the data that you're feeding into it. And especially if you're using an unsupervised model, you're actually using the model to try to help tell you things about your data that you weren't able to pick up on your own. You can handle a very large number of input variables with artificial intelligence, machine learning algorithms. Complex multifactorial data is where these algorithms really shine. However, there's a huge problem with artificial intelligence and machine learning in that the reason for the output is not always clear or explainable. And you'll hear me refer to this term the black box problem several times because that's one of the biggest issues with these algorithms. So uses and benefits. So in anatomic pathology, it's really hard to find a journal that does not have papers that include machine learning algorithms nowadays. The biggest thing that we use them for in anatomic pathology are classifications. Now, there's a lot of hype out there about the AI algorithm did better than the pathologist. And the pathologist and radiologists aren't going to have jobs anymore. That, in my opinion, is a lot of hype. There's a long way to go before computers are taking over everyone's jobs. So any time you see a paper like that, you should always read it. I have found sometimes that the title is far more inflammatory than the data that's actually in the paper. So make sure that you're taking a look at that and judging those effectively.

However, where I see some real promise for the use of this technology in a safe way in our laboratories is to really use it in smart and assistive ways, things that help us not make mistakes, things that help us be more objective. As an anatomic pathologist, I can tell you one of my least favorite things to do is to count mitoses. And if you have an algorithm that's able to actually identify where all your mitoses are and to count them according to the total number of tumor nuclei that you see, for example, you can turn something that currently can be pretty subjective into something objective, which could be very helpful as we're trying to grade tumors. Finding tiny metastases in lymph nodes. Detecting microorganisms that might otherwise be very sneaky. Those are things that AI and machine learning image analysis algorithms really can help us with.

You can also have potential predictions based on histologic features. There's a lot of stuff talking about the prognosis of a patient based on individual features that you might see, for example, in prostate biopsies. There's a lot of work now looking at molecular sub-characterization. Can an image analysis algorithm actually predict what molecular changes you may see in the tumor before testing has been completed or to help direct what testing needs to be done? And then, one of my favorite things about machine learning algorithms is the idea of doing anomaly detection. So for example, there's this fascinating paper that was put out several years ago about detecting errors in your pathology reports and using machine learning algorithms to be able to pick up on those so that you can get them corrected. In clinical pathology, there's a huge wide array of things that you could use these tools for. So there's predictions, such as being able to tell in advance when a patient-- this is a very common thing-- when a patient might be heading toward sepsis. So most of the machine learning things that you see out in the literature are really focusing on the ability to predict sepsis before it occurs so you can intervene early. There's been a lot of work on, for example, predicting future anemia from trending data in CBCs. During the pandemic, we saw a lot of interest go into where are patient volumes going to be. Can we adjust staffing appropriately? And then there's helping you to determine what the best future state workflow might be for a particular thing. And another big area is being able to use these algorithms to actually help predict or detect or subvert malware attacks. I'm currently at the Children's Hospital Association meetings. That's what it looks like I'm in a hotel because I am. And we have a couple of people here from Lurie Children's about what they have gone through where their systems have basically been offline for a month. And just try to imagine having to go through that. And if you could have an AI algorithm that could help you prevent something like that, that would be amazing. Obviously, classification is just like an AP being able to do pattern detection. In next generation sequencing, a lot of people are using these when you have massive amounts of data to determine which variants may be the most indicative of what may be causing the patient's symptoms. There's decision support, such as prior authorization decisions that some people have been looking at these algorithms for. And then, obviously,

there's natural language processing, voice recognition, and other things. And then, again, anomaly detection. Problem solving for when we have shifts or trends in our data that we weren't expecting. Trying to indicate where those might be coming from, again, with this idea of intervening as early as possible.

However, with all uses and benefits, there are always a number of challenges. And machine learning is certainly no different to this. Many of the challenges are similar to other non-AI software. Cybersecurity risks, I think, are probably at the top of everyone's priority nowadays. Any software can be developed with bad data or bad science, just like they can be developed with good data and good science. So bad science is bad science. So make sure you're reading those papers before you believe that it is the end all, be all to everything. We're going to use this term bias in a couple of different ways when it comes to machine learning, but it can mean different things. And so you need to be aware of that. So automation bias is a curious effect that you can see, especially among sometimes trainees, where they assume that the computer is correct, even when the computer isn't making sense. And so you have to be aware of this, that once you start putting an AI tool into the mix that you'll see some people who start thinking that the computer is right when everything else about what's going on with the patient or with the data doesn't make sense. And then, you can have very inaccurate assumptions made about how accurate the tool is, and whether it is actually representative. And IBM Watson, unfortunately, has been sort of the poster child for a lot of this in health care because there were a lot of people who thought that IBM Watson was really going to revolutionize, for example, molecular medicine. But one of the biggest problems that happened with IBM Watson is that it started ingesting PubMed verbatim without any assessment of the data quality for some of the journals that are listed in PubMed. And was using that data to help it make decisions. And I think many of you are probably aware, there have since been estimations that up to 80% of what's in PubMed is not reproducible. So now, you have a machine learning tool that is basing its decisions off of what is 80% bad data, potentially. So just be aware of that. I use this story a lot to talk about machine learning because I think it is a very tragic example, but it is a very good way of talking about how AI and machine learning can go wrong. Now, I want to preface this by saying that this MCAS system, Maneuvering Characteristics Augmentation System, it is a machine learning and AI tool. It actually was performing as expected. The issue was is that this tool was very poorly implemented. So this is a very good example of what not to do with machine learning systems.

So as many of you know, in 2018 and 2019, there were two very tragic plane crashes, which killed all of the passengers on board. And what happened was is the planes had these angle of attack sensors, which were intended to detect when the plane might stall. So generally speaking, when a plane's nose is up, and it is flying too slowly, that is when the engines can stall. And then the plane, obviously, is doing a nosedive down back to the ground. And so these planes were set up to only have one sensor on them. And in both cases, the sensor began to fail. Because there was no redundant sensor on board, there was no way for the AI algorithm to know that the data that was being fed to it was bad, so the plane thought it was at risk for a stall. So what did it do? It was trained to basically speed the plane up and nose it down to avoid a stall. Because the planes were actually not at risk of a stall at the time, it sped the plane up and nosedived into the ground. There was no usable human override mechanism. Now, Boeing will tell you that there was a human override mechanism, but basically, the pilots were not told where it was. And they were told not to worry about it. The default configuration did not show any alerts for when the application started to get a lot of errors. The system was not set to disengage when there were multiple errors in the system. And errors that were discovered during simulations using the software were not reported to the FAA by Boeing because they were considered advisory rather than critical. And I do want to point out that currently with FDA approved or cleared devices, manufacturers similarly are not required to report it unless they are considered significant. And on top of all of this, the FAA citing lack of funding and resources, basically, had delegated more and more of the authority to govern itself to Boeing. And I think almost every day of the news we're hearing about quality issues with Boeing that have been happening over and over. So that probably was not the best decision for FAA to make.

So the challenges with AI and ML, you have to have very good quality data in order to develop these. If you have bad data, you're going to have a bad model. I mean, that's just what's going to happen. Some models actually need a very large amount of good quality training data. And if you don't have enough of it, your model isn't going to perform the way you want it to. If your data don't have sufficient quality, or if it doesn't have sufficient variability-- as we all know, we have patients coming in and going

out from all over the place. Patient demographics can change. The disease patterns that we're seeing can change. When you're developing AI algorithms for medicine, you really have to take all of that variability into account. We'll talk about the terms we use for that in AI in a minute. You have to make sure that you have vetted your algorithms. That you have not fed human bias or false beliefs into your algorithms. Algorithms are amazing at picking up patterns. And as we've seen with some algorithms that were being used for court sentencing, it was picking up on that human bias without necessarily recognizing that it was human bias in prior histories of how people were sentenced based on their demographics sometimes. And it was then recapitulating that into these decisions that they were giving to judges about the recommended penalties to give to people who were found guilty. And in these instances, sometimes AI was actually not just continuing human bias but exacerbating it, which is definitely not what we want to be doing in medicine. If you have data that's got incomplete, inaccurate, or variable labels-- we'll talk about labels in a minute-- that can cause you a lot of problems. There's also this other really interesting thing that you have to be aware of when you're generating an algorithm. And it's called Polanyi's paradox. And this is that-- and I'm sure all of you have experienced this-- this is when you, and especially if you're an experienced physician, for example, you walk into a room into a patient, or you pick up a slide or what have you. And you know that this is not characteristic. That this is going down this other way. Some people will describe it as gut instinct. Personally, I think it is there's a million different little signals that's telling you, based on your experience, that this is need to take a different path or work this up a different way. And this is why you find that people who do that are often right. It's because they've got this human decision making that they can't necessarily verbalize as to how they're picking all of that up. And if you can't verbalize it, then you can't get it into your data so that you can't get it into your model. And so if you have humans who are labeling data, but they don't necessarily know what's contributing to making those decisions, it's very hard to get AI to mimic those decisions and to be able to pick up on all of those things.

Another thing about machine learning models you have to be aware of is that they can be brittle. And so what does that mean? It means that you can have very-- especially for a more overfit algorithm, very small changes in your input. And I mean minuscule, like humans wouldn't necessarily pick up on this, can result in some pretty big changes in your output. So one of my favorite things to show people is that there's this very clever MIT group. And so what they did is there's the famous cat in the guacamole story, which I don't have here. But this one was a little bit more impactful for me. Basically, as you can see here up on the right, they have a picture of-- and we as humans know that these are all turtles, right? You can tell from looking at the picture because humans are really good at seeing the forest instead of the trees. However, what I want you to note this is that these two turtles right here that have a black box around them, these are ones that the algorithm, the image analysis algorithm from Google accurately called turtle. The rest of these that are outlined in red were classified as rifles. And the reason why is because this MIT group went into these images and changed very critical tiny little pixels that none of us can actually see but which the image algorithm picked up on. And based on those tiny adversarial, as in hacking or intentionally misleading changes, you had an algorithm that completely classified these images incorrectly. Because it's an AI algorithm and not a human, it doesn't know these things right off the bat, right?

So you have to be aware that you have to test your AI algorithms against things like this. You have to protect your algorithms from adversarial attacks, like you can see here. Because as you might imagine, having an AI algorithm make a mistake like this, especially if it is one that is being used to monitor airport traffic in a ticketing area, that would not really be a good way to operate your airport. Cybersecurity. That leads us into cybersecurity. AI can be hacked just like any other software. As you might imagine, out in the military where they're looking at robotic surgical systems, having something hack into a system like that would definitely not be a good thing. In addition to that, we have patient security and privacy issues. Systems that are hacked into have the potential for having all kinds of unauthorized disclosures. Again, having a human-in-the-loop can really help you detect malfunctions before they become a huge problem. And in the media, there have been some more recent efforts, but the United States does have some pretty big national efforts headed towards AI cybersecurity, which is a good thing because this technology is incredibly powerful. And if we don't get ahead of it, we could get into some real trouble.

Transparency is another huge challenge for AI. There's a lot of definitions for what transparency means. For AI developers, often it means the reasons for how the model performs or known and understood, but there's--ethicists who mean that transparency-- is there sufficient information published about the tool so that the public, for example, could monitor the performance of the model to make sure that it wasn't doing wrong things? The lack of transparency, again, is this black box problem. The rules that are developed by AI may actually be completely indecipherable. And especially, you can have, sometimes, these spurious misclassifications of data that no one can explain after the model is trained. Now, there is a lot of work being done in AI/machine learning algorithms to build, ironically, machine learning algorithms that can help you pick up-- help you determine how the model-- what features the model used most to make its decisions. And so I'm really interested in that and hoping that that's going to make things a lot easier for us to understand.

Like I mentioned earlier, there are a lot of ethical challenges with AI because of some pretty noted failures that I described. A lot of people have been talking about beneficence and making sure that we're maximizing the benefits while minimizing the risks and the harms. We don't want to be promulgating or exacerbating human bias. The American College of Radiology and the RSNA have recommended to not approve any autonomous AI until sufficient human-supervised AI experience has been obtained. And we are a long way off from having sufficient experience, in my opinion. You want your tools to be auditable. You want there to be accountability. And right now, there is a huge question that if you have an AI tool that is making decisions in health care, and especially if there's not a human in the loop, if the AI tool makes a mistake, who is liable? There's no regulations in the US for this. As we know, in the United States, we are a very medicolegal litigious society compared to some other places. So this is a question that, really, we need to look at before we start down this path of really putting in too many algorithms in our areas.

Intelligibility is another term that's been put out by NIST that basically says that algorithms are intelligible if they're sufficiently transparent and explainable. You'll often see explainability referred to with the X capitalized and then XAI at the end of it. And it's this desire to be able to show a human explanation as to why the tool is functioning the way that it is. And, again, that's challenging because of how these models are developed and trained. There are a host of other challenges with artificial intelligence. In medicine, in particular, we don't really have a whole lot of data scientists. We lose them to places like Google-- to Google and to Microsoft. Many data scientists lack experience in medicine. So when you are lucky enough to be able to hire one, you're spending a lot of time training them on how medicine and the health care environment works. There's a lot of organizational challenges. A lot of organizations lack AI strategies. Our organization developed one about a year ago. And deploying models in clinical environments is very challenging. You have to worry about patient safety, population differences between locations, monitoring these things over time, and it's expensive. It's expensive technology on top of that. There's a lack of reimbursement mechanisms when you're looking at financial challenges. So it's really harder to define the returns on investment, although I can tell you at the Children's Hospital Association meeting this morning, we had a very interesting presentation from AREP about how they are getting returns on investment for some of the stuff that they're putting in in into their flow cytometry lab. There's also technical challenges. Many of us in health care organizations deal with not having enough resources for what we need computationally. And then, when you start talking about bringing in something like machine learning and AI, that gets even more challenging. And as many of you are aware, most health care organizations only spend about 3% of their budgets on IT and cybersecurity, although I think that number is changing. That's compared to banks, who spend 60% of their budgets on IT. We have a long way to go.

In response to some of the challenges, there have been a number of guidelines that are starting to come out. So United States, FDA, Canada Health, and the UK National Health Service have come out with guidelines for machine learning model development, which are very handy. There's also a number of AI ethics guidelines and white papers that I have linked here that you can go take a look at. These are all really important things to know about before you decide to start implementing machine learning tools in your labs. So I'm going to switch gears a little bit and just talk about some high-level machine learning.

So supervised learning-- so supervised versus unsupervised learning. So machine learning tools can be used to train on data which you have already classified or labeled. So, for example, if you have all of these pathology images, and you've got them of all of the different kinds of non-Hodgkin lymphoma, for example, then you can train your image algorithms to classify it the way that a human would by feeding it those labels of what you diagnosed it at the end of the day. So that's supervised learning. Unsupervised learning is when you are just feeding it the images with no labels whatsoever and asking the machine to tell you what it thinks the classifications are. So you have no labels or no classifications on your data. Unsupervised learning is very handy when you're trying to discover new or previously unknown patterns or relationships. Supervised learning is what you use when you're trying to get the tool to do something a human could do faster or more objectively. There are different variations of supervised learning. You can have something that is considered fully supervised, where all of your data is labeled to the same extent. Semisupervised means that some of your data is labeled while other data isn't. And then weakly supervised is when you only have a small amount of data with labels and the rest of them are unlabeled. Now, the reason why we talk about these things is because getting a model to be-- getting data for a model that is completely fully supervised, when, usually, these models require about 100,000 or so different instances of data, that's challenging for any of us to come up with. So there's a lot of interest in these semisupervised or weakly supervised models where we don't have to label and annotate everything. We can label some of it and then let the algorithm figure the rest of it out. Reinforcement learning-- you probably see these pictures here. This was the initial IBM Watson that beat the two highest-playing Jeopardy champions ever. This is a long time ago. But this was built on a reinforcement learning AI model, basically, where you have the model perceiving a state of the environment that the question's been asked. The agent, the model, basically executes an action, which is the answer. The environment tells you whether you're right or wrong. And then the AI algorithm determines that and then figures out what the new state is and then repeats the process.

So the interesting thing about IBM Watson is when they first developed it, it was failing at all of these Jeopardy matches because there's a lot of puns and other patterns into the way that the answers are put out that the model had a hard time with, until they built into it this ability to be able to tell whether it's right or wrong, go back and look at the category of the question, and then figure out what the pattern was in the questions. So it used this very reinforcement learning state to be able to do that. Transfer learning is another type of learning. And it's kind of in the supervised/semisupervised state. But it's where you're basically gathering data from a related domain and then using it to train your model because you've got more of it than the specific data that you're looking at. So, for example, this would be like taking all of the natural images from ImageNet, for which there are huge amounts of data, and training it-- training your image classifier on it, and then actually doing a validation data set on your pathology images to enable that image classifier to work better on your finely-tuned training exercises. The reasons for this, obviously, is because, like I said, getting fully labeled, high-quality data where you have enough instances to look at is very, very expensive and have been practically impossible for these algorithms. And so sometimes, they go to other samples and then try to transfer that learning from the bigger set to the smaller set to be able to do this in a more cost-effective way.

When you're talking about machine learning, you'll hear this word "instance," you'll hear "label," and you'll hear "feature" a lot. This is a really basic way to look at this. And, no, I did not put matrix examples in front of you, because this is trying to give you the bare bones of this. But basically, what an instance is-- an instance is like a row in your spreadsheet. It's all of the data that belongs to this one instance of your data. A feature is basically a column. So, for example, if you had a feature of color, you would have red and green in your labels. These are the labels which are actually the cells in the middle here. If you had speed as your feature 2, then you would see slow, fast, and medium. And if you had a Boolean or yes/no answer as your feature 3, then those would be the labels under that particular feature. Outliers are exactly what they sound like. These are instances that you have that don't meet the general pattern that the rest of them do. And just like in any other algorithm, sometimes people will exclude the outliers to get their algorithms to perform better. But that can give you an impact on generalizability. Features can also be called dimensions in unsupervised learning. So be aware that there is that similarity but just having a different term. An algorithm basically is the process that's used to train a model. A parameter are these internal values to the model that generally nobody ever sees. They can be weights and bias values that are used as the machine learning tool is learning the patterns and setting itself up.

The model is the algorithm plus the parameters. And when a model is used for classification, you'll hear it referred to as classifier. A weak learner means a model whose performance is really only slightly better than random chance. So none of us really want to have weak models in medicine, right? We don't want to be kind of throwing darts at something and the answer not necessarily representing accuracy.
A good model, though, in machine learning is one that they typically say generalizes well. So what does that mean? It means that when you feed the model new data, it performs with the same accuracy and reproducibility as it did on the training and the test data. And, again, because these models are so very good at picking up tiny, tiny little nuances in patterns-- we'll talk about overfitting and underfitting here in a second-- generalizing well is not as easy as it sounds.

So I do want to cover a few things because, in laboratory medicine, we tend to use the terms "accuracy" and "reproducibility" when you look at these targets over on the right. So, for example, an accurate and reproducible model would be something that would be this low-variance, low-bias model. High variance would be it's relatively accurate but not terribly reproducible. High bias and low variance is when you have it very reproducible but not terribly accurate. It's outside the bull's eye. And then a not-good model at all is one that's not terribly accurate or reproducible. That's called high-bias and high-variance. So the way-- so, again, this is a different term for bias. And you have to be aware of that when you're reading these papers. But bias, when it is referred to in this context, means the measure of inaccuracy. So it's kind of like the opposite of accuracy. It's the measure of the inaccuracy. Variance is the measure of imprecision, or the lack of reproducibility. And then irreducible error is error that you can't get rid of no matter what you do to optimize your algorithm. So be aware of that. So bias is not just talking about ethics. Remember, we have automation bias. We have bias when it comes to an algorithm unfairly judging a population based on things that have nothing to do with what you're looking at. And then you've got bias from a measure of the inaccuracy of the model's performance. So a model that has a high amount of bias means that it is very inaccurate. And generally, it means it's underfit. And we'll talk more about that in a minute. Low bias means the model is fairly accurate, but it may be overfit, and it may not generalize well. Variance is the amount of imprecision, and it's usually the square of the standard deviation of your error. And it is due to the model sensitivity in the fluctuations in the training set. If you have a high degree of variance, it usually means that the model is imprecise and very likely overfit to your training data. And if you have low variance, it means that it is precise, but it may not be terribly accurate and could be underfit.

So there's this thing in machine learning called the bias-variance tradeoff. Many of us are familiar with similar terms in laboratory medicine. But basically, things that reduce our variance increase our bias, and vice versa, so just like things that increase your accuracy may worsen your reproducibility and vice versa. Total error is calculated by doing the square of the bias. And so basically, you get-- your inaccuracy is squared, and then your imprecision plus your irreducible error. OK, so goodness of fit-- so the ideal machine learning model has a very good fit to the data, meaning it generalizes well. So good fit is generally what you see here in the middle. So here are your data points here, and your model is not quite over the Xs, but it's kind of close, generally speaking. If your model is underfit, it basically means it's kind of far off. It's in the general trajectory but not necessarily very close to your individual data points. An overfit model is very much right on the Xs, but it is not a generalized trend. And the separation is actually not generalizable. It's too fit. It's overfit to your training data. And machine learning models-- actually, the most common problem with machine learning models is that they tend to overfit themselves. So when you're developing a model, you have to make sure that you're putting things into place to prevent that from happening, because if you overfit to your training data, then, when you start to feed it new data that it hasn't seen before, it will get the answers wrong.

For time considerations, I'm not going to go over this too much, only to say that in laboratory medicine, as we all know, when you have a very low-incidence disease that you're screening for, for example, you have to use different tools when you are evaluating them. It is no different in machine learning and artificial intelligence. You can often-- when you're trying to use these algorithms to screen for things, you have to use different statistical methods when assessing their accuracy. So a couple of other points about model development-- and I do this because the way we think in laboratory medicine and the terms that we use are a little bit opposite from how they're used in machine learning. So, for example, when you are validating a laboratory test-- so we'll start over here on this column. When you're validating a laboratory test, generally, that means that you have already done your initial testing, you have locked down your test

that you're going to be doing, and you're running samples through it to make sure that the test is working as expected. By contrast, in machine learning, validation means you're at a much earlier stage of your model development. It means you're kind of doing just preliminary testing of your model to see if it is working correctly. If it doesn't validate well, you're going to go back and tweak it, maybe retrain it, and then revalidate it. Testing, on the flip side-- when we say testing in the laboratory, often, we're either referring to our formal testing that we're doing clinically in laboratory, or sometimes it means we're at that very early stage of a new laboratory test and testing samples through it to make sure that we don't need to tweak anything or change anything. However, in machine learning, testing means that you're doing a final evaluation of that model to see if it is ready to be deployed. And so in testing, you really want your error rates to be as low as possible without overfitting your data. So be aware that there's a little bit of difference between how those terms are used. This is the generalized process of model development. A lot of people-- the mistake that I see people make when they're writing papers, for example, is they tend to focus on exactly what model I'm going to use and this really cool tool that I want to use for whatever it is. But what they haven't done is focused on these first three steps up here, which are really the most important. The number one thing you have to do with any model development is determine exactly what problem you're trying to answer. And then you have to gather appropriate data that you're going to use for training the model. And these two steps alone can be some of the biggest ones that you have to do. Prepping, cleaning, and transforming that data on top of it, between those first three steps, that is where the vast majority of your time and your expense should actually go into for model development. After you have all of your data, then you're going to partition it into a training data set, a validation data set if you're going to use one, and then a testing data set. You're going to select your features if you're using a supervised model. If you're using an unsupervised model, you would skip that step. You're going to select which model you're going to use. You're going to get your quality metrics that you're going to use to determine how your model is performing. And then you're going to do your training. You may then evaluate or run the model, the developed model, on a validation data set. That may allow you to tune it or tweak it if you need to, which you would then go back and repeat this cycle as you need to. And then, when you think the model is trained or in its final state, then you're going to test it on your separate testing data set. Choosing what data is going into your training set versus your validation set and testing data set, it is very important how you do this. You don't want to have data leaks across because you don't want your test data set to look like it's working perfectly and then, as soon as you put new data into the deployed model, it breaks, because that means you had problems with how you were selecting these to be partitioned. If your model is ready for production, then you will put it at the side of deployment. You'll deploy it, and then you have to monitor it. It's just like any other laboratory test or algorithm that we run in the lab. You have to monitor it to make sure it is working as expected. If it is a model that starts to drift or shift, then you will have to go back and repeat this process to retrain it based on the new data that you're starting to see. When you're deciding what models to select, it all depends on exactly what you're doing. So if your data has known output, meaning it has labels, you've classified it, you've determined what patterns already exist in the data, then you would use a supervised method for that. And if your expected output is categorical or classifications, then you would use a classification method. If it's really a ranking or numerical or continuous metric, then you would use a regression method. And there are hundreds of different methods, algorithms that you can use for each one of these. If you're really just trying to get the model to tell you what the patterns are, then you would use an unsupervised method, which is different. If you're looking for categories or clusters, then you would use a clustering method. We use hierarchical clustering in next-gen sequencing research all the time. And if you're trying to find associations between independent variables such as-- this is kind of like the Amazon algorithm where it's like, people who bought this also bought these things, and that's using association rules, which are not necessarily-- they're not dependent. They're actually independent variables that you're looking at. And then, if you're actually using an unsupervised method to help you reduce the number of features that you're looking at in a supervised model, you can use what's called dimensionality reduction methods.

So machine learning algorithms generally fall into all of these different categories. If you're doing a neural network-- and we'll talk about those in just a few seconds-- those can be either supervised or unsupervised. Supervised methods are usually going to be your regression methods, your classification methods. And an ensemble method is referring to things like random forest, where you have a number of different smaller, weaker algorithms that you're using in series or in parallel to generate a final answer to increase the power of your overall method or model in a very cost-effective, computationally effective

way. Unsupervised models, again, are going to fall into these clustering methods or association rules or dimensionality reduction methods. So artificial neural networks, they're a bit of a different class of algorithms. And these are the ones that you often see people using, especially with image analysis. The goal of these neural networks is to really solve problems like a human, just like any machine learning or artificial intelligence. The difference is how they're constructed. So they're constructed-- the idea behind them is that they were working kind of like neurons, where you've got neurons and then synapses, and that data is flowing through the system in the same way it might through a human brain, right? These algorithms in particular can be very hard to unravel as to how it was making its decisions. And these are also the ones that are usually used for the deep learning types of algorithms. So you can have nodes which are basically transfer functions that happen at each one of these circles that you see here. The connections are the passing of the data from one node to the next. And then you can have-- some neural networks will do what's called backpropagation. And this is where the algorithm can actually learn from its mistakes. It assesses the error as the data gets into each node. And if there's an error, it can actually recursively go back and send the data back through to try to reduce that error rate. You can have the input layer, you can have hidden layers in the middle, and then you can have output layers. And when you have a shallow neural network-- you can actually have shallow shallow neural networks-- those typically only have between one to three hidden layers in between, depending on who you read. A deep neural network, on the flip side, will have sometimes greater than three or up to thousands of these nodes in between. And so these networks-- there's a huge amount of computational power that goes into developing these models. And this can also help you understand why it can be very difficult to figure out how the algorithm is making its decisions based on how the model is set up. So, again, this is a very high, very superficial covering of this particular topic. When I give this lecture for the clinical informatics board review course, for example, that presentation is 139 slides long, not 40. And we're only just scratching the surface with that presentation as well.

So at this point, I'm happy to take any questions. I won't be able to stay for the full hour of discussions afterward, but I can answer a few questions for the next 5 or 10 minutes. And then I will have to get back to my other meeting.

CLIAC CHAIR: Yeah, thank you. That was a fantastic presentation. Yeah, recognizing that you may have to drop, before we move on to public comments, are there any questions from the committee members? And we'll take a few of those, and then we'll move on to public comments. [CLIAC MEMBER], you're up first.

CLIAC MEMBER: Alexis, thank you so very much. Wonderful presentation. When you mentioned Polanyi's paradox and sort of the instant I know the answer, what I've done in my own career as a pathologist is recognize the mantra "you can diagnose cancer in 1/10 of a second, but you better make sure you're not wrong." And that may take 10 to 20 minutes, which, to me, is backpropagating a different answer through whatever you consider your decision making and saying, but could it be this? Could it be that? Could it be that? How can I be wrong? And what I didn't hear you mention in either the neural network or the more horizontally layered machine learning, is backpropagation of different answers to see how you can pressure test an answer. And the reason that I conceptualize it this way is you can wind up in multidimensional space and think you're in a correct answer, but you're actually in the wrong valley. And so backpropagation of alternate solutions to see how well they test against the input data is, to me, a cognitive thing I do as a pathologist. But I wonder if it plays into AI and machine learning.

DR. ALEXIS CARTER: It absolutely plays into AI and machine learning. And the talk we heard this morning from somebody who actually has a lot more experience in this area than I do, David Ng from ARUP, just like anything we do in informatics, you know, I often talk to people about the non-happy path cases, the ones that are hard when you're developing a workflow to make sure that we can account for those, when you're gathering your data for machine learning algorithms to train them, you have to have appropriate edge cases and thinking about things that might have led you down the garden path that you need to go back and make sure that you're not going down the garden path and feeding those into an algorithm and making sure that it's still coming up with the right answers when you do that. As you might imagine, the proportion of cases that you're doing like that need to be representative. And so that's why a lot of these algorithms, to be generalizable, they say you kind of need to have 100,000 to a million of well-

labeled cases to be able to do that. What you're talking about is very challenging. I don't think AI does that very well just yet, in part because I think getting these data sets that we need in order to train them is hard. But on the flip side, that is what, still, humans do a lot better than AI is looking at it, having your gut response, and then going back and saying, what could I be wrong about in this, and thinking about it from that perspective. Does that make sense?

CLIAC MEMBER: Yes, it does. And it requires framing the logic right so that you can test both the input data for how well it matches alternate solutions and look for rejection of alternate solutions on the basis of those input data.

DR. ALEXIS CARTER: Right, and that brings up a really good point. So what you often see happen when you have AI algorithms developed in primarily research environments that don't have medical expertise is that you have IT developers who have a very limited understanding of what we do in the laboratory or in medicine or how a pathologist is making decisions about what they're looking at in an image algorithm. And then they develop an oversimplified protocol that doesn't include any of these edge cases or any of these decisions about, is this atypical ductal hyperplasia or is this invasive-- is this ductal carcinoma in situ? You can get 30 pathologists into a room who are all breast experts, and nobody will agree about half of those. So it's really important to have medical input as these tools are being developed because otherwise, you will end up with tools that don't work well. And I could give a ton of molecular examples of that as well.

CLIAC MEMBER: Thank you.

CLIAC CHAIR: Thank you. [CLIAC MEMBER]?

CLIAC MEMBER: Hey, Alexis. That was amazing. Thank you. And I kept thinking about how in your first few slides, I'm with you. I'm with you. And as you're going further, I'm like, I don't know what you're talking about anymore, which brings me to one of my questions, because this is not what we were trained for, right? I think this is why we have you guys, the informatician. But you made a good point in terms of some of the publications out there. Even if I'm the one reading this, I don't know what I don't know, right? So I take this at face value and just hope for reviewers and editors to have done due diligence to tell me that this is the future of microbiology or oncology or so on and so forth. Is there anything that, as a laboratorian, should be sort of our cheat sheet of things we should be aware of as we're evaluating the technologies and publications, including whatever bias is out there for those, that you could guide us in a way?

DR. ALEXIS CARTER: So, yeah, I mean, first of all, I do think it's helpful if you can even just read some of the publications that are out there that are meant to be introductions into machine learning. But going a step back from that, like I said, good science is good science. You don't have to be an expert in machine learning to understand that the way that they developed this particular algorithm was doomed from the beginning. I'll give you an example. I saw a paper that was looking for a relatively low-incidence condition. It was stomach cancer here in the United States. I'm making that tumor up. It actually wasn't that. I'm trying to protect the people who got dinged. But when they developed their model, three-quarters of their cases were stomach cancer cases, and then only a quarter of them were noncancer cases. That's just as bad when you're developing machine learning models as it is for any other study that you do. And unfortunately, people get so excited by the tools that they forget the good science piece of things.
So understanding your good science, understanding detecting error, understanding-- microbiology is not my area. So I'm not even going to try to give you an example there. But you get the idea. So, for example, there's all the classic studies, for example, on HIV, screening for HIV, which is a relatively still a very low-incidence condition in most places. And so you don't want to be developing something that is going to be overcalling it or is going to miss it simply because you only see it in 1% of cases.

CLIAC MEMBER: Thanks.

CLIAC CHAIR: Excellent. We're slightly behind schedule, which is fine. This is a fantastic presentation and discussion so far. But I do want to move on to the public comments. We do have three public

comments. Two of them are written comments. One of them is from the National Society for Histotechnology. The other one is from Andrea Pincus. Both of them are written comments and will or are already available online. But we do have a verbal comment coming, again, from the College of American Pathologists, given by Dr. Diana Cardona. So let's-- Diana, are you on?

Public Comments

DR. DIANA CARDONA: Good afternoon. So once again, the CAP appreciates the opportunity to provide verbal comments to the CLIAC. As previously stated, the CAP is the world's largest organization of board-certified pathologists, leading provider of laboratory accreditation and proficiency testing programs, and continually strives to improve and advocate for excellence in the practice of pathology and laboratory medicine worldwide.

In regards to AI and machine learning, the CAP believes that training and use of artificial intelligence and machine learning algorithms introduces a fundamentally new kind of data analysis into the health care workflow that requires an appropriate regulatory framework. By virtue of their influence on pathologists and other physicians in selection of diagnoses and treatments, the outputs of these algorithms can critically impact patient care. The data patterns identified by these systems are not exact, and there is no perfect separation of classes or predictions. Thus, there are analogies with sensitivity, specificity, and predictive value of other complex tasks performed by clinical laboratories. However, in machine learning, the patterns and data are identified by software and often are not explicitly revealed. Biases or subtle errors may be incorporated inadvertently into machine learning systems, and these must be identified and mitigated prior to deployment.

Naturally-occurring variations in health care contexts, such as case mix changes, updated tests, or sample preparation or new therapies, may also change the input data profile and reduce the accuracy of a previously well-functioning machine learning system.
The CAP anticipates that in the near future, AI- and ML-based technologies will power highly useful applications in a broad range of medical settings, including some that are performance-critical, particularly these termed Machine Learning-enabled Device Software Function, MLDSF. For success and safe operation, the performance quality of these applications must be verified after installation and monitored over time.

Performance problems may occur if there are differences in details of local data in comparison with the use-- or with the data used to train the software or if the characteristics of local data drift over time. Updates to software affecting the machine learning components inherently redefine the relationship between the training and local data and require a practical and appropriate reverification of performance to ensure safe and effective operation. Hence, MLDSF are analogous to high-complexity diagnostic testing in requiring verification at installation and a robust quality control/quality assurance process. Because the particular-- or, sorry, because of the partial analogy of these new technologies with current diagnostic testing, the expected impact of these technologies on the practice of pathology and laboratory medicine, and the need to adhere to CLIA in the laboratory setting, the CAP has a keen interest in the regulatory approach for AI and ML technologies.

CAP members have extensive expertise in providing and directing laboratory services under CLIA regulations, which require compliance with requirements through a quality system approach for overall operations and administration of the clinical laboratory. This includes the verification and validation of any new or modified tests and devices. It's important to note that there are quality practices in the laboratory specified by CLIA that are separate from operational requirements defined by a manufacturer of a medical device or approved by the FDA. While CLIA regulations are not directly applicable to other medical specialties, they may inform thinking about performance quality goals in ways that strengthen current efforts to develop AI and ML regulations and improve the consistency of their application across medical specialties. As these tools support the decision making of providers, the role of pathologists and other specialties to interpret results must be defined.

We encourage the CLIAC to work with the FDA in drafting regulation to ensure harmonization and consistency across all requirements. The FDA proposed to regulate types of AI- and ML-based software as a medical device. Modifications include clinical and analytical performance improvements, changes in data inputs, and intended use of the software.

The details of these kinds of modifications and the requirements for local verification and reverification are critical and need to be better specified. Furthermore, data inputs to software as a medical device may be subject to variation in the real world. For example, laboratory test results can vary based on testing kit or instrument platform utilized and produced by various vendors, or microscope slides produced and stained by different histology laboratories or scanned with different devices. As such, an effective and equitable regulatory framework for machine learning and health care will-- one, define requirements based on risk and tailored to the likelihood and magnitude of possible harm from each machine learning application; two, will require best practices for system developers, including bias assessment and mitigation; three, will define appropriate best practices for verification of system performance at deployment sites, such as local laboratories; four, will define best practices for monitoring the performance of these AI/ML systems over time and mitigating performance problems that may develop; and five, will clearly assign responsibility for problems if and when they occur.

Many considerations must be addressed before regulations can be drafted. It must be determined, for example, if a software as a medical device will require explicit validation for use with test kits or scanning devices. For example, if a laboratory test is used as one of several inputs for an AI/ML predictive algorithm, if that test is changed for cost reasons to a similar test from a different vendor, would that change or invalidate the software or require local reverification? If the latter, what form of reverification would be acceptable? In a setting where multiple algorithms are deployed, to what extent do the requirements for validation of those algorithms lock in methodologies and workflows for the clinical data elements upon which they depend? This kind of lock-in has the potential to reduce the organizational agility that the FDA is hoping to promote with these regulatory changes. So can general purpose validation and performance monitoring practices be defined that identify and mitigate these kinds of problems? Should data input devices such as a whole slide imaging system and chemistry and hematology analyzers be held to reproducibility standards such as color reproduction, resolution, and absorption that keep them within some performance envelope that all Software as a Medical Device manufacturers can target?

Lastly, these systems must ensure excellent performance monitoring and maintenance. Given the inherent black box nature of the advanced mathematical approaches that underpin the Software as a Medical Device applications, these applications in question, and the potential for drift over time, there must be a robust quality control, quality assurance, and quality improvement process, including strict delta checks and a high frequency of mandatory result review prior to verification. Furthermore, any modification of inputs or the intended use, including software's prespecification concept, should be viewed as an entirely new product and in need of FDA approval. Once again, thank you for your time to discuss the CAP's concerns and recommendations, and we welcome the opportunity for further dialogue.

Committee Discussion

CLIAC CHAIR: Thank you for those thoughtful comments. So let's transition over to the committee discussion. We have just under a half an hour to do so. [CLIAC EXECUTIVE SECRETARY], are there any guiding questions that we can flash in front of the screen? Excellent. So, yeah, take a second, read them, and let's start the discussion. No brave soul yet? Yeah, [CLIAC CHAIR]?

CLIAC MEMBER: So given Alexis's presentation, and taking advantage of the comments just made from the College of American Pathologists, I think it's a reasonable statement that this discussion is a high-altitude one to provide guidance to how artificial intelligence and machine learning can be assessed by CLIAC and recommendations brought forward. We have 25 minutes for a deliverable from this conversation. And looking at the questions, on the one hand, should a workgroup be formed? I'll let the discussion develop. But I think we can take advantage of this time to articulate what CLIAC's deliverable

can and might be for bringing forward, rather than trying to answer questions, formulate the questions to our satisfaction.

CLIAC CHAIR: I think it's a great call. [CLIAC MEMBER]?

CLIAC MEMBER: Yeah, no, I second that exactly. I think it's way too involved a process to make it too specific at this point in what do we want to ask.

CLIAC CHAIR: OK. [CLIAC MEMBER]?

CLIAC MEMBER: I think there's so much. I think there is so much because it's here, right? We have it in the laboratory. It just depends on the extent to which different labs would apply it.
I mean, when I order an ova and parasite and send it to ARUP, they're using AI to help with that particular test. I have a wasp lab in my microbiology-- in my bacteriology section. And they have tools for that to interpret the culture to say, group B strep or not? It's all sort of assisted right now, and we are already using it. So that ship has sailed. I guess how much of it-- what do we need to do right now? I think it's such a complex question that I'm thinking, yes, a workgroup might be helpful to even start drafting the right question that we should be asking, not necessarily to put rules and regulation, but start thinking through, what do we need to do? How do we need to manage this? Alexis' presentation had me thinking about-- we had this conversation about bioinformaticians and the type of personal requirement we should be thinking of. She mentioned data scientists. Is that another group of people that, as we think about AI and some of the potential challenges, that we should be thinking about who, how, where would they fit into the personal of the clinical laboratories? So I'm almost tempted to say the workgroup is needed, but just to even draft the questions that we should be asking, not necessarily answer specific questions right now and make recommendations.

CLIAC CHAIR: So it seems like we're aligning towards one potential output. [CLIAC MEMBER], then [CLIAC MEMBER]?

CLIAC MEMBER: Thank you. I concur with what's been said so far and want to add that this is a tremendous change. And it brings new opportunities for us to look at laboratory testing in a different way and look where the potential for errors are and potential for harm to the patients. But I think our core principles of a quality management system are still in place and still apply in the AI environment.
So I think we have to look at what's available and what's going to become available in the light of what we know we have to do from what the principles of quality management tell us. So I'm in favor, too, of a workgroup to study this in greater depth. And I think it's going to not be a quick process for a workgroup, not something-- and may take several workgroups, maybe the first workgroup just to tease out what the questions are, and then other workgroups take over from there. Thank you.

CLIAC CHAIR: Yeah, it's a great point. And to kind of take a quick break-- I see, obviously, [CLIAC MEMBER], [CLIAC MEMBER], and [CLIAC MEMBER] and [CLIAC MEMBER] also have their hands up, but just to get something down from a draft recommendation because we're hearing the same thing from a few of you already. It sounds like everyone's aligning on the creation of a workgroup, right? So the recommendation could be creating a workgroup to explore AI/ML or the intersection between AI/ML-- sorry, the current and future intersection of AI and ML of pathology and laboratory medicine. And I think what everyone's been really saying is like, we're not going to answer the questions here. But our opportunity, say, in the next 20 minutes is to, what do we want this workgroup to potentially consider? And so under the column of things to discuss or include, I would propose a few of them. I'll just start rattling them off, even though I know, yeah, [CLIAC EXECUTIVE SECRETARY], I know you're trying to keep up. So to Alexis, one of her early slides-- even just aligning and what is the definition of AI/ML and the terminology around it in the context of pathology laboratory medicine? I think just identifying the touchpoints of AI/ML with pathology and lab medicine-- what are the current touchpoints and the future ones, crosswalking the regulations and standards and doing a crosswalk gap analysis of where AI/ML may touch and how well does it fit or not fit into the current regs, and maybe recommendations as well. So the outputs could be recommendations to the agency, maybe a best practice document for the pathology and laboratory medicine community, or just a list of resources for the community to use. So

let's have the discussion continue. Hopefully, we'll continue to flesh this out. I'm sure I missed a whole bunch of them. So, [CLIAC MEMBER], why don't you go next?
CLIAC MEMBER: So, yes, I think that in the same way that the FDA defined the complexity of laboratories, we could use that as a basis for talking about the complexity of the application because, as [CLIAC MEMBER] mentioned, it is being used now to augment choices. Usually, that's in reflexive test actions, and that's a rule-based algorithm, which is not as obscure and easy to bungle as some of the deep learning algorithms. So I think having some framework for saying, OK, these are low-complexity, these are higher-complexity, and then also being able-- and I think someone alluded to it-- is to make sure that where there may be a laboratory variation, that the sensitivity of the algorithm to that is understood. So, for example, red, blue, green settings on digital imaging-- is the algorithm sensitive to that, and making sure that those definitions come forward. And then, finally-- and I think, actually, [CLIAC MEMBER] may speak to this also-- the fact that data is not interoperable. So how do you make an algorithm that fits everywhere? So being able to test the robustness of the algorithm when it's using imported data, data from other sources, et cetera, and tying this into the SHIELD project of the FDA, I think, is very important. OK. I'll put my hand down now.

CLIAC CHAIR: OK, yeah. Before we go on to [CLIAC MEMBER]-- so in terms of a topic of the workgroup to potentially discuss, I heard interoperability. Is there a word or two for the first--

CLIAC MEMBER: Yes, I think we can talk about the complexity of the application--

CLIAC CHAIR: Complexity.

CLIAC MEMBER: The complexity of the application, the interoperability, and the sensitivity to normal lab error, what we might consider acceptable within the laboratory, but is it acceptable to the routine? So that would be a sensitivity analysis in mathematical terms-- so complexity, interoperability, and sensitivity analysis of input variables.

CLIAC CHAIR: Excellent. [CLIAC MEMBER]?

CLIAC MEMBER: Yeah, I think this speaks to maybe the first point about the challenges of regulations and kind of oversight of AI applications, et cetera. So now I come from the angle of genomics and the variants of uncertain significance, for example, that are constantly evolving as more information becomes available, as variant classification changes because of clinical information and growing data sets in this space. And the complexity of that, from an AI perspective, it certainly can help with the interpretation, I think, as these data become available. But that seems a lot more complex to me than-- and, [CLIAC MEMBER], I don't mean to belittle anything you've said here, but with the determining what's growing in a culture, right? That's a very different, more concrete concept. So I see a challenge, fundamentally, in defining these different areas. And I think I heard before you have different categories. How does this wide variety of different possibilities-- how is that accounted for in a regulatory-- from a regulatory perspective?

CLIAC CHAIR: Yeah, I think it's a good point. And I saw [CLIAC EXECUTIVE SECRETARY] typing the continuous verification, validation. And I do think that partially covers what you're mentioning, [CLIAC MEMBER]. Correct me if I'm wrong. And the way it's written right now makes it feel like that's a QA process or quality management process. But also, what I hear you're saying is, how is the systems enabled? Is it possible to be enabled with evolving inputs? It's a VUS today, but it may not be a VUS tomorrow. But you trained it on today-- you trained it today. How do you manage evolving inputs?

CLIAC MEMBER: It adds another dimension, almost, to the process.

CLIAC CHAIR: Yeah, the dimension of time, right? Yeah. [CLIAC MEMBER]? Can you hear me?

CLIAC MEMBER: Yeah. So I guess one of the things that I struggle with is that this is so different from what we normally deal with in laboratory medicine, where, in laboratory medicine, we have a testing system that is relatively self-contained to the lab. The rest of the hospital could go with a different EHR

vendor, and that doesn't necessarily impact the output of the testing. But in terms of AI and ML, we actually-- it's hard to think of a regulatory model because it's a moving target. We can think about ways that it can be applied today. But tomorrow, it could be used in an entirely different way that we haven't thought of and we don't have the good guardrails for. And so even-- there's literature that says even at the same institution, a model can degrade because a hospital changed EHR vendors because the format of the data is now different and appears in different fields than what the model was expecting. And so how do you approach that from a purely CLIA-centric model, which is that the laboratory is self-contained and isn't impacted by the rest of the hospital? There are decisions that will be made that is outside of the laboratory but yet can impact what the AI and ML use. And also, [CLIAC MEMBER] also alluded to that we have a huge future role to play in the development of these tools because laboratory data is going to be part of the data set that is applied to these models. And yet our data is not harmonized. And oftentimes, it's incomplete. And so the models will try their best to do what they can with the data. But the fact that we don't have methodology or instrument and test kit, that means that the biases that are inherent in those different assays is not visible to the models and isn't necessarily going to be informed by just the reference range. And so I think that the struggle is we are trying to treat AI and ML as self-contained, like we've always done, with laboratory instrumentation. But the fact of it is this is much bigger than lab. And so I think it needs a more comprehensive approach than just saying, we're going to regulate this as a instrument.

CLIAC CHAIR: So just to reflect back some terms that maybe we could document on the workgroup on the topic ideas, I was hearing something along the lines of data quality metrics. How do we define what is good in data, what's good input? I heard also interoperability there a little bit with the EMRs and the new inputs and new fields located in different places. I think that also ties in together with, again, the concept of, how often do you have to revalidate? What are the triggers for revalidation? Maybe the frequency-- how do you identify shift and drift in these models if they occur? And someone said it before. Sorry, [CLIAC MEMBER], it wasn't you. You didn't say it. But I wanted to mention and make sure it's captured-- is the personnel, right? We're introducing a whole new type of person to the laboratory. And obviously, there could be personnel requirements. [CLIAC MEMBER]? [CLIAC MEMBER]: Yeah, no, I think we had a little bit of this discussion in our last workgroup. And Alex had done a presentation for us then, too. So it was good to hear that all again. And I think one of the things that I'm concerned about, given the FDA just saying, oh, we're going to make it easier to move this stuff along is-- and I'm the one who put up the stuff about the continuous verification validation by the laboratory of new systems. And one of the issues we had previously was some of the data that's being interpreted for, say, NGS in pathology is coming back from sites that we don't know what they're using for their validation, verification, and if it was good. And so that's why Alex actually gave us that first presentation. So I am kind of concerned about-- and I would say that this workgroup would have to work with the FDA to understand how that new program was working, to facilitate the vendors such that the laboratories aren't really knee-deep in data they can't get out from under. So I think that's one of my big concerns.

CLIAC CHAIR: Yeah, see, that's a good point because this is really going to span across the agencies. I do believe—[CLIAC EXECUTIVE SECRETARY], you can keep me honest here-- I do believe in these workgroups, we still have representation from the three agencies on them?

CLIAC EXECUTIVE SECRETARY: Yes. We have ex-officio representation on all of our workgroups, and we have subject matter expertise representation through the three agencies on all of the workgroups, too.

CLIAC CHAIR: Great. [CLIAC MEMBER]?

CLIAC MEMBER: Thank you. I have three related recommendations, two of which dovetail with what [CLIAC MEMBER] and [CLIAC MEMBER] were just saying-- number one, provenance of the data input. We take as a given that there's data input, there's data output, but I think the variants of uncertain significance is an example of-- I would recommend that the workgroup have a sense of how to provide guidance for tracking the provenance of the data inputs. Number two, and reminiscent of our discussion this morning about the role of the laboratory director, is for the workgroup to provide guidance on where the responsibility for the AI/ML ends and where the responsibility for the medical practitioner begins. In other words-- and that's why I link provenance and responsibility together because AI is a tool. The

practice of medicine is by a licensed provider. And then, number three, drawing upon what Alexis was giving us from other professions and industries, is for the workgroup to consider learning from other medical disciplines-- and I immediately think of imaging-- but also looking across the way at how AI is deployed on a broader sense and backtest what we think might be reasonable recommendations for pathology and laboratory medicine against the failure points that have been identified elsewhere in the industry, because it's a way of pressure testing recommendations that we might think are great but in fact have failure points.

CLIAC CHAIR: Yeah. And to your point, not even necessarily restricting us to the medical industry of AI--

[CLIAC MEMBER]: Exactly.

CLIAC CHAIR: We'll be learning from other industries.

[CLIAC MEMBER]: Electrical grid, take your pick. Where are the failure points, and how can we pressure test our recommendations against pressure points-- failure points that have been identified in other industries?

CLIAC CHAIR: Yeah. So we have just under 10 minutes left. I love-- I mean, it sounds like we have a strong recommendation. We're really fleshing out topics that this group could consider. I do want to just say that if we have a-- if anyone has another recommendation in addition to the creation of this workgroup, please bring it forward. Otherwise, let's continue the conversation. [FDA EX OFFICIO], you're up.

FDA EX OFFICIO: Yeah, I actually have a question about what we're talking about here. So, obviously, AI/ML is an important topic and something that we're really invested in at FDA. And obviously, laboratories are going to have to need to grapple with it. So I think it's an important topic to discuss. Some of these bullets, though, appear to be related how to develop Software as a Medical Device and not necessarily related to how a laboratory may use an AI-enabled Software as a Medical Device. And so I'm not sure it's within the purview of this committee to talk about development of a software AI/ML device. So I encourage us to maybe prune out some of these bullets and see if we can focus this working group on things related to the questions around, is use of AI/ML-type tools under CLIA at all? If it is, in what ways, or what types of them and things like that-- and not around data inputs, data quality metrics, and things like that. So that's what I just wanted to throw out there.

CLIAC CHAIR: And we appreciate those comments. I think scoping this is the right tool-- or the right move. And I would propose, and consistent with what you were just saying, is that we do scope this to the implementation and deployment of AI in the pathology and laboratory medicine setting at the exclusion of developing AI algorithms, to your point, because I do feel like that will likely exist outside-- likely exist outside, and certainly could exist inside and, if we-- or if this group felt the development was so important, to maybe consider an additional workgroup if that's appropriate. But I agree with your scope--

FDA EX OFFICIO: I think it's important. I just question whether it's under CLIA to develop some--

CLIAC CHAIR: I agree. Yeah. [CLIAC MEMBER], I can't tell if your hand's back up or always up.

CLIAC MEMBER: Oh, I'm taking it down, sorry.

CLIAC CHAIR: OK. Yeah, no worries. Just wanted to make sure. I didn't want to just skip you. [CLIAC MEMBER], you're up.

CLIAC MEMBER: Yes, I was-- so the last point is very interesting because while we may not necessarily focus on development, part of the things we do in the lab is verifying that a test or a software performs the way it's supposed to, right? And I think a lot of this could be considered under sort of your verification plan, what kind of things you should be thinking about. And I was just thinking about the example that Alexis gave with the turtles that were labeled as rifle. I thought that was an insane example but perfect

when you think about some of the things that, as you think about your validation and your verification, what sort of question you should be asking when it comes to AI for your laboratory, right? So maybe not about the development, but are we going to have the same-- is there anything beyond what's already part of our clear processes or validating or verifying a FDA-cleared test that we should be thinking of AI? And I can think of health equity issues, like, how is this developed, and is it right for my patient population? Maybe those are things that maybe you don't think about when you think of a PCR test. But if there is an AI that was trained to interpret things a specific way, is part of the data that the manufacturer would give you include information on the patient population, and was it diverse enough? And all of these things, I think, might be a way to also frame what the working group should be thinking about in terms of these methodologies.

CLIAC CHAIR: Yeah, I'm trying to think of the way of reflecting that back in the context that's clearly CLIA, and not necessarily the development. But to your point, it's important to know if the algorithm or the AI/ML tool was validated on patient demographics that represent the demographics in which you're going to deploy the tool.

CLIAC MEMBER: Yeah.

CLIAC CHAIR: And so that, I think, is very much a lab question, right? I'm going to bring this test in. Is it applicable to my patient population here?

CLIAC MEMBER: Yeah. Yep. And I don't know how the FDA-- because, yeah, this is hopefully things that are already FDA-approved. But like I said, we're using some of these. It's all assisted. So it's not, like, self-- in a sense.

CLIAC CHAIR: Right.

CLIAC MEMBER: But you can imagine a future where that would be. And so what sort of information would be in the package insert to guide us? We should start thinking about these as part of this workgroup.

CLIAC CHAIR: Yeah. Yeah, I'm trying to think of the bullet point-- patient population appropriateness, both in the training or the development and the deployment, and, again, not giving guidance on how to develop, but understanding how it was developed so you can deploy it in the right population. So we-- oh, we're actually just about at time. So we have one recommendation with a lot of fleshing out, which is great. Obviously, if this recommendation gets approved, we'll leave it to the group who gets formed to sort out which one of these they'll be addressing. But I will put forward the motion of this recommendation, which is CLIAC recommends the creation of a workgroup to explore the current and future intersection between artificial intelligence, machine learning, and the clinical laboratory.
[CLIAC MEMBER], you have a question?

CLIAC MEMBER: Yes. You haven't asked for a motion yet. So I'll just ask if this is the recommendation or, given the comment from [FDA EX OFFICIO], whether this recommendation should be honed a little bit to define scope in the context of regulatory framework.

CLIAC CHAIR: Yeah, I agree.

CLIAC MEMBER: I mean, it's implicit, but I was thinking make it explicit.

CLIAC CHAIR: I agree. So maybe add to the end of this "pertaining to the deployment of tools in the clinical laboratory." We can wordsmith it afterwards. But again—

CLIAC MEMBER: You can wordsmith it. Just make sure it aligns with the scope of CLIAC.

CLIAC CHAIR: I appreciate the scoping element being explicit.

CLIAC MEMBER: Then I'll happily motion when you ask for a motion.

CLIAC CHAIR: Well, no one else has a hand off. So I will ask for a motion.

CLIAC MEMBER: So moved.

CLIAC CHAIR: Any seconds?

CLIAC MEMBER: Second.

CLIAC CHAIR: Second. Thank you. Any discussion before putting up to a vote? OK. All those in favor, please raise your virtual hand. I'm not counting, but it looks like we have a majority. All those against? Now everyone lower their hand, and then we can say anyone against. Oh.

CLIAC MEMBER: Can you all hear me?

CLIAC CHAIR: Yes.

CLIAC MEMBER: I just want to say-- I was trying to find my hand. I'm for it. Count me as a vote for it.

CLIAC CHAIR: OK. I didn't know if there was a follow-up. Yeah, perfect. Thank you. So, [CLIAC EXECUTIVE SECRETARY] am I right? It passes. Yeah. Any other closing questions or comments? Otherwise, we'll leave for a break before returning for our last session for the day. OK. Hearing none, let's take a 30-minute break. We will return at 4:15 Eastern. Again, please make sure you come back on time so we can continue for our last topic. Thank you very much.

The Use of Clinical Standards to Improve Laboratory Quality

Introduction to Topic
Víctor R. De Jesús, PhD

CLIAC CHAIR: OK. Perfect. OK. Welcome back, everyone. So our final topic for the day is the use of clinical standards to improve laboratory quality. We'll start with an introduction by Dr. Victor De Jesus, followed by a presentation on "CDC's Clinical Standardization Programs, Ensuring the Accuracy and Reliability of Chronic Disease Biomarker Tests" by Dr. Hubert Vesper, and a presentation on "Clinical and Laboratory Standards Institute, CLSI, Consensus Standards to Support Operational Excellence and Regulatory Compliance," by Dr. Barb Jones. As always, after the presentations, we'll have time for public comments and committee discussion. So with that, Victor, why don't you kick us off?

DR. VICTOR DE JESUS: Thank you, Jordan. Good afternoon, members of CLIAC. I'm Victor De Jesus, and I'm the acting director of the Division of Laboratory Systems at CDC. It is my pleasure to introduce to you the next session on the use of clinical standards to improve laboratory quality. Next slide, please.

So while the CLIA regulations do not specifically address the use of standards, subpart K, which is quality system for nonwaste testing, does suggest that there is a role for clinical standardization programs and consensus standards to help laboratory professionals strive for high-quality test systems. In regulation cite 493.1230, the emphasized language on the slide suggests that laboratories could use standardization programs to help evaluate and correct identified problems. Additionally, the use of consensus standards, such as those that the Clinical and Laboratory Standards Institute develops and promulgates, can assist laboratories in the establishment and verification of performance specifications, as required in regulation cite 493.1253. Today, you'll hear from our speakers on how clinical standardization programs and consensus standards can support laboratory quality within the context of CLIA regulations. Next slide, please.

First Dr. Hubert Vesper is the director of the Clinical Standardization Programs at the CDC's National Center for Environmental Health. He leads CDC's Clinical Lab Standardization Programs to improve the diagnosis, treatment, and prevention of selected chronic diseases, and oversees and represents specific biomonitoring programs to assess human exposure to environmental chemicals, as well as their potential impact on human health. He is also cochair of the steering committee of the Partnership for Accuracy in Tests for Hormones, a member of the steering committee for the National Glycohemoglobin Standardization Program, as well as an adjunct faculty member in the Nutrition and Health Sciences program at Emory University here in Atlanta. Next slide.

Our second presentation will be delivered by Dr. Barb Jones. She was appointed as Chief Executive Officer of CLSI in May of 2022. She is the third CEO in CLSI's 54-year history. Dr. Jones's experiences include operations leadership, laboratory management, pharmaceutical and quality standards development, regulatory policy, and business development at both the national and international levels. Before her role as CLSI's CEO, Dr. Jones was senior vice president for scientific operations and regulatory affairs at Vyant Bio in San Diego, California. Next slide, please.

As you listen to our two presentations, we ask the CLIA members to consider these questions during the discussion portion of this session. First, clinical standardization programs improve the accuracy and reliability of laboratory tests for key chronic disease biomarkers. How can the CLIA program agencies promote participation in these programs by laboratories and test manufacturers to improve analytical performance? And secondly, currently the FDA provides a list of recognized consensus standards related to medical devices. What are other ways that the CLIA program agencies and professional organizations can promote the use of standardization programs and standards? I want to thank you again for the opportunity to introduce the session. And, Jordan, back to you.

CLIAC CHAIR: Excellent. Thank you for the intro. Yeah, let's move right on to Dr. Hubert Vesper's presentation.

CDC’s Clinical Standardization Programs: Ensuring the Accuracy and Reliability of Chronic Disease Biomarker Tests
Hubert W. Vesper, PhD

DR. HUBERT VESPER: Well, thank you, Victor, for the introduction. And thank you for giving me the possibility to talk about our clinical standardization programs here at CDC. Next slide.

The reason why we develop these programs and maintain these programs is because we have been approached by the research, clinical, and public health communities about concerns and problems with certain biomarkers. And some of these concerns have shown here, in this slide. For example, the Institute of Medicine stated that a single individual might be deemed deficient or sufficient for vitamin D depending on the laboratory that the blood test is being done. Similarly, the Endocrine Society raised concerns about the quality of testosterone in estradiol tests because they had problems effectively implementing clinical practice guidelines in the public health community. Next slide.

To give you an idea what this problem-- how this problem looks like in the laboratory, I'm showing you here some data from the College of American Pathologists' accuracy-based vitamin D survey. In this survey, there was a sample with a true reference value of 36.7, which would indicate that a patient with value would be sufficient for vitamin D based on the current society guidelines. Now, all of the lowest values reported for all of the peer groups in the survey indicate or would classify that particular sample as being insufficient for vitamin D. And even two of the assays, assays 1 and 4, that the median is below this cutoff value, are suggesting that a major part of laboratories in this peer group would classify this sample as vitamin D-insufficient. Next slide.

This is a study we conducted a few years ago, where we sent out samples to laboratories and asked them to measure vitamin D-- estradiol. They reported the results back. We compared the results to the reference value and calculated the percent bias of that reported value to the reference. And what you see

here in the box plots is the distribution of measurement bias we observed and results reported back to us for individual samples. Now, the European Menopause and Andropause Society recommends a cutoff value of 14 picograms per mil to confirm the diagnosis of premature ovarian failure. In our study, we had one sample with a reference value of 14.1 picograms per mil. And for that sample, we received results back ranging anywhere between 9.4 and 64.8 picograms per mil. So with such a variability in measurements, it's really hard to implement clinical practice guidelines. Next slide.

This slide shows data from a recent study we conducted where we sent 40 samples to different laboratories, asked them to measure these samples, report results back-- again, we calculated a bias to the reference. And each box now represents the distribution of bias observed in one participant. And the majority of assays for free thyroxine underestimate the target value, meaning they are measuring lower, with a bias of, in average, up to 40%, 45% in some essays. But on the other hand, other assays are fairly close to the target value, or to the 0 bias, which is where we want essays to be. The good message about these data is that this problem can easily be fixed by recalibrating the assays. And this is what we are currently working on with manufacturers. I'd like to point out that the data I showed you-- I'll show you in this slide-- in the previous slides are all obtained from FDA-cleared essays operated in CLIA-certified laboratories. Next slide.

The biomarkers we address in our program are actually high-volume assays. So on the left side, the table shows the top 20 tests based on Medicare Part B payments in 2016. And, for example, vitamin D is on number 5 of the 20 most-- 20 top tests based on reimbursement. And also, we did see over the years quite an exponential increase in vitamin D testing. That increase kind of plateaued a little bit. But still, vitamin D is one of the high-volume tests and also, cost-wise, very important. Next slide.

So in our program, the aim is to improve the diagnosis, treatment, and prevention of diseases by standardizing CLIA laboratory measurements. And we do this by creating measurement results that are traceable to one accuracy basis and, therefore, are comparable across methods, location, and over time. And I want to point out that our focus is on measurement results. That means laboratories can use whichever technology they deem suitable for their purpose. What we care about is the accuracy and reliability of the result that is obtained with that particular assay. Also, standardization is often used in different ways and different meanings. When we talk about a standardized laboratory test, this is a test that has demonstrated through a thorough independent assessment that the analytical performance meets clinical needs. Also, I want to point out standardization is a continuous, ongoing process because assays and laboratory performance can change over time. So we need to continuously monitor the analytic performance. And I'm going to talk a little bit more about it in the upcoming slides. Next slide.

From a technical point of view, the way we conduct standardization is basically a three-step process. In the first step, we establish a point of reference, or a reference system. We develop analytical reference methods and reference materials. And we then use these methods and materials in the second step to assess and improve the analytical performance of assays. And we typically do this at the manufacturer level or laboratory level for lab-developed tests. And then, finally, we verify end user test performance to make sure that whatever we achieve at the manufacturer level really reaches patient care. And we do this through our own CDC monitoring programs and through collaborations with accuracy-based proficiency testing programs. Next slide.

This slide just provides you some information about the reference methods that are available-- are operating at CDC on a daily basis. We have 10 different analytes covered right now. And I want to point out that for some of these analytes, we are the only laboratory in the United States providing a point of reference. So if you want to know whether we're going to assess the accuracy of your glucose device, we are the only laboratory right now in the United States that can provide these kind of measurements. Our laboratory operates in compliance with international standards. So we are certified or accredited for ISO 15195, calibration laboratories, which is the highest level of quality that can be accredited. And we develop additional new reference methods for PDH, [INAUDIBLE], testosterone, and, of course, work with our international partners to increase laboratory capacity for reference measurements. Next slide.

The program and the data we provide in our program are very unique and cannot be obtained with other programs. So, for example, we provide 40 single-donor serum samples to our participants. By having 40 samples, we can actually assess the measurement performance over the whole analytical measurement range. And that allows us to distinguish, for example, problems related to calibration and problems related to nonspecificity and other issues with DSA. Also, by using individual single-donor serum samples that are not modified or altered in any way, we obtain information that is as close as possible to a patient care setting. We ask for replicate measurements to get information on imprecision. And when we do a performance assessment or certification, we look at data collected over four consecutive quarters and then pull these data to make our assessment. So we can also detect trends or changes in measurement performance over time. And the samples we provide, of course, are customized to our participants. We would not send samples to them that are outside the measurement range. And we take special care of data entry errors or clerical errors. So when we talk about [INAUDIBLE] performance, it's really the analytic performance and not the performance of the person who enters the data in the matrix. Next slide.

The reports we provide to our participants are multipage reports. And, for example, for the bias assessment, we follow CLSI document EP09. And we provide graphs like the ones that you see over here in our reports. And next.

So by looking at the graphs, we can then identify whether an assay has a good calibration. In this case, the samples or the bias of the samples is distributed by the zero bias line nicely, with a mean bias of 0.3%. So we can assume that this assay is very well calibrated. Next. Next.

But if we look at the lower concentration range, we do see a much higher scatter. And this means that this assay is well calibrated but does have some problems with interfering compounds. And so this is the type of information we provide to our participants so they can actually act upon and improve their assay accordingly. It also points out that you have to have at least 40 samples to properly assess the analytic performance because it can be different across the concentration range. Next slide.
The information we provide to our participants, we also provide them in a summarized, condensed form on our public CDC website. Next.

So for this particular vitamin D assay, the mean bias is 3.3%, which is within the allowable bias of plus/minus 5%. And with that, we consider this assay sufficiently well calibrated and list this assay on our website as certified. So if you go to our website and see a certified assay-- this is the calibration bias-- this means that the calibration bias is within criteria. Next.

You also look at individual samples and whether they meet the required bias. So in this particular example, 78% of the samples have a bias that is-- individual sample bias that is within plus/minus 5%. And that information is also provided on our website. So people can see how reliable the assay is on an individual [INAUDIBLE] basis. Next slide.

These three graphs show you data we have collected in our programs over a period of 10 to 16 years. And each dot represents the mean of one sample measuring four replicates of certified and noncertified participants. And what we are aiming for is something that looks like total cholesterol, where we have a measurement bias tightly-- the distribution tightly arranged around the zero-bias line across the whole concentration range. But if you look at vitamin D, we do see quite some scatter. The data are still somewhat normal distributed around the zero-bias line, but a much higher scatter. And if you then look at testosterone, again, a different picture-- we have some scatter around the zero-bias line at a higher concentration-- fairly tight, but a very wide scatter at the low concentrations typically observed in women and children. And the point I want to make with this slide is that each analyte is different, which means we need to customize our programs to address the specific problems we see with these analytes. And, of course, we need to collect sufficient data to customize our programs accordingly. Next program-- next slide.

I mentioned that standardization is an ongoing process. And we constantly need to monitor the performance. And that's what we are doing here on the left slide. These are data from our LSP program, where we have several laboratories using the same assay for total cholesterol. And we monitor the

performance of all these cholesterol measurements over time, which actually is quite good and consistent around the zero-bias line. But then we detected a trend. And at some point, we realized if that trend continues, the bias becomes so big that it may affect clinical decision making. So we contacted the manufacturer, informed them about our observations. They did some internal investigations and fixed the problem. So the measurement bias is back to where it's supposed to be. And this is one of the key features of our program is really to detect trends, address them before they become a problem. On the right side, we have data from our CDC Hormone Sensitization Program for testosterone. These are data collected over seven quarters from one participant. And at the beginning, the participant was performing reasonably well. All the dots are within the red limits box. But then the bias was very high and very scattery. It turns out upon further investigation that there was an operator problem. The operator was trained. Accordingly, performance went back to normal. But what we are seeing now is a trend that looks like a calibration bias. So the laboratory needs to look into the preparation of calibrators and how they can improve the situation there. So on the right side, the pattern that you see is something that we sometimes see with lab-developed tests. Overall, in both cases, our program was able to detect the problem that the laboratory or manufacture was not able to detect with their own QA system. Because we provided them with the information, they were able to fix the problem and optimize and improve their QA system. Next slide.

Now, our program is voluntary. So people don't have to participate in it. But those who participate really make an extra effort to improve the quality of their testing. And it also shows in external quality PT programs. So the left side, we have data from the College of American Pathologists, their vitamin D survey. And those assays that are certified by us mostly show very nice analytic performance compared to those that are not certified. On the right side, these are data we created together with the New York State Department of Health, their proficiency testing program a few years ago. At that time, only one assay was standardized for testosterone. And indeed, that assay shows the highest accuracy and the lowest scattering measurement bias as compared to those that are not certified. What these slides also tell us is that certified and noncertified tests, or standardized and nonstandardized tests are used in patient care without distinction. And we are currently working with stakeholders to educate them, make them aware of the standardization and potential problems unstandardized assays may have. Next slide. Next one.

So most of the data and information are provided to you today deals with the testing performed in patient care. However, in order to make this evidence-based decision-making process work, we also need to look at data generated in research. Next?

And that's what we basically do in our programs. We work with PIs of large clinical trials and epidemiological studies, make sure that the measurements they perform in their studies are standardized. Next?

We then work with the Endocrine Society or other professional organizations in assisting them with developing clinical practice guidelines and making sure that the cutoff values and decision points that they mention in their clinical guidelines are based on standardized tests. So physicians and health care providers dealing with patient care data can reliably compare the patient result with the result mentioned in clinical practice guidelines. Next.

And we, of course, work with stakeholders, such as payers, to inform them about those kind of guidelines in closed circle kind of standardization that we have in place for certain analytes. Next slide.

And with that, I want to reiterate that our programs help manufacturers and laboratories with improving and maintaining the analytic performance and, ultimately, to improve patient care. Our laboratories comply with international standards. And I also want to point out that in many cases, we have situations where just recalibrating an assay is not sufficient. We need to address other analytical performance parameters as well. And that's what we are doing with our programs. The programs that we-- the information that we provide is complimentary to and helpful. So what we try to do in our-- helpful to manufacturers and laboratories. What we try to do, really, is to provide our program participants-- with information they can act upon. So to us, it's not enough to just say you are within or outside criteria. We

want to provide information to indicate whether they need to improve calibration or other performance parameters. And lastly, very important, our program is voluntary. Not everybody participates in our program. And as a result, we have standardized nonstandardized tests currently used in patient care, which can create some confusion with some of the people or laboratories out there. We work with stakeholders to educate the laboratory community, but also researchers and physicians about the importance of standardization. And that's, in a nutshell, what we are doing in our program. If you want to know more, feel free to send me an email or visit our website. Thank you.

CLIAC CHAIR: Excellent. Thank you so much. What I think we're going to probably do for this session is let's go through all the presentations, and then we'll defer all the questions to the discussion period. So with that, why don't we move on to the next one, Dr. Barb Jones?

Clinical and Laboratory Standards Institute (CLSI): Consensus Standards to Support Operational Excellence and Regulatory Compliance
Barb Jones, PhD

DR. BARB JONES: Hi. Thank you all for allowing me to come and speak here. I see that you left the most scintillating subject for the last. But believe it or not, I think it is very exciting and just-- Dr. Laser, I see you on my screen. Can you hear me OK and everything's fine? Perfect. OK. Wonderful. So what I'd like to do in this presentation is I'd like to introduce you a little bit to CLSI, what CLSI does. But I have some objectives here. It's not just to tell you about CLSI. I'd like for you to walk away understanding the importance of using accredited standards development organizations for standards, why those guidelines are set apart, and why it's important to recognize that SDOs provide guidance that is very robust.
And finally, I'd like to be able to give you some actionable recommendations, some things that I think that CLIAC could implement or recommend that will dramatically improve laboratory excellence in CLIA labs.
So-- excuse me just one second. OK. So first of all, before I get started, I want to just take one second to explain the difference between CLIA standards and CLSI standards as I'm discussing them because I think that's an important distinction.

CLIA, you hear a lot of discussion about standards. And then I'm going to talk about standards. They're very different things. So here you see the CLIA LDT standard, something that's at front of mind for all of us. And as you look at that, you'll see that it's a very small number of words. To the side, you see the relevant CLSI standards. This is just some of the standards relevant to this particular CLIA standard. So there are over 700 pages of guidance that are the CLSI standards for this. So I'm going to go through this presentation referring to CLIA standards as "regulations" to reduce that confusion.

So let's talk about the CLSI organization. CLSI, as you know-- many of you know-- is a nongovernmental and neutral, not-for-profit organization, and we develop laboratory standards worldwide. CLSI has a role in the diagnostics ecosystem that stretches back well before CLIA, in fact. The act itself was enacted two months after the birth of CLSI. And then, 20 years later, what we understand to be CLIA, the amendments were promulgated. So CLIA-- CLSI has been around a very long time. And it was created by 36 member organizations-- or 36 organizations, including some who are around the table right now, definitely some who are likely in the audience. But the very idea for the conception for CLSI was as an advisory group for the improvement of standards in clinical laboratories and to serve as a mechanism to achieve consensus.
And CLSI has held to that mission all of these years, 56 years now. And we continue to do so.
We've been accredited as a Standards Development Organization since 1977. And I will hopefully convince you shortly why it is so important to be an SDO.

So as an accredited Standards Development Organization, CLSI has to follow and is accredited to a number of factors, a number of policies and procedures and standards, really-- it's a standard that we're set to-- including things like openness and balance, which you might see other guidance provide, and coordination and harmonization, but indeed, things like consensus vote, appeals, public comment, those are things that set Standards Development Organization apart and make it very important to consider that as you go forward in terms of use of standards as a federal agency.

Importantly-- I put this in there for you to read. I won't read it all to you. But some important things that I'd like to point out is that we are globally recognized. We're a global organization. We have over 300 products. But more importantly, we are recognized by laboratories and government and accreditors as that harmonizing thread that goes through all of these different organizations. And indeed, we include all of those voices in the development of our standards. Our standards are used around the globe.
And because of that, we have to be sure that our standards meet a varied level of complexity in terms of laboratory operations, industry operations, and language. So we take particular care to be accessible and available.

Our global consensus-based standards bring together constituencies that are incredibly important to this ecosystem-- professions, which includes hospitals, research, college and university pharmacy, many of whom are represented on CLIAC; government-- so not just regulatory bodies, but also those bodies that, while don't regulate, do work to improve laboratory excellence; and, finally, industry. This is particularly important-- this triad is particularly important to us because it allows us to be sure that all the voices that are included allow for harmonization and the needs that really affect each other. So if industry is producing a diagnostic and is able to use one of our standards, and then someone who's working in a laboratory is also able to use one of our standards, this is an important harmonization. And we take that very seriously. We include the voices of our constituencies through our members and subject matter experts in document development, governance of our organization, and public comment. So there are many ways in which the voices of the people who really matter in this are heard. And indeed, we have over 24,000 people who have access to membership benefits through their organizations. At any given time, we have between 1,500 and 2,500 of the world's experts in laboratory medicine developing guidance through CLSI.

So how we work is important. I won't spend much time on this, but I will tell you that for 56 years, CLSI staff has supported the world's experts in laboratory medicine for the development of our standards, the revision of our standards and products, for the governance of our organization, and particularly, and very importantly, through the consensus council, through the oversight of our consensus process.

Our consensus process is indeed rigorous. It is meant to be rigorous. Standards development is not meant to be something that happens very quickly or knee-jerk. It is meant to be arduously put through a wringer. And indeed, our consensus process does just that, sometimes to the frustration of our volunteers who give generously of their time and expertise and would like to have the standard come out.
But we do make sure-- a couple of really important points that I want to make sure are noted here is that we vet all of those who are recruited for the development of the documents. So it truly is the world's experts contributing to these documents. And when I say documents, our standards are more than that. We have many ways to put our standards forward, and we utilize these subject matter experts in all kinds of ways. But we also have, importantly, periods of time where there is voting, and there is public comment. And both of those are incredibly important for the development of a harmonized consensus standard. They're part of a consensus that absolutely cannot be hurried.
And then, importantly, not listed here, we do have an appeals process. So the public and our members have a way of continuing to come back to us with concerns about any standards or any part of our standards.

So we have 11 expert panels, through which, as I keep saying, the world's experts-- and truly it is so-- are able to give generously of their expertise. And through these expert panels, we have the development and maintenance of over 300 standards in areas that cover the breadth of the laboratory.
And indeed, as you can see from this-- this is an illustration-- I love this illustration-- that talks about the direct effect of our standards on particular areas within the laboratory or diagnostics ecosystem. So you'll see that 57 of our laboratories will go to clinical chemistry, directly utilized by clinical chemistry. 132 are directly utilized by IVD development, 28 by medical office practitioners, et cetera, and veterinary medicine and emergency response.

So we cover the breadth of everything that you can think of that CLIA covers, we pretty much cover. So I'm very proud of what we've been able to achieve over 56 years. I have the great honor to be able to be

the person who speaks about this. Importantly, for CLIA specifically, we support CLIA through Accreditation Crosswalk. So accreditors have worked with us to provide crosswalks that look at accreditation criteria and crosswalk that over to CLSI documents, where guidance can be found. And indeed, the quality system essentials that CLSI has promulgated speak directly to the CLIA quality regulations. In fact, there are over 2,800 pages of guidance, believe it or not, on quality to at parties-- talk about at parties.

So federal agency use of standards-- now, this is my goal, to get you to understand a little bit about what the options are around federal agency use of consensus standards and how agencies such as FDA have used consensus standards in their programs. Indeed, it is a federal law. The National Technology Transfer and Advancement Act mandates that all federal agencies use technical standards developed and adopted by voluntary consensus standards when available and appropriate. And the Office of Management and Budget put together Circular A19, which further discusses details around how those voluntary consensus standards can and should be used by things such as defining the standard or technical standards-- and you can see through this. I picked out a few of them. The definition is longer than this. I obviously picked out the ones that are appropriate for CLSI, but there are others-- and also considerations for standard selection, which includes the use of standards that are already in use by federal agencies for harmonization and to cut down on confusion.

So quickly, there are two major ways that federal agencies use consensus standards. The first incorporation by reference is very binding. Indeed, it has the force and effect of law behind it. And the rule change process has to be followed. So if an agency chooses to incorporate by reference, meaning this standard, start to finish, is now part of regulation, part of law, if they choose to do that and the standard changes, they are forced to change the rule. So it's difficult to convince a federal agency that they would want to incorporate by reference, but they can do something else-- and FDA does this-- which is recognize the standard. Through the recognition of standards, the use of the standard is voluntary. The agency has the discretion to define the process, the procedure, and the requirements. They can be partially recognized, which is incredibly important. They are not legally enforceable. Revocation of the recognition doesn't require a lengthy rule change. It's something that they can just simply say, hey, we revoke this recognition. And the recognition can be easily modified as standards are revised, which our standards are revised every five years.

So briefly, the FDA Recognized Standards Program can be used by CMS if they choose to institute a Recognized Standards Program. So I wanted to be sure you understood what they do in brief. Their recognition is actually in the Food, Drug, and Cosmetic Act. And importantly, it states that the standard should be established by a nationally or internationally recognized Standard Development Organization. And recognized Standard Development Organization is often conceived to be an accredited SDO. FDA recognizes over 1,400 standards from 32 different SDOs. And CLSI has 132 of our standards fully or partially recognized by FDA. FDA is very clear on the process for recognition, withdrawal, and external request for recognition and, indeed, how to use these voluntary consensus standards.

So finally, my recommendations-- these are the actionable recommendations for CLIAC regarding standards. And please forgive me for reading these. I think these are really important, and I wordsmithed them. CMS can and should provide CLIA-certified labs with further guidance regarding how to meet regulation. This is illustrated in what the standard looks like in CLIA and what the CLSI standards are. There's a true need for the how to meet those regulations. CMS can and should develop a Recognized Standards Program. FDA's RSP can serve as a model for that development. And there is plenty there to help with that model-- that development. CMS has the discretion to develop an RSP without legislative authorization and should take steps towards implementation. CMS can compel accreditors to refer laboratories to recognized standards when applicable. Indeed, those accreditors are already doing so. CMS, FDA, and CDC can provide communication to CLIA-certified laboratories about recognized standards and the Recognized Standards Program. And with that, I'm in on time, and thank you so much for this opportunity.

Public Comments

CLIAC CHAIR: Thank you very much for the presentation, both of you. Before we get to questions, let's roll into the public comments. I think we only have one, a verbal comment from the College of American Pathologists, again by Dr. Diana Cardona.
DR. DIANA CARDONA: Hello again. I promise this will be the last time you see me today. So, again, thank you. The CAP appreciates the opportunity to provide verbal comments to the CLIAC on clinical standards. As previously stated, the CAP is the world largest organization of board-certified pathologists and a leader and laboratory accreditation and proficiency testing, all in its mission to foster and advocate excellence in the practice of pathology and laboratory medicine. CAP believes that clinical standards are an important tool to improve laboratory quality. Clinical standards and guidelines, such as CAP's Practice Guidelines, help define the current standard of care practice. The ability of clinical guidelines and standards to improve quality is enhanced when used appropriately in tandem with regulations.

Clinical guidelines and standards are developed in a consensus-based framework in which all relevant stakeholders are invited to participate, and they are regularly updated as technology and practices evolve and are applied to individuals. Regulations apply to entities and are meant to be comprehensive and broad to allow for flexibility in meeting their objectives of quality, safety, and other public health needs. Clinical guidelines and standards can fill the gaps within regulations. Additionally, clinical guidelines can be revised and updated regularly and quickly to adapt to changing practices, needs, and technology. Regulations, meanwhile, take significantly longer to revise and update due to the necessary and valuable process of public comment periods. And thus, relying solely on regulation or regulatory updates to account for changes and developments is not feasible.

The CAP uses clinical guidelines and standards in our accreditation and proficiency testing programs. These take the form of the CAP's Practice Guidelines and the CAP's checklists. The CAP's Practice Guidelines is a form of translational research that becomes increasingly valuable as they facilitate the delivery of evidence-based care. Our Practice Guidelines provide standardized procedures when, which followed, produce more precise and useful test results. This is a win-win for both physicians and patients. This should entail a defined and transparent process for determining if a Practice Guideline once complete is appropriate for use in assessing performance or as an oversight mechanism. The CAP's checklists also provide current standard-of-care practice. CAP checklist requirements are complete and educational, with the goal of not simply identifying issues, but ensuring processes exist that prevent them from occurring in the first place. Because CAP checklists are updated annually, they reflect the latest requirements and most recent advances in best practices. The CAP also draws on the collective expertise of our scientific resource committees to introduce new checklists with detailed requirements to support advances in modern laboratory medicine.

Additionally, the CAP checklists incorporate various US regulations, such as OSHA for employee chemical and biological safety, CDC and APHL for infection control, Nuclear Regulatory Commission for radiation safety, National Fire Protection Association for fire safety, Environmental Protection Agency for hazardous chemical waste disposal, US Department of Transportation for shipment of specimens, and FDA guidelines for blood banking and tissue practices. CAP checklists are based on guidelines and publications from nationally- and internationally-recognized standard-setting organizations, such as CLSI, ISO, WHO, Cystic Fibrosis Foundation, American College of Medical Genetics and Genomics, American College of Surgeons Commission on Cancer, and ASCO. CAP checklists also draw from CAP's Q-Probes, Q-Tracks, and evidence-based guidelines developed by the CAP's Pathology and Laboratory Quality Center. This iterative and comprehensive effort produced the CAP's 21 discipline-specific checklist, which define the accreditation program requirements and reflect the most recent advances and best practices. For example, the added next-generation sequencing requirements to the molecular pathology checklist in 2012 and continues to update them annually as advancements in technology occur and as its uses expand to different applications, such as inherited genetics, oncology, histocompatibility, testing, pharmacogenetics, and infectious disease testing.
Thank you once again for this opportunity, and the CAP welcomes the opportunity to discuss any of today's topics further.

Committee Discussion

CLIAC CHAIR: Thank you very much. OK, let's open it up. We have about an hour for committee discussion and coming up with any recommendations. So I will open it up to the floor to see if anyone wants to kick us off. [CLIAC MEMBER], go ahead.

CLIAC MEMBER: Yeah, this is in context of Dr. Vesper's excellent presentation and the whole effort there that the CDC is doing. This is wonderful. This is exactly what the CDC should be doing. And I have a couple of comments and then a couple of questions leading to what-- the CLIAC group and what we can do to help. I really like, Hubert, what you did with the 40 specimens and the nice distribution across the reportable range when you're doing the assessment and checking the calibration. That's very appropriate. And I'm wondering, both of you-- and maybe Victor can answer this question. Are you getting enough support, enough financial resources, to keep this program going and maybe even expand it? So that's my first question.

DR. HUBERT VESPER: Well, I cannot speak for the program Victor is overseeing. But in terms of our program, the funding is difficult. Let's put it that way. So we do request that when we provide materials, the participants pay for the costs of producing the materials. But we are at a point where we have a very hard time to expand our programs. We do have a lot of requests for improving the analytical quality of other biomarkers-- biomarkers related to cancer, kidney disease, and so forth. But our program has very minimal funding, and that funding that we receive has been flat for the last 10 years.

CLIAC MEMBER: And that's what I had surmised. I think I knew that but just wanted to ask that question again and then if there's something that CLIAC can help with in this regard.

DR. HUBERT VESPER: I don't know enough about CLIAC. I think-- my thought is the laboratories and manufacturers-- people participating in our program make an investment in time and resources in order to improve the assay and make sure the assay are of appropriate quality. I think it would be very helpful for CLIAC and other organizations to recognize the effort done by our participants and make sure that the high level of quality they're aiming for, the investment they make in order to improve the quality, is recognized appropriately, either through checklists or as part of a quality assessment item. But I think it's more important for CLIAC to look at the laboratories and the participants and recognize their efforts. And then we'll figure something out. In the financial portion, whatever CLIAC could help would be very much appreciated. But I think the focus should be on the labs and the manufacturers. And those who do all the extra work, all the extra investment, I think that effort should be recognized accordingly.

CLIAC MEMBER: OK. I agree with that. I actually have a second question, and that's, how are the manufacturers responding to these efforts? You mentioned that you're in contact with manufacturers on some of these efforts. Are they responding weakly, strongly, in favor, or in the middle someplace?

DR. HUBERT VESPER: I would say those who participate have a real interest in finding out how their analytical system performs. In general, the manufacturers are supportive, and they also support efforts to increase funding so we can do more for them. Implementing these changes and improving the assays is a slow process. Typically, what we see is when manufacturers come up with a new product line or update the product line through a new FDA proposal-- FDA clearance, that's normally when we see that they actually implement improvements that we help them to achieve. But the process is very slow. It takes a long time. But we are here for the long run. So our Lipid program is running for over 50 years. And so we plan on doing the same thing for all of our other analytes that we do. So long-term, I think we do see some improvements. But it's going to be slow with the manufacturers.

CLIAC MEMBER: OK. Thank you.

CLIAC CHAIR: Excellent. And to the group, while we have the speakers still here, just prioritize the speaker questions before we move on to the deliberation. [FDA EX OFFICIO]? No? Did you just—

FDA EX OFFICIO: It wasn't really a question. I was just going to comment on what Hubert said, that sometimes, we've incentivized standardization through a lower regulatory bar. For example, we actually made vitamin D assays exempt from premarket review if they were standardized and not exempt from premarket review if they're not. So after Hubert and his team put that great program together, we hoped to leverage the quality assays by putting a lower bar on those. So that's one way we can work together to do some of that.

CLIAC CHAIR: Great.

DR. HUBERT VESPER: Outstanding. Very well done.

CLIAC CHAIR: Any other questions for the speakers? OK. So hearing none, I again want to reflect back as to what I'm hearing in this session, make sure I'm, A, thinking about this correctly, and then we could use these questions to frame the discussion. So clinical laboratories, we are subservient to CLIA and the accrediting agencies which do the accreditation on behalf of CMS and CLIA. How I'm interpreting these two presentations-- there are these incredible programs that are out there that are defining standards-- defining standards and basically providing services for improved laboratory quality and processes. And so I think the crux of the question is here. Do we want to, how could we, and how would we prioritize the increased connective tissue between CLIA and these programs that are going? I don't think we're looking for the incorporation of another body sitting over clinical laboratories. So first, I want to just ask to the speakers, actually, is that a fair reflection, that we're looking for the increased connective tissue between the programs that are being run in CLIA? So did they drop already? Oh, maybe. OK. Well, what do you all think? [CLIAC MEMBER], your hand's up first.

CLIAC MEMBER: So I guess my first question is to Hubert. Thank you so much for all your work. And obviously, this is a topic that's near and dear to my heart. You had mentioned that we want to be able to make it clear to the end user which laboratory values are applicable to which clinical guideline in that there are so-- Hubert is gone. But there are some-- even like calculations, such as eGFR, that should only be used with creatinine values that are harmonized. But we know that not all of them are traceable. But right now it's not transparent to anyone. And so I guess that is, I think, a function of the fact that CLIA is limited in what it recommends as information that needs to be conveyed to the end user. And so is there a way to make sure that complete information is provided so that the end user can make use of information and know which results are applicable with which clinical guideline?

CLIAC CHAIR: So, yeah, so the speakers have dropped. So I know that was targeted towards Hubert. I don't know if anyone else wanted to chime in in terms of addressing that question? Yeah, probably hard. [CLIAC MEMBER]?

CLIAC MEMBER: Thank you. This is a difficult issue because even with Hubert's program-- and he told us approximately the number of labs that participate in the voluntary program. But when you look at CLSI, you have a number of labs that are participating, but we don't have that crosswalked with the number of labs that have a CLIA certificate, for example. And we don't know to what extent those labs that have gotten the standards and hopefully utilize them, how much of the standards are they using. Are they using all of those recommendations, or are they just filing those documents away for potential reference? And the same goes for CAP. I'm sure there's a lot of consensus on our part that the use of standards is really important for us. And I know I've gotten a lot of value out of the standards in directing a laboratory. But it's really hard to what depth it's being used across. And maybe one of the ways to look at this is, would CMS be willing, in their auditing process, to determine if the laboratory is using a standard or not, and to what extent?

CLIAC MEMBER: Or I would even say, are they using-- what are they using, to start? Because I think you're right, [CLIAC MEMBER]. With everything that's ongoing, there's so many standards. And there's sometimes conflicting information between them. And I'll just give you one example of sepsis. There's a difference between CMS and CDC recommendations. And so it gets very confusing for what people are supposed to do when they're doing. And I think if we throw more things into the pie, it's just going to get

even more difficult. So it would be nice if we knew where the crosstalk was and if we could get the agencies to crosstalk and come up with some consistency. That's my concern.

CLIAC CHAIR: Yeah, so also looking at the two questions-- and let's take the first one first, which, in regards to the CSPs, the Clinical Standardization Programs, how can CLIA promote participation in those CSPs? And it's really a two-pronged question because one is on the laboratories and the test manufacturers. So I really see the value-- personally, I really see the value of the CSP on the manufacturer side. And so I don't know what lever CLIA has in terms of promoting test manufacturers to participating in CSP. But certainly, from a manufacturer perspective, I would imagine some stamp of approval from a CSP on a particular analyte may be some commercial advantage if there's no way of making it a requirement for them to do so. And the way Hubert described the CSPs really was you get that feedback and, especially, like in the testosterone example, seeing the high degree of variability, particularly in the low levels, that's the phase in which the test manufacturer can modify the test to improve performance. All of the examples that were really provided there were the relatively poor performance of the FDA-approved assays to what Hubert was using as the gold standard, which was LCMS. So given that environment, the clinical laboratory is very little opportunity to modify the performance of that assay on an FDA-approved platform. And we may have less opportunity in the near future. So I think the real value there from being able to tinker with the test is really in the manufacturer's side. On the lab side, it sounds like a wonderful PT program, right? And we have these PT programs. They're commercially available PT programs as part of our requirement as a laboratory to participate in those. So, you know, I think awareness about that as a potential program-- I mean, I would imagine it has to be certified as a PT program in order to be able to qualify as that. But a really rich amount of data that I would love to use, but I wouldn't want it to be in addition to my existing PT requirements-- just time, resources, money. If it could satisfy that PT requirement, what a great tool.

CLIAC MEMBER: Right.

CLIAC MEMBER: That's OK. No, we don't need any duplication.

CLIAC CHAIR: Yeah. [FDA EX OFFICIO]?

FDA EX OFFICIO: Yeah, so I've been involved in some of these through the years with respect to the FDA side of vitamin D, testosterone, estradiol, hemoglobin A1C, et cetera. So I can give you what I have learned from the manufacturing community. [FDA EX OFFICIO] may also want to weigh in on their perspectives on some of the things that you raised. But before I do that, I want to point out that for some of these-- a lot of them are laboratories participating in these programs-- you may have heard Hubert talking about the vitamin D and testosterone. A fairly high proportion of those tests going through the standardization program were available from-- those were laboratory-developed tests and not manufacturer kits. So the immunoassays are kits. A lot of the mass spec tests are not. But with respect to the manufacturers-- like I said, [ADVAMED LIAISON] may want to weigh in-- but what we have heard is that what drives them to adopt standardization for the tests that they offer to labs is customer demand. So I think it relates to whether or not laboratories ask for standardized tests. And that relates to whether or not the laboratories know that there is an issue with standardization with that particular analyte. If they care, if there is demand from the clinicians that are laboratory customers, and then, if the laboratories ask for it, the manufacturers adjust their tests as fast as they can do. So that's our experience with this type of thing. So I suspect what Hubert is asking, is there ways to incentivize laboratories and other users to want to move toward standardized testing where appropriate? But I don't want to put words into his mouth. So I just wanted to share the perspective that we have heard over the years of what makes a manufacturer want to put resources into standardization, which could be very easy for them to adjust or sometimes more difficult.

CLIAC CHAIR: And I think you bring up a good point where the—

FDA EX OFFICIO: Follow the manufacturer.

CLIAC CHAIR: Sorry, the need for standardization really comes from the clinic, right? I've heard-- we have some assays that there's a really low degree of standardization, and it's clinically OK, right? Liver enzymes is a classic example. From manufacturer to manufacturer, they're all over the place. Reference ranges bounce, too. So as long as you're tested in the same lab over time, it's meaningful information. Comparing lab to lab or assay to assay has been very challenging but also, at least from what I understand, not a clinical conundrum, right? On the flip side, I've heard requests in the past from clinicians for D-dimer standardization and the benefit from there. So you bring up a good point where it's like, where is the driver for the standardization coming from? And is it from the clinic? Is it from the lab? Is it from the CSP? [ADVAMED LIAISON]?

ADVAMED LIAISON: Yeah, and just to echo the comments that were made, yeah, what is the challenge that needs to be solved with the standardization, and what is the patient benefit? Those are key factors to consider in terms of the standardization approach.

CLIAC CHAIR: [CLIAC MEMBER]?

CLIAC MEMBER: Yeah, so I think one thing that we need to do is to convince the laboratories out there that this is important, and it's all about the patient. So somehow we have to summarize all the evidence that Hubert kind of hinted at, that more standardization of the assays that we're using in the laboratory produces better patient care, better outcomes for the patient. And if we can help put resources together or can point to the right people that can get that work done and can disseminate it then to the laboratory community, so that we can do what [FDA EX OFFICIO] is suggesting and leverage that information, so that the manufacturers then feel the pressure to standardize or at least harmonize their assays.

CLIAC CHAIR: Yep. [CLIAC MEMBER]?

CLIAC MEMBER: So I guess the most salient example for me is the albumin because that's used for a variety of uses in nephrology, particularly to determine whether or not to put patients on anticoagulant therapy pre-emptively. And the fact that we have two methods, from cresol purple, from cresol green, which we know have a 30% bias to each other, yet they still both exist despite the fact that a lot of the guidelines are only based on one of the methods. And I guess at this point, most of what I found was surprising was that some of them, if not all the manufacturers, often actually have kits for both on their instrument. So you're able to select. Either you want to do from cresol purple or from cresol green. So at this point, I feel like being able to switch to a single method would be-- it might have some financial implications. But it wouldn't be that hard because of the fact that there is already an existing alternative for the same instrumentation. And so it just seems to me that there is just a question of awareness and will in terms of-- we could potentially switch to only doing cresol purple and not significantly impair patient care.

CLIAC CHAIR: Mm-hmm. OK, so let's-- we'll go [CLIAC MEMBER], [CLIAC MEMBER], then [CLIAC MEMBER]. I do want to, recognizing the time, I do want us to really start thinking about maybe coming up or suggesting a recommendation for that first question. And then, of course, we have the second question to go through as well. So, [CLIAC MEMBER], go ahead.

CLIAC MEMBER: Yeah, I just think some of this is a little bit overwhelming. And we have key chronic disease biomarkers. So my question is, are we looking to focus on the things that are most devastating here, or are we looking at the things that are most erratic in differentiation, you know? And I think, if there was a limited menu that people knew what we were targeting, and how does that get picked-- I'm not a chemistry person, so I can't pick those biomarkers in that realm-- in microbiology, I'm going to stay out of that realm for now. But in this sense, I think if it was a more limited menu in what we want to focus on, it would get more people on board as far as labs as well as the manufacturers. We just can't boil the ocean. And this kind of sounds like it's boiling the ocean, so.

CLIAC CHAIR: [CLIAC MEMBER], before you go, if I may, I'd like to suggest something for a recommendation, hearing everything. And I want to put it out there in case you want to add to it. But I think we're all in somewhat of an agreement that the need for this type of standardization or harmonization comes from the clinic. And so I think really understanding what that need is and

recommending that, really, all three agencies-- CMS, CDC, and FDA-- engage with professional societies to identify the clinical needs for standardization. Even going back to Hubert's presentation, if you remember one of the first few slides, those targets that he selected, that they all came from professional societies. The Endocrine Society was for estradiol and testosterone. And I forgot which one was for vitamin D. But that was the input of what suggested this need for standardization. And so if we want to go down this path, I think identifying those opportunities through professional society is the right way. [CLIAC MEMBER]?

CLIAC MEMBER: Yeah, just to add, maybe, to something [CLIAC MEMBER] mentioned, because as I'm reading this question and listening to the presentation, being a microbiologist is where I go. And I couldn't figure out what and how you would word this for infectious disease, right? We have struggled with standardization, particularly when it comes to viral load testing, as an example. Even as we've moved from doing a lot of LDTs, where you couldn't compare your CMV viral load from one lab to another, now we have different manufacturers that have calibrated it to international unit. But you still see differences. But as long as you're using one assay in your laboratory and you're monitoring patients over time with that one assay, it's fine. However, we also know that patients are traveling from one lab to another, and their medical record may have different results because the tests were used differently. But how to loop this into one recommendation? I think, to [CLIAC MEMBER] point, maybe we need to focus on the things that are really critical as a start. Maybe the recommendation should not be to provide a recommendation for all tests in all of the different laboratory specialties, but maybe targeting things that are key and maybe important at this point. And maybe they'll use that as maybe a template or an example of how we can move forward when we're ready to expand to other subspecialties. So having it focused might be the way to go at the beginning.

CLIAC CHAIR: Excellent. [CLIAC MEMBER]?

CLIAC MEMBER: Yeah, so may want to concentrate on the ones that have the deepest clinical needing, perhaps, and then also most common. I mean, one thing that comes to mind, and that standardization, I think, benefits everybody, is that certainly the endgame is to be consistent with patients. But with ACOs these days and value-based care, a lot of incentives, even, are based on-- for instance, hemoglobin A1C, some clinics are using the portable, quick A1Cs versus sending them out. And they get different results. And, again, when it gets down to the down and dirty in terms of your take-home pay, you want to make sure that the A1C that you're doing is accurate and reproducible and equivalent to one that your competition may be doing across town, you know?

CLIAC CHAIR: So, again, it seems like we're aligning on identifying the greatest need for harmonization, right? I think not everything needs to be harmonized. Ideally, everything would be harmonized, but it's probably not a reality. And it sounds like we're focusing more on these harmonization efforts with the IVD manufacturers as opposed to the clinical laboratories that are deploying them. I also want to make sure we bring up the second question in relation to the recognized standard.

FDA EX OFFICIO: Real quick, can I add to the first one here?

CLIAC CHAIR: Yeah, of course.

FDA EX OFFICIO: It sounds like some of the question is participation in existing programs. So do we want to consider adding that into the draft recommendation? So not just what new standardization or harmonization programs might be needed, but considering whether there should be increased participation in existing harmonization standardization programs. I don't know. I would love to hear the input of the other folks.

CLIAC CHAIR: Yeah.

CLIAC MEMBER: I would say-- can I just say one thing, [FDA EX OFFICIO]? Because this is what I was trying to say before. I think there's so many options, and we don't know who's doing what. So I think that is one of the issues—

FDA EX OFFICIO: Options for tests or options for programs?

CLIAC MEMBER: I think both. I think—

FDA EX OFFICIO: I don't think there's a lot of programs. So there's not a lot of standardization programs for tests. There's a couple. But mostly, the CDC ones are in the lead. But—

CLIAC MEMBER: Well, there's CDC. There's CLSI. There's—

FDA EX OFFICIO: Well, CDC and CLSI are different types of standards. I think the word "standard" is confusing. So the word "standard"—

CLIAC MEMBER: Right. And maybe that's where we need to start.

FDA EX OFFICIO: The word "standard" that Hubert might use may mean a reference standard, like a comparator, a reference method, or a material, whereas CLSI, the word "standard" is a document, so like a protocol or something. I just wanted to—

CLIAC CHAIR: Yeah, so-- to answer your-- or give my opinion on your question, [FDA EX OFFICIO], is the CSP, I think, from a harmonization perspective, is really good for manufacturers. Again, I think from the clinical lab side, we have very little opportunity to harmonize. We can see how we perform by using the CSP. But how we could actually then take that information and modify the assay to harmonize it, the clinical labs have very little ability to do that. So, again, I think the harmonization component of it is really IVD manufacturer-facing. I think the participation of CSP from a clinical lab perspective is much more akin to proficiency testing. That would be the value that I see in it, and it sounds like a great program. So in terms of promoting participation, I think first and foremost is awareness. I didn't know these programs existed. So I think that's step one. I will say, though, there would be a barrier because I have to participate in PT. I expect these are not PT programs.

FDA EX OFFICIO: Yeah, these are not the same as PT programs. These are quite different, yeah.

CLIAC CHAIR: So I have limited time, money, and resources. So driving awareness would be like, that's cool. Maybe I'd participate in one, maybe not. But clearly, without a mandate to participate, I think participation would be low, given that the value is PT-like, from a clinical lab perspective.

CLIAC MEMBER: Much.

CLIAC CHAIR: So we could make that-- we could make a recommendation, certainly, about driving awareness of such programs. Yeah, [CLIAC MEMBER]?

CLIAC MEMBER: So I just wanted to add that participation is great and that there has actually been a lot of work being done on this. I tried to post a link to harmonization.net, which is a website that actually is the website for the International Consortium for Harmonization of Clinical Laboratory Results that coordinates the harmonization effort. And so on that website, it lists the different efforts that are ongoing and also lists the measurements that are considered harmonized and also what organization or what reference standard they are harmonized to. And so I feel like there is a lot of effort that has gone into this. I feel like the missing piece is still the fact that when you get a result, there is a significant effort on your part to determine whether or not that result is a harmonized test or is comparable to your own. And so part of the SHIELD Initiative is working on what we call a harmonization indicator that could be attached to results to let people know that if you get a creatinine result or something, or albumin, that there would be this harmonization indicator that would let you know that those two results are comparable. And so I guess the point I'm trying to make is that we can go through all this effort of encouraging vendors to go through the traceability studies and do the harmonization. But in the end, it's only helpful if there is a way to flag these results and let people know that they are harmonized and make use of them because right now, that's not anywhere in the results, right?

CLIAC MEMBER: Are you saying between labs? I don't understand. Harmonize, who's trying to know if it's harmonized? The lab people, between other labs, or a patient when they go to a different setting?

CLIAC MEMBER: Both, actually.

CLIAC MEMBER: OK.

CLIAC MEMBER: They're portable now. They could be seeking care at a--

CLIAC MEMBER: Right, right.

CLIAC MEMBER: --yeah, ambulatory care clinic and then going to have surgery somewhere else. And they could have very different lab values coming back. But right now there's no way to let them know that, hey, these are different, and not just because the reference range is different, because it could be the same platform and still have a different reference range. But they're actually-- the performance characteristics are different.

CLIAC CHAIR: Sorry, [CLIAC MEMBER]. Go ahead.

CLIAC MEMBER: Yeah, hi. This is an interesting and challenging discussion. So I'm sitting back and saying, OK, where is there a standard? When have we ever done this? What's the example? The only real example I can think of is the PT, where we have used the INR now, and we've used an international external standard to allow that testing to be comparable across laboratories. So when we go further than that, I think your point, [CLIAC CHAIR], to encourage the focus on values that are very important and can be very injurious if they are not standardized, is really where we want to focus the problem. I'm not sure that encouraging the existing CSPs is appropriate. We may be vetting up people that maybe aren't-- that may be not what we want to do. But you're asking for awareness. So I don't find that particularly bad. I can give a couple of interesting clinical examples because as we are commingling lab results from different testing labs-- and, really, it's not so much the different laboratories as it is the different manufacturers' IVD platforms, we are putting results into patient records that are not copacetic with one another. And the most recent example I saw was a PSA. Our PSA has a relatively middle-of-the-range value. And one of our local hospitals who also does a PSA has a much, much higher value. This individual was used to looking at ours, saw the higher value from the external lab, and was sending that patient to biopsy before there was intervention. And so there's a very concrete example. I'm not sure albumin has that same potential impact. I'm not sure cholesterol, even though the standards are variable and the numbers are quite different, really have that impact. So where do these things have a direct impact? So to that point, I went to [CLIAC MEMBER] little website, I looked up PSA, and that came up as high-- high need for standardization. So that might be a place to even start is to create a recommendation for the top 10 that would have direct clinical impact and to provide some guidance. And I don't know if that's in CLIA's purview. But I just wanted to share that I am seeing direct patient impact because of the variable results that we see and the fact that we are now commingling them into the EMR, which, by the way, we would never have done 10 years ago. And we fought like dogs to prevent that from happening and to make sure that those tests went over into their own little bucket. And we lost that battle. It's called "happy together" in epic speak. Pardon me.

CLIAC CHAIR: Yeah, so first off, great story. Second of all, hearing what you were saying, I would actually say I suspect that recommending CMS, CDC, and FDA to engage with professional society is a little bit of a clunky pathway. So maybe swapping out professional societies for harmonization.net-- I personally haven't had the time to look at it like you did during the call. But it sounds like some of this work may be done in terms of what's the prioritization level and the clinical need for harmonization. So why reinvent the wheel? So I want to be careful. We have 15 minutes left. I will get you done and home. We have three draft recommendations. I know we're going to spend some time probably deliberating on them. I would love to get a recommendation done before we part ways. So I just want to put that out there. I'll have [CLIAC MEMBER] talk now, and then let's start to go through these recommendations and see which ones we want to keep, throw out, and modify. Go ahead, [CLIAC MEMBER].

CLIAC MEMBER: Quickly, I was thinking back to [CDC EX OFFICIO] presentation this morning about some excellent education training programs that CDC is putting on for laboratorians. And I think we should recommend that this topic be part of their education and outreach training so that laboratorians and the front lines can recognize the importance and value of standardization so that we can have more of a groundswell approach to the need for this and pointing this out to manufacturers as well. And it might be able to be incorporated into one of our already-formed recommendations.

CLIAC CHAIR: Great. Great. All right. So let's start talking through, in the last 15 minutes, talking through the recommendations themselves and seeing if you want to keep or modify or throw out. So in this first one-- and I see you, [CLIAC MEMBER]. I'll call you in a second. But the first one-- CLIA recommends CMS, CDC, FDA to engage-- we can say professional societies or even harmonization.net-- to identify the top clinical needs for standardization harmonization and provide guidance to IVD manufacturers on compliance participation. So how does everyone feel? Keep? Throw out? Modify? I'm not hearing any comments.

CLIAC MEMBER: This would be very worthwhile.

CLIAC CHAIR: OK. Thank you. Yeah, are your other comments related to this draft recommendation or another one? Or more general?

CLIAC MEMBER: Not this first one, no.

CLIAC CHAIR: Is it related-- is it related to another draft recommendation?

CLIAC MEMBER: Yes.

CLIAC CHAIR: OK, all right. Then let's hold off for one quick second. So does anyone not like draft recommendation 1?

CLIAC MEMBER: [INAUDIBLE] What's that?

CLIAC CHAIR: Does anyone not like draft recommendation 1?

CLIAC MEMBER: No. This is [CLIAC CHAIR] here, sorry. So when we say "identify the top clinical needs for standardization and harmonization," we want CLIAC to partner-- or, sorry, CMS and CDC and FDA to partner with CAP and others to create a list that they would then recommend-- that then what? Pardon me.

CLIAC CHAIR: And then try to provide some guidance to IVD manufacturers as they're developing those tests for harmonization. So I don't want to be descriptive of how they do that. I don't know the levers that—

CLIAC MEMBER: Yeah.

CLIAC CHAIR: --that these agencies have.

CLIAC MEMBER: You mean the professional you mean the professional society? When you say leverage—

CLIAC CHAIR: No.

CLIAC MEMBER: --you mean the professional societies?

CLIAC CHAIR: No.

CLIAC MEMBER: No.

CLIAC CHAIR: I mean, I don't know what leverage CMS, CDC have-- and I know a little bit more about the FDA-- with the IVD manufacturers of, like, you must harmonize, or we recommend this type of harmonization. I don't know what those levers are.

CLIAC MEMBER: Should we find out and include that in the recommendation? I mean, it seems like it would be, since we are part of CDC and CMS-- it just feels like the more vague we make it, the less strong it is, right?

CLIAC CHAIR: Agreed. The alternate side-- and, again, this is what I understand that they generally prefer from us-- is more vague to give them more freedom to leverage the tools that they have as opposed to painting them in a corner. Right? They may go through this process and realize like, we wanted to take path B instead of path A. And, of course, they could do that anyway, regardless of our recommendation, right? Our recommendations are not binding. But the spirit of that recommendation is identify what the needs of the top 10 and work with manufacturers to improve standardization. How is figured out.

CLIAC MEMBER: Oh, I didn't-- yeah, I didn't mean how. I just meant when we say "provide guidance," I didn't know what that meant. Identify the top clinical needs-- you could probably-- the "provide guidance" piece is probably extra. I think we're just going to identify the top clinical needs, right? They're going to decide what to do.

CLIAC CHAIR: Sure.

CLIAC MEMBER: But I'm not married to changing it, yeah, just simplifying.

CLIAC CHAIR: Yeah, that's fine. Jim, you have a question?

CLIAC MEMBER: Yeah, there's an art to remaining silent and giving freedom to the people receiving a recommendation. I continue to come around to "encourage participation in existing CSPs," by whom? The phrase that seems to be on the process of being deleted is "IVD manufacturers." But our first presentation was focusing on the end user laboratories. And, again, we can remain silent on who is supposed to be encouraged. But I want this group to be cognizant of the silence because it is quite vague.

FDA EX OFFICIO: Yeah, I would second that. I think it's any test developer. Staying silent would make it so you don't have to specify. But I don't think it's just IVD manufacturers who make these tests who are not standardized or harmonized.

CLIAC MEMBER: Yeah, and so "test developers" is a very different statement-- and, by the way, I think this is an appropriate and friendly edit because what's sort of sticking in my craw is the galaxy of end user laboratories because are those-- should those-- estrodiol and vitamin D3 and so on and so forth, is the CSP program supposed to be to the end laboratories which are inspected by deemed agencies?
And I am not sure there's a groundswell for the end laboratories to be participating in CSPs. But maybe that's true.

CLIAC MEMBER: No, this is for developers. So the harmonization and standardization piece of this is for somebody who's made a test, whether it's a laboratory, an IVD manufacturer making a kit that's going to be distributed or whoever. I think the angle for user laboratories is if they value this. Do they value standardized and harmonized assays, whether they're making them or buying them?

CLIAC MEMBER: And actually, your comments of clarification to me, I think, are what are needed for this recommendation because as it was originally written, I had difficulty in considering it. But there was a period there-- "encourage test developers to participate in existing CSPs," period. Whether that should then be a top 10 is a separate question. I want to make sure what I'm voting for.

CLIAC CHAIR: OK. I think it was an excellent callout on the test developer comment. The other ones-- six of one, half-dozen-- at this point, I'd prefer to get a recommendation out. And I think that we're starting to get into wordsmithing beyond the test developer edition. We have nine minutes left for recommendations. So we could leave some on the table. That's fine. I'd like to give the agency some guidance. As it's written right there, draft recommendation 1, is there a motion for-- a motion?

CLIAC MEMBER: So moved.

CLIAC MEMBER: So moved.

CLIAC MEMBER: --question at the top down so we can see it? Thank you.

CLIAC MEMBER: Second.

CLIAC CHAIR: So I heard a moved. I heard a second. Any other discussion? All those in favor, raise your virtual hand. OK, we have majority. So it will pass. OK, so now, everyone, lower their hands. The next one was that-- the next recommendation was a little bit more literal in terms of the request. And when we were thinking about participation of the CSPs for the end user labs, again, I put this recommendation forward just because you got to start by driving awareness, so a marketing campaign. So it reads, "CLIAC recommends CDC create a marketing campaign to promote CSPs to clinical laboratories to encourage participation." [CLIAC MEMBER], you have a comment?

CLIAC MEMBER: And this is where I struggle, and I'm not pretending to offer an answer. But this recommendation is that what I'm calling the galaxy of clinical laboratories themselves participate in CSPs. And if that is the wish of CLIAC, so be it. But I want to make very clear on what the recommendation is.

CLIAC CHAIR: Yeah, and it was rooted in the question. So, [CLIAC EXECUTIVE SECRETARY], I don't know if you can show both the draft recommendations--

CLIAC MEMBER: I think the clarification here is that I think it's awareness of standardization and harmonization, not the CSPs. So recommendation 1 relates to people who develop tests participating in standardization harmonization programs. Recommendation 2 looks like you want to put something like creating awareness of standardization harmonization, not promoting participation in CSPs.

CLIAC MEMBER: Thank you, and that's the clarity. Thank you, [FDA EX OFFICIO], times two.

CLIAC MEMBER: Recognition.

CLIAC MEMBER: It's recognition of tests having undergone CSP-- yeah, and, again—

CLIAC MEMBER: Or even what it is.

CLIAC MEMBER: Yeah.

CLIAC MEMBER: Right, what it is, yes, what it is.

CLIAC MEMBER: Raise awareness.

CLIAC CHAIR: It's a double-- it's a double uplevel, right? It's the awareness of the need for harmonization and then also the ones that have been—

CLIAC MEMBER: But participation in a program is very-- potentially misleading because it's not the clinical laboratories are doing the CSPs. It's the IVD manufacturers, if I understand at least the implicit consequence of recommendation 1.

CLIAC CHAIR: So to raise the awareness of standardization harmonization efforts and benefits. And maybe I'll just—

CLIAC MEMBER: Do the wordsmithing as you see fit.

CLIAC CHAIR: Yeah.

CLIAC MEMBER: Yeah.

CLIAC CHAIR: And then leave it at that.

CLIAC MEMBER: And that's very consistent with the two talks that we heard.

CLIAC CHAIR: And very complementary, right? So draft recommendation 1 is to the test developers who are going to be actually executing on harmonization and then the end user who then needs to be aware of it and the benefits of it. So I'll put this up for-- is there a motion to-- is there a motion?

CLIAC MEMBER: I'll move.

CLIAC CHAIR: Second?

CLIAC MEMBER: Second.

CLIAC MEMBER: Discussion, [CLIAC CHAIR]?

CLIAC CHAIR: Discussion?

CLIAC MEMBER: Is it just the CDC that's doing the marketing campaign-- tri-agency, professional societies? There's been some editing here.

CLIAC CHAIR: So, originally, it was put in CDC because it's the CDC's program, but—

CLIAC MEMBER: I'm just asking the question. I want to make sure we know what we're voting for.

CLIAC CHAIR: Actually, I'd let [CLIAC EXECUTIVE SECRETARY] make that call—

CLIAC EXECUTIVE SECRETARY: Yeah.

CLIAC CHAIR: --or anyone else make that call.

CLIAC EXECUTIVE SECRETARY: We can encourage professional societies to do a marketing campaign, but that's pretty much the extent. It would just be—

CLIAC CHAIR: No, but isn't the CSP a CDC program?

CLIAC EXECUTIVE SECRETARY: Yes, the CSP is a CDC program. And it is, as you heard in Colette's presentation, DLS, that has a lot of communication outreach via clinical lab partners and the training and workforce development branch.

CLIAC CHAIR: So is it appropriate for CDC to be there alone, or should we add another agency? Or can you not answer the question?

CLIAC EXECUTIVE SECRETARY: I think that it's not-- well, I think it's not inappropriate. It's just that we don't have jurisdiction over any other agency to say that they should. We could recommend it, I guess.

CLIAC CHAIR: Yeah, to be clear, we have no jurisdiction over anyone. We're just making recommendations.

CLIAC MEMBER: Well, we recommend earlier in the first part that we partner with professional societies. So perhaps we want to keep that consistency. But I don't feel strongly about it.

CLIAC CHAIR: Yeah. I think, if it's all right, for the sake of time, I'd say leave it at this.

CLIAC MEMBER: Just leave it. Yeah.

CLIAC MEMBER: Call the question.

CLIAC CHAIR: Say that again?

CLIAC MEMBER: Just call the vote. Call the question.

CLIAC CHAIR: Yeah.

CLIAC MEMBER: Hold on.

CLIAC CHAIR: We have the motion. We have the second. We had the discussion. All in favor, please raise your virtual hand. Great. Looks like a pass. Thank you. All right, everyone.

CLIAC MEMBER: My hand was raised originally to—

CLIAC CHAIR: Yeah, sorry, go ahead, [CLIAC MEMBER].

CLIAC MEMBER: I think there's a word missing. CLIAC recommends CDC create a marketing campaign to raise awareness. And then the comment that I put in the chat was related to this. And how is the CDC going to promote this? Well, then my recommendation fits here because it's producing data and showing that the value of standardized methods in patient care is valuable.

CLIAC CHAIR: So I absolutely agree. And I would say, following our rubric for recommendations, to absolutely put that into the "things to consider" or "should include" under the broader recommendation.

CLIAC MEMBER: Sure. That's good.

CLIAC CHAIR: And then, [CLIAC EXECUTIVE SECRETARY], once you're done, if you could pull up recommendation 3. So this was really to address the second question of the guiding discussion-- the questions to guide our discussion. And it was-- I don't know if, [CLIAC EXECUTIVE SECRETARY], you're able to show both of those at the same time. But, again, the presentation demonstrated that there are these great resources of standards that are out there. And I think we all agree that the-- we're not going to be-- the only way to encourage or enforce laboratories to comply with them would be through CLIA, not as a standalone regulatory body-- so, therefore, recommending that CMS review those recognized consensus standards to see what would be incorporated into future CLIA updates. This may be something that CLIA already does. I don't know. But it was one of the guiding questions. So I wanted to at least try and get an answer for them. [CLIAC MEMBER]? I don't if you have your hand up from the previous vote or if you want to say something.

CLIAC MEMBER: And you're on mute.

CLIAC CHAIR: OK. Maybe she stepped away. How does everyone feel? Is there a motion?

CLIAC MEMBER: [CLIAC CHAIR], incorporation into CLIA? Is that the intent of this recommendation?

CLIAC CHAIR: For consideration into incorporation of CLIA, right? Again, the standards are there. Do we want to make it a standard in CLIA? And, again, this may already be done.

CLIAC MEMBER: I think the question was meant to be-- it's the process for standards incorporation, not necessarily use of the current standards, although that could be done.

CLIAC CHAIR: I don't remember the question. I'd have to see it. But so I do also want to call out that it's 5:01. And I [INAUDIBLE] to get out of here. So, [CLIAC EXECUTIVE SECRETARY], I don't know how to deal with this when there's kind of draft recommendations that are pending. And I feel bad. I don't want to keep people over. Is there a mechanism to review this afterwards, or do we just drop them?

CLIAC EXECUTIVE SECRETARY: So there's not a recommendation to review afterwards because it has to be done in the public forum. But what we will do is keep these as bullet points in the meeting summary as far as something-- if you've seen our meeting summaries, you see that we bullet-point everything in there. So we will keep both these as committee discussion bullet points.

CLIAC CHAIR: OK. So with that, again, I don't want to keep you any longer. I want to thank you all for your participation today. I think we had some really great presentations, really great discussion, really meaningful recommendations that we're being able to put forward. So, again, thank you all. We will have-- our next meeting will also be a virtual meeting. It's going to be held November 6 and 7. And please email any CLIAC topic suggestions or suggested member candidates to cliac@cdc.gov. And with that, thank you, and enjoy the rest of the evening.

CLIAC MEMBERS: Thanks very much, Jordan.