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

Summary Report

November 3 - 4, 2021

Atlanta, Georgia

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

Clinical Laboratory Improvement Advisory Committee (CLIAC) November 3-4, 2021 Summary Report

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RECORD OF ATTENDANCE

Committee Members Present

Dr. Valerie Ng, Chair
Dr. Birthale Archie
Mr. Michael Black
Dr. Kimberle Chapin
Dr. James Crawford
Ms. Heather Duncan
Dr. Mary Edgerton
Dr. Susan Gross
Dr. Lee Hilborne
Dr. Ewa King
Dr. David Koch
Dr. Lavinia Middleton
Ms. Carole Moss
Dr. Nirali Patel
Dr. Michael Pentella
Ms. Jennifer Rhamy
Dr. Gregory Sossaman
Dr. Mark Tuthill
Dr. R.W. (Chip) Watkins
Dr. Donna Wolk
Mr. Andy Quintenz, AdvaMed (Liaison Representative)

Ex Officio Members

Dr. Collette Fitzgerald, CDC
Ms. Monique Spruill, CMS
Dr. Peter Tobin, FDA

Designated Federal Official

Dr. Reynolds Salerno, CDC

Executive Secretary

Ms. Nancy Anderson, CDC

In accordance with the provisions of Public Law 92-463, the meeting was open to the public. The meeting was a full virtual Zoom webcast, and approximately 203 public citizens attended one or both days of 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. The Secretary is authorized under Section 222 to establish advisory committees.

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.

As a result of the different perspectives among its members, CLIAC is at times 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 Official (DFO), Clinical Laboratory Improvement Advisory Committee (CLIAC), and Director of the Division of Laboratory Systems (DLS), Center for Surveillance, Epidemiology, and Laboratory Services (CSELS), Deputy Director for Public Health Science and Surveillance, CDC, welcomed the Committee and the members of the public. Dr. Salerno expressed gratitude to the CLIAC members and laboratory community for their ongoing efforts in responding to the COVID-19 pandemic. Dr. Valerie Ng, CLIAC Chairperson, welcomed the Committee and reviewed the process for public comments, quorum requirements, and official CLIAC recommendations. Dr. Salerno introduced Dr. Peter Tobin, who served as the FDA ex officio for the meeting and introduced the new Committee members, Mr. Michael Black, Dr. Kimberle Chapin, Dr. James Crawford, Dr. Ewa King, Dr. David Koch, and Dr. Mark Tuthill. All members then made self-introductions and financial disclosure statements relevant to the meeting topics. Dr. Ng stated that the agenda topics would include updates from the CDC, CMS, and FDA, including an overview of the FDA's Center for Biologics Evaluation and Research (CBER), a laboratory safety update, and a status report on the new CLIA Regulations Assessment Workgroup. In addition, the meeting would include presentations and discussions on next generation sequencing in clinical and public health laboratories and laboratory data exchange and harmonization.

AGENCY UPDATES AND COMMITTEE DISCUSSION

Centers for Disease Control and Prevention (CDC) Update ***Addendum 1***

Collette Fitzgerald, PhD
Deputy Director for Science
Division of Laboratory Systems (DLS)
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Deputy Director for Public Health Science and Surveillance (DDPHSS)
Centers for Disease Control and Prevention (CDC)

Dr. Fitzgerald updated CLIAC on CDC's DLS activities, including laboratory preparedness and response, laboratory quality and safety, health equity, partnership, communication and outreach, and laboratory training. She provided an overview of CDC's COVID-19 response, and the DLS work to support the response. She noted that DLS created a response team to specifically support the Laboratory and Testing Task Force. The response team responsibilities include developing and supporting public-private partnerships, providing clinical laboratory technical support through laboratory guidance development, leading the tri-agency task force for emergency diagnostics, improving clinical laboratory community outreach, and providing training and education development support. In the area of laboratory quality and safety, Dr. Fitzgerald explained that the CDC and the Association of Public Health Laboratories (APHL) established the Next Generation Sequencing Quality Initiative in 2019. The initiative has developed over 80 free tools and resources to introduce or strengthen quality management NGS workflows. She next highlighted the agency's efforts to address health equity. In April 2021, CDC announced an agency-wide health equity science and intervention strategy called CORE. Dr. Fitzgerald summarized the three DLS health equity CORE goals covering Electronic Test Order Results (ETOR), diagnostic errors and fellowships, and internships. She continued by outlining CDC's work in partnerships, communications, and outreach. To inspire

the next generation public health workforce, CDC launched a new Science, Technology, Engineering and Math (STEM) website that offers public health education, training, and resources. The website can be used by K-12 students and their teachers, college students, and professionals. Dr. Fitzgerald concluded by discussing laboratory training activities. DLS expanded the OneLab initiative to bridge, train, and sustain a capacity-building community among public health and clinical laboratory communities. The new features include the development of a virtual reality multiplayer clinical laboratory environment and launching CDC's first targeted and customized learning management system specifically for laboratory professionals, OneLab REACH (Rapid Education and Capacity-building Hub). Dr Fitzgerald also highlighted five new eLearning courses and shared an update that DLS now offers a laboratory eLearning course syndication program.

Centers for Medicare & Medicaid Services (CMS) Update ***Addendum 2***

Ms. Monique Spruill
Director
Division of Clinical Laboratory Improvement and Quality (DCLIQ)
Center for Medicaid and State Operations (CMSO)
Centers for Medicare & Medicaid Services (CMS)

Ms. Spruill began by giving an overview of the reorganization of the five branches within the DCLIQ: two policy branches and three operations branches. She provided the August 2021 count of laboratories enrolled in the CLIA program, which was almost 310,000, and gave statistics on the number of facilities with each CLIA certificate type. She said that since the start of the public health emergency, over 46,000 new laboratories had enrolled in the CLIA program, with the majority applying for Certificates of Waiver. Ms. Spruill described several updates to the CMS 116 CLIA application form and CLIA data systems. She also highlighted the CLIA brochures posted on the CMS CLIA website that provide guidance to surveyors and laboratories. Next, Ms. Spruill discussed CMS efforts to increase outreach and stakeholder engagement and provided an overview of the CLIA Communications Listserv. She emphasized the importance of CMS corresponding with professional organizations and stakeholders to strengthen partner engagement. Ms. Spruill provided an update to the Regulations.gov listing of the CMS spring 2021 Unified Agenda of Regulatory and Deregulatory Actions. She concluded with an overview of recent temporary enforcement discretions and 2020-2021 guidance documents.

Food and Drug Administration (FDA) Update ***Addendum 3***

Peter Tobin, PhD
Chemist
Division of Program Operations and Management (DPOM)
Office of In Vitro Diagnostics and Radiological Health (OIR)
Office of Product Evaluation and Quality (OPEQ)
U.S. Food and Drug Administration (FDA)

Dr. Tobin began his presentation by summarizing how the FDA has supported test development, specifically COVID-19 point-of-care and over-the-counter (OTC) at-home tests during the public health emergency. He highlighted several emergency use authorizations (EUAs), including OTC antigen tests, and a recent revision to the EUAs for molecular, antigen, and serology tests to establish additional Conditions of Authorization to address the impact of SARS-CoV-2 viral mutations on test performance. Dr. Tobin noted that the number of EUA

authorized tests continues to increase with over 400 COVID-19 tests and over 650 revisions since February 2020. Dr. Tobin discussed the FDA's efforts to support test developers and stakeholders via outreach, including more than 70 town hall meetings with more than 49,000 participants. The FDA's COVID-19 diagnostics mailbox team has responded to over 185,000 email inquiries since the beginning of the public health emergency. Dr. Tobin continued updating the Committee on the FDA's Center for Devices and Radiological Health collaborative community activities such as the International Liquid Biopsy Standardization Alliance (ILSA). ILSA is an international group of public and private sector members, including academia, industry, government, patients, and end-users. They recognize the importance of working toward the global use of liquid biopsy and common reference standards in oncology. The measurement of cancer biomarkers in blood is key to fully realizing the benefits of precision medicine as a safe alternative to traditional invasive tumor biopsies in cancer diagnosis and treatment.

FDA's Center for Biologics Evaluation and Research (CBER) Overview of the Office of Blood Research and Review and Device Regulation ***Addendum 4***

J. Peyton Hobson, PhD
Division of Emerging and Transfusion Transmitted Diseases (DETTD)
Office of Blood Research and Review (OBRR)
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

Dr. Hobson provided an overview of the FDA's OBRR CBER. He explained that five offices are involved with the review and regulation of biologics, and meetings between OBRR and industry to discuss medical devices are arranged using the Q-Submission Program. Dr. Hobson noted that most OBRR devices are governed under two acts, with the first being the Public Health Service Act which regulates blood products and therapeutical biological products. Dr. Hobson continued by pointing out that some diagnostic devices are regulated under the Food, Drug, and Cosmetics Act. He described the types of devices reviewed by the DETTD and the Division of Blood Components and Devices, provided an overview of the in-vitro diagnostic (IVD) submission types received by OBRR, and explained how CBER interacts with CDRH as part of the CLIA test categorization process. Lastly, Dr. Hobson provided an HIV diagnostic device reclassification update, including a description of the Blood Products Advisory Committee (BPAC), which is an FDA federal advisory committee.

CDC Laboratory Safety Update ***Addendum 5***

Víctor R. De Jesús, PhD
Chief, Quality and Safety Systems Branch (QSSB)
Division of Laboratory Systems (DLS)
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Deputy Director for Public Health Science and Surveillance (DDPHSS)
Centers for Disease Control and Prevention (CDC)

Dr. De Jesús opened his presentation by highlighting the current goal areas of DLS and focusing specifically on activities to enhance the safety, surveillance, and response capabilities of clinical and public health laboratories. Dr. De Jesús continued by outlining the five CLIAC recommendations that address laboratory safety. He reviewed the April 2016 recommendation and several DLS projects to address biosafety in clinical laboratories, including the recently updated *Biosafety in Microbiology and Biomedical Laboratories* (BMBL) 6th Edition,

development of several e-learning courses for clinical and public health laboratories, and the Laboratory Outreach Communication System (LOCS) for information exchange. Dr. De Jesús announced a recent publication, *Clinical Laboratory Biosafety Gaps: Lessons Learned from Past Outbreaks Reveal a Path to a Safer Future*. He emphasized that DLS staff provided biosafety expertise to stakeholders during the CDC's COVID-19 response, including creating COVID-19 biosafety guidance web pages, developing frequently asked questions, and addressing over 250 biosafety inquiries. DLS staff were also deployed to support the response. He next provided an overview of DLS biosafety-related collaborations with the APHL, including committee membership, assistance with the development of guidance, checklists, and job aids to assist clinical and public health laboratories in conducting a risk assessment. Dr. De Jesús announced the upcoming 17th annual CDC International Symposium on Biosafety on August 27-31, 2022, in Atlanta, Georgia, and concluded by summarizing the DLS commitment to laboratory safety.

Introduction to the CLIA Regulations Assessment Workgroup ***Addendum 6***

Nancy Anderson, MMSc, MT(ASCP)
Senior Advisor for Clinical Laboratories
Division of Laboratory Systems (DLS)
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Deputy Director for Public Health Science and Surveillance (DDPHSS)
Centers for Disease Control and Prevention (CDC)

Ms. Anderson presented updates on the CLIA Regulations Assessment Workgroup. The workgroup was developed to address the CLIAC recommendation that HHS update the CLIA regulations to address new technology. She outlined the efforts of CDC, CMS, and FDA to organize topics and develop questions. Ms. Anderson continued by naming the CLIAC members who will serve as Co-Chairs, the agency ex officio members, and the workgroup members. She concluded by sharing that the introductory call for the entire workgroup would take place on December 10, 2021.

Committee Discussion

- A Committee member inquired about CDC's outreach to primary care and related specialties, including related laboratory specialty societies, to make them aware of the valuable DLS educational resources related to laboratory testing. Dr. Fitzgerald indicated several methods to communicate information, including LOCS and the DLS Clinical Laboratory Partners Forum. She noted that OneLab REACH is identifying stakeholders, including specialty organizations, and welcomes input on new partners for DLS engagement.
- One member asked about CMS coordination with CDC to set up hubs to expand school testing. Ms. Spruill noted that CMS efforts were focused on CLIA applicability and working with schools to provide guidance on multi-site exceptions and the Certificate of Waiver application process. Dr. Salerno added that the CDC's Testing and Diagnostic Workgroup initiated Operation Expanded Testing (OpET) to set up hubs across the country to offer laboratory testing in schools, particularly in disadvantaged communities. He added that CDC recently created the Expansion of Screening and Diagnostics Task Force to strengthen state and local communities by providing large contracts to make laboratory-based COVID-19 testing more widely available to schools.

- A member asked about the number of testing sites that have not obtained a CLIA Certificate of Waiver. Ms. Spruill indicated that the CMS complaint process could identify sites performing testing without the appropriate CLIA certificate. She added if a site is determined to be performing testing without a certificate, CMS will issue a cease-and-desist letter.
- Another CLIAC member asked about false-positive COVID-19 test results. Dr. Tobin responded that if notified of a test device resulting in a high level of false-positive results, the FDA would investigate to determine the root cause and take appropriate action to include a device recall or safety communication. Dr. Salerno added that CDC had published studies on the clinical performance of some COVID-19 tests, but with over 400 EUA tests, not all devices have been studied.
- A member inquired about CMS' next steps to address the recent point-of-care testing expansion. Ms. Spruill responded that CMS would partner with CDC to provide educational resources for these new testing sites.
- One member inquired about the quality of EUA tests and whether additional data are collected once the tests are in use. Dr. Tobin responded that the FDA provides a SARS-CoV-2 reference panel to test developers to evaluate the performance of tests in the post-authorization state. Manufacturers send panel results to the FDA for evaluation, and if issues are identified, the FDA works with manufacturers to address the concerns. FDA also collects independent evaluations to understand real-world performance of tests better.
- A Committee member inquired about the process for providing advanced notice to laboratories and test developers once the public health emergency ends and EUA tests are no longer authorized. Dr. Tobin commented that CDRH is working on a transition plan to help developers transition from a EUA to full 510(k) device authorization.
- A member asked if CBER had a process to forecast potential endemic diseases. Dr. Hobson commented that prediction is difficult but provided an example of the mandatory *Babesia* testing in certain states. He said that a recent emergence and spread of the parasite had resulted in mandatory blood testing in those states where there is a high endemicity.
- Another member inquired about home collection kits for testing. Dr. Hobson encouraged developers to contact the FDA to engage in the best approach to the approval process.
- A CLIAC member asked if HIV reclassification for blood screening would apply to reproductive tissues and cellular transplants. Dr. Hobson replied that those guidances fall under CBER's Office of Tissues and Advanced Therapeutics.
- A member asked about performance requirements, reference ranges, and labeling for serological assays based on their intended use and whether a test is used for diagnosis, screening the blood supply or approved for home use. Dr. Hobson noted that reference ranges are often not provided in the labeling, but the BPAC experts provide guidance on the topic.
- A Committee member inquired about collaborations with the FDA to establish guidelines to include safety information in manufacturer instructions. Drs. Salerno and Tobin noted that partnerships between the CDC and FDA in this area are working to improve the labeling to include additional safety considerations.

PRESENTATIONS AND COMMITTEE DISCUSSION

Next Generation Sequencing (NGS) in Clinical and Public Health Laboratories

Introduction to the Topic ***Addendum 7***
Addendum 7a

Heather L. Stang, MS, MT
Deputy, Quality and Safety Systems Branch (QSSB)
Division of Laboratory Systems (DLS)
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Deputy Director for Public Health Science and Surveillance (DDPHSS)
Centers for Disease Control and Prevention (CDC)

Ms. Stang presented a brief update on the CDC and APHL NGS Quality Initiative and the comprehensive plan to implement an NGS Quality Management System (QMS) in CDC and public health laboratories. She promoted over 85 customizable products available on the NGS Quality Initiative webpage and provided a few metrics, including site visits and top product downloads. Ms. Stang updated the Committee on the NGS Best Practices Forum membership, which is providing an opportunity for an open discussion among organizations to share accomplishments, priorities, and challenges for NGS. She noted the emerging themes after the first series of presentations. To conclude, Ms. Stang introduced the topics and presenters for the NGS session and reviewed questions for the Committee to consider during their deliberations.

CDC NGS Request for Information Summary Report ***Addendum 8***
Addendum 8a

Ira M. Lubin, PhD, FACMG
Geneticist, Quality and Safety Systems Branch (QSSB)
Division of Laboratory Systems (DLS)
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Deputy Director for Public Health Science and Surveillance (DDPHSS)
Centers for Disease Control and Prevention (CDC)

Dr. Lubin provided a summary of a request for information (RFI) published in the Federal Register in May 2020 to solicit public input on the personnel and the retention of NGS data in clinical and public health laboratories. The RFI resulted in sixteen responses from diverse respondents that included reference laboratories, public health laboratories, academic clinical laboratories, professional societies, industrial partners, and private citizens. Although there were few responses, the professional groups responding represent many interested parties. Dr. Lubin described the five topics addressed by the RFI and provided a summary of the responses for each. He emphasized that the responses to the RFI questions provided insights into many issues surrounding recruitment, retention, training, and competency assessment of bioinformaticians and pathology laboratory informatics personnel. In conclusion, Dr. Lubin noted that the RFI responses indicate a variation in practices and perspectives regarding the requirements for NGS personnel, what NGS files to keep and for how long, and the archiving and maintaining of NGS software no longer in use.

Perspective from the Frontlines: A Public Health Laboratory's Experience with NGS Validation and Reporting ***Addendum 9***

William A. Glover II, PhD, D(ABMM), MT (ASCP)
Assistant Director, Infectious Diseases
Division of Public Health, State Laboratory of Public Health
North Carolina Department of Health and Human Services

Dr. Glover provided a high-level overview chronicling the experiences of the North Carolina State Laboratory of Public Health as it relates to NGS validation and reporting. Dr. Glover described the hurdles encountered while validating and implementing NGS in the North Carolina State laboratory. He provided an overview of several challenges faced, including hiring qualified supervisory personnel who oversee testing in an NGS laboratory. He explained the difficulty of finding qualified bioinformaticians who had the requisite skillset and would meet the educational and laboratory experience requirements for CLIA testing personnel. Dr. Glover noted another challenge included the rapidly evolving nomenclature and frequent naming changes of NGS variants. He emphasized that often there is a lack of information technology resources to modify their laboratory information management system (LIMS) and institutional security policies, leading to challenges with reporting data to public databases. He added that problems developing control schemes that consider the cost, the sample to control ratio, the organism's complexity, the mix of sequencing runs, and integration into the workflow are common. In addition, Dr. Glover noted that diverse and well-characterized samples to use for validation were difficult to obtain. He summarized his experiences and provided areas where additional guidance was needed.

Public Comments
Addendum PC1

Committee Discussion

- A Committee member inquired if data security was mentioned in the RFI responses. Dr. Lubin responded that there were a few references to data security, but it was not addressed in most responses.
- A member commented that it is often less expensive to replace data files with newer data that may be of higher quality. Also, separate test positive and test negative data retention requirements should be considered.
- Another member commented that interpretations of flow cytometry tests for clinical decisions about transplants are often outsourced to consultants who work for multiple laboratories. The member asked whether this scenario is similar to the personnel recruitment and retention challenges mentioned in the RFI. Dr. Lubin responded that NGS requires highly skilled individuals to develop quality control and ensure that the informatics pipeline and analytic components generate reliable results. Few personnel have those skill sets.
- Two members suggested addressing the microbiology perspective since NGS SARS-CoV-2 variant detection has been increasing in microbiology laboratories. The number of instrument platforms is increasing and guidelines describing the appropriate use for NGS would be beneficial.
- A member asked about FDA regulating software pipelines and providing a uniform standard for validation. Dr. Lubin responded that the issue of oversight is a topic that

requires additional discussion noting that the RFI comments did not provide a consensus.

- A member emphasized the difficulty in recruiting a bioinformatician and the subsequent need to utilize a distributive test model for laboratory sequencing bioinformatic analysis. Dr. Glover commented that it is beneficial for a bioinformatician to be on-site when performing pipeline validations for CLIA compliance.
- Several members expressed challenges with the bioinformatics workforce recruitment and retention and the need to address several aspects of the workforce, including compensation, licensure requirements, job titles, and job duties, and to determine the role of Federal and State agencies, laboratory professional organizations, and academic institutions.
- A member suggested creating a program such as the APHL bioinformatics fellowship program that can be used to prepare bioinformaticians for infectious disease testing.
- Multiple CLIAC members commented on the need to incorporate bioinformatics and other information technology personnel requirements into the CLIA regulations, including requirements for responsibilities and educational qualifications that need to be met.
- A member commented that there needs to be a distinction between the personnel roles and responsibilities required under CLIA with respect to generating a clinically actionable test report versus the practice of medicine and the responsibility for interpreting that report to make a diagnosis. That distinction could help clarify the changes needed to the CLIA personnel regulations.
- Members inquired about the need for a catalog of the software that is being used for NGS pipelines.
- Another member commented that PulseNet is an excellent example of an established system utilizing NGS to compare bacteria's DNA fingerprints from patients to find clusters of diseases that represent unrecognized outbreaks. It can be used as a model for other NGS-based testing.
- Multiple members noted the importance of data file and software management and how the lack of interfaces to emerging technologies such as NGS may result in patient identification and reporting errors. Another member suggested working with vendors to develop nomenclature standards for reporting as specified in the 21st Century CURES Act interoperability guidelines.
- One Committee member suggested utilizing existing structures such as the National Accreditation Agency for Clinical Laboratory Sciences Medical Laboratory Scientist programs and the Center for Personalized Education for Physician programs in medical genetics and medical microbiology to help define bioinformatics personnel requirements.

The Committee deliberated, voted, and approved the following recommendations on the topic of Next Generation Sequencing in Clinical and Public Health Laboratories:

Recommendation 1: CLIAC recommends that CDC, CMS, and FDA convene a workgroup to define the scope of practice and the requisite CLIA qualifications for personnel performing bioinformatic data analysis and interpretation to produce test results that inform clinical decision-making.

Workgroup topics and needed input:
Provide recommendations and cross-reference existing guidelines regarding education, training, experience, and competencies for various bioinformatics levels, for example:

- An MS or PhD level individual that provides analytic leadership, tool selection, and database oversight.
- A bioinformatics technician that, for example, ensures data files are appropriately formatted for analysis, to run the analysis, and to check for the adequacy of the run.
- The skill sets required for the Laboratory Director (MD/DO or PhD) who carries overall responsibility for the clinical laboratory.

Seek input from institutions of higher learning (universities) to develop, in concert with clinical laboratories, a curriculum and training for each level.

Engage certifying bodies (e.g., The American Board of Pathology and the American Society for Clinical Laboratory Science Board of Certification) in developing certification or other credentialing opportunities for clinical bioinformaticians that will work in CLIA laboratories.

Recommendation 2: CLIAC recommends that the CDC, CMS, and FDA create a workgroup to review real-world practices as they apply to NGS for:

- the end-to-end processing of data, including the acquisition, analysis, and transmittal of data (including the Admission, Discharge, Transfer (ADT) message, orders, and results) between instruments and health records, including but not limited to electronic communication between the electronic health record (EHR), laboratory information system (LIS) or laboratory information management system (LIMS), and IVD vendors, as well as interoperability between institutions.
- quality management systems, including documentation, regarding data security, fidelity, transmission, curation, retention, and retrieval.
- validation of software algorithms used to generate interpretations

Laboratory Data Exchange and Harmonization

Introduction to Topic ***Addendum 10***

Jasmine Chaitram, MPH, MT(ASCP)
Chief, Informatics and Data Science Branch (IDSB)
Division of Laboratory Systems (DLS)
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Deputy Director for Public Health Science and Surveillance (DDPHSS)
Centers for Disease Control and Prevention (CDC)

Ms. Chaitram described the role of laboratory data transmission and exchange during the COVID-19 pandemic and explained the many pathways that data can flow through before reaching CDC. She discussed the challenges laboratories faced and how CDC overcame them. Ms. Chaitram gave a brief overview of the session's topics and introduced questions for the Committee to discuss.

CDC's Data Modernization Initiative ***Addendum 11***
Daniel B. Jernigan, MD, MPH
Deputy Director for Public Health Science and Surveillance (DDPHSS)
Centers for Disease Control and Prevention (CDC)

Dr. Jernigan began with an overview of the goals for the CDC's Data Modernization Initiative (DMI) and the challenges it addresses. He discussed each of the five priorities of DMI and explained the various activities associated with each one. Dr. Jernigan provided examples of how these activities would help CDC, its partners, and stakeholders share data quickly and efficiently. Examples included automating electronic case reports, training workers in data analysis, and identifying policies that need to be changed or developed for data management. He illustrated that COVID-19 led to a significant increase in electronic case reporting, with over 10 million COVID-19 reports from healthcare facilities. Dr. Jernigan closed with the vision of what DMI will accomplish for CDC and public health partners.

CDC Laboratory Data Exchange Strategy ***Addendum 12***
Robert W. Pinner, MD
National Center for Emerging and Zoonotic Infectious Diseases (NCEZID)
Centers for Disease Control and Prevention (CDC)

Dr. Pinner started his presentation with the history and implementation of laboratory data exchange (LDX), including electronic laboratory reporting (ELR) and Electronic Test Orders and Results (ETOR) for public health, beginning in 1997 through to the present DMI. He emphasized that the current pandemic resulted in unprecedented reporting volumes, and he illustrated the complicated pathways data flows from laboratories to the CDC. Dr. Pinner highlighted the SimpleReport tool developed by U.S. Digital Services in collaboration with CDC and discussed the tool's role in sharing COVID-19 testing data. He also mentioned the APHL Informatics Messaging platform that has been actively engaged during the pandemic. Dr. Pinner described the future of LDX, including the guiding principles used for developing an LDX strategy, and concluded with possible topics of discussion for the Committee.

Systemic Harmonization and Interoperability Enhancement for Lab Data (SHIELD) Update ***PowerPoint not Provided***
Micky Tripathi, PhD, MPP
Office of the National Coordinator for Health Information Technology (ONC)
U.S. Department of Health and Human Services

Dr. Tripathy began his presentation with an overview of the ONC and described one of its functions, electronic health record systems certification. He discussed laboratory interoperability and how the lack of standardization impacts the accessibility of the data for use within the healthcare and public health systems. Dr. Tripathy explained the activities of SHIELD, including working with IVD manufacturers to provide standardized information, leveraging FDA regulatory requirements to create a data hub to help assure consistency, and working with other federal agencies to provide uniformity throughout the various systems that use laboratory data. In conclusion, Dr. Tripathy said he expected the first version of the SHIELD strategic and business plan process to be available in a few months.

Real World Data for In Vitro Diagnostics ***Addendum 13***

Wendy Rubinstein, MD, PhD
Director for Personalized Medicine
Office of In Vitro Diagnostics and Radiological Health (OIR)
Food and Drug Administration (FDA)

Dr. Rubenstein began with a brief overview of her presentation, including key points, before describing real world data (RWD) and real world evidence (RWE). She explained how RWE is used for regulatory decisions and discussed the characteristics of the data used. Dr. Rubenstein continued with examples of regulatory decisions that used RWE and illustrated the different data sources used. She emphasized that RWE can be combined with other data for regulatory decisions. Dr. Rubenstein described characteristics of RWD that encompass relevance and reliability and how this information is used to consider RWE. She listed a few cases where RWE was used for IVD regulatory decisions and provided more detail for a few of them. Dr. Rubenstein finished her presentation with a discussion of the "Open Hand" process to use RWE to convert an FDA Emergency Use Authorization to a 510(k) submission, including the goals, the steps of the process, and what has been learned through this process.

Public Comments
Addendum PC2
Addendum PC3

Committee Discussion

- A Committee member asked how data sharing is impacted because the U.S. does not have a unified medical record using common patient identifiers. Dr. Jernigan answered that not having a single patient identifier presents challenges. He explained that the U.S. has a distributed model of healthcare that does not lend itself to having a specific identifier for each person and that high-level discussions are occurring to explore ways to make data flow more easily. He also mentioned that pilot studies are trying to integrate a way to keep patient data private while still allowing easier access to needed data.
- One member asked if using data to inform or make medical practice recommendations has been considered part of DMI. Dr. Jernigan clarified that while the data can certainly be used in this way, the DMI priority now is to use the data to inform public health policy decisions.
- Another member inquired if there have been discussions to include data flow for patient-facing tools, such as patients viewing their vaccine records. Dr. Jernigan explained there had been discussions about how the current system could incorporate patient-facing applications to improve the overall system.
- A Committee member asked if it would be possible to share data from SARS-CoV-2 variant calls back to the laboratories or providers who submitted the samples for sequencing. Dr. Jernigan stated that there are information technology solutions, but the overall framework and standards were still needed to accomplish this. Ms. Chaitram noted that, in some cases, laboratories performing the sequencing for epidemiological purposes were not CLIA-certified, and the decision was made not to report results from those laboratories. Another member added that it would be beneficial to see variant analysis presented at the zip code or county level similar to the way vaccination rates are presented.

- A member inquired if there was a relationship between the surveillance modeling performed and the supply chain because as testing increases, the supply chain is affected, which affects surveillance testing. Also, some laboratories observed that supply chain issues affected items that were not associated with SARS-CoV-2 testing. Dr. Jernigan answered that the supply chain management occurs at the White House and the Office of the Assistant Secretary for Preparedness. The new CDC Center for Forecasting and Outbreak Analytics would not specifically focus on the supply chain. However, that work would be supported in the future.
- One member commented that because the availability of personnel is vital during the pandemic, it would be helpful if that could be tracked so stress points could be identified. Dr. Jernigan responded that he would pass that on to those working on a strategy for public health resources.
- A CLIAC member asked if there was a timeline for the roll-out of the top priorities and updates. Dr. Jernigan responded that he expected the implementation strategy to be available in several weeks. Additionally, he summarized work already accomplished at CDC and ongoing work with other partners and stakeholders.
- One member asked if there would be real-time reporting for at-home testing. Dr. Jernigan answered that work was being done at the U.S. Digital Services, CDC, and NIH to develop these and related tools, but he did not have a timeline.
- A Committee member asked how laboratories can better provide data to be acted upon by physicians, providers, and patients in a timely fashion. Dr. Pinner had two suggestions: contributing more demographic data to help distinguish patients from one another and integrating laboratory reports and electronic health records more completely. Another Committee member asked what demographic data were missing and its impact on the timely completion and issuing of reports. Dr. Pinner responded that the additional data could help the state public health laboratory do work, such as identifying outbreaks and understanding the characteristics of the affected population. Having the demographics in the electronic health record would remove the need to ask laboratories to follow up with clinicians to receive that data.
- A member noted that leveraging both small and large laboratories involved in the pandemic would help move laboratory data exchange forward.
- A CLIAC member asked what security is being considered to prevent medical practices and laboratories from being hacked and ransomed. Dr. Pinner responded that CDC is working in a zero-trust environment that involves continuous patches and authentications.
- A Committee member asked that a common data dictionary with standardized LOINC codes be created and used by all vendors. Dr. Tripathy responded that it is challenging to orchestrate federal levers to move the process forward. Another committee member commented that international standards do not exist for most chemical analytes tested, such as troponin, which hampers harmonization. A member suggested that funding is needed to support standardization. A Committee member commented that the American Association for Clinical Chemistry (AACC) articulated the need for funding to Congress, which has resulted in money being provided to CDC for harmonization of results for specific analytes. Still, vendors need to be amenable to a particular standard. Dr. Tripathy commented that ONC is very engaged with the CDC, but public health cannot drive the work because providers consider clinical care to be their fundamental work.

- A member suggested that vendors be required to provide LOINC codes for users of their tests. He also asked if there is a process like the FDA has for IVD manufacturers for EHR or laboratory information systems. Dr. Tripathy answered that for EHRs to be certified, they must be able to “store and maintain data provided as LOINC encoded data” and that there is no certification authority for laboratory information systems.
- A CLIAC member inquired if ONC can fund demonstration projects, especially as methodologies constantly change. Dr. Tripathy answered that a SHIELD activity is to identify and define the scope of the data hub implementation. From there, pilot projects and a funding model could be developed. Dr. Tripathy stated that ONC’s budget does not include this work. He agreed that investment is necessary to improve interoperability.
- A Committee member suggested creating a map of the different entities involved in the data harmonization process, including the different federal levers. He also commented that industry is a necessary partner for this work, although it could be considered a conflict of interest and that it would be helpful if all laboratory data networks were included. Another member agreed that metadata could not come from just the largest laboratory corporations, and others must be included in the process for it to be successful. Another committee member commented that this work should not lead to more regulation of the laboratory.
- A member provided a list of what is needed to aid laboratory interoperability regardless of what type of laboratory it is. The list included electronic and discrete data, use of standard codes, and proper messaging structure. The member added that there is broad stakeholder representation on SHIELD and that endorsement of their work by CLIAC would be helpful.
- Multiple members commented on the usefulness of manufacturers providing LOINC codes for their tests. Another member cautioned on the practicality of manufacturers providing unique LOINC codes for every permutation of a specific test (e.g., each different unit of measure reported, different specimen type) and concern for off-label testing with the associated LOINC inferring a performance claim.
- One member described instances where data were unintentionally reported multiple times and stated that redundancy and data integrity are essential to keep in mind. Another member commented that discrete data are still necessary with the narrative processes in pathology. Another member commented that microbiology tests moved from a text-based system to one with discrete digital data. Multiple members agreed that increasing harmonization and standardization among vendors and other stakeholders require the federal government's help.

The Committee deliberated, voted, and approved the following recommendation on the topic of Laboratory Data Exchange and Harmonization:

Recommendation 3: CLIAC recognizes SHIELD’s efforts and encourages collaboration with CDC, CMS, FDA, other HHS organizations (e.g., ONC), IVD and EHR vendors, and professional organizations to leverage current standards and fund a phased approach by which specimens, actionable test results, and methods are coded for interoperability. EHR vendors, bioindustry suppliers, and non-profit and commercial laboratories must implement the standard(s) within a specified timeline. HHS should identify an appropriate mechanism for compliance.

Future CLIAC Topics

Topics suggested by Committee members included:

- The role of the clinical laboratory productivity consultants and the need to examine the transparency of this consulting practice.
- A presentation on the various data projects mentioned during the Laboratory Data Exchange and Harmonization topic to show how the programs may be interrelated.
- Expanded discussions on health equity disparities, such as the language used in patient portals.
- Discussion on non-traditional testing sites including the following:
    - In-home testing in the patient-centered medical home includes the rising use of continuous monitoring, implantable, and wearable laboratory devices.
    - The expanded role of telehealth and at-home health.
    - The implementation of good testing practices for rapid tests at outpatient facilities, doctors' offices, ambulatory care facilities, and other non-traditional testing sites.
- The laboratory personnel shortage, including linkages to personnel standards and the need for recruitment efforts for the medical laboratory profession.
- The impact of laboratory consolidation on the quality of testing.
- Defining the role and requirements of the personnel responsible for developing informatics and bioinformatics pipelines, including working with medical technology programs to create educational programs.

CLIAC NOVEMBER 3-4, 2021 MEETING AGENDA *Addendum 14*

CLIAC MEETING TRANSCRIPT *Addendum 15*

ACRONYMS *Addendum 16*

NOMINATION INFORMATION *Addendum 17*

ADJOURN

Drs. Ng and Salerno acknowledged the staff that assembled the meeting agenda and thanked the CLIAC members and partner agencies for their support and participation.

I certify this summary report of the November 3-4, 2021 CLIAC meeting is an accurate and correct representation of the meeting.

Dr. Valerie Ng, CLIAC Chair Date