Clinical

Laboratory

Improvement

Advisory

Committee

Summary Report

November 18-19, 2015

Atlanta, Georgia

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

Clinical Laboratory Improvement Advisory Committee
November 18-19, 2015, Summary Report

Table of Contents

RECORD OF ATTENDANCE

Committee Members Present

Dr. Burton Wilcke, Jr., Chair
Dr. Ramy Arnaout
Dr. Sheldon Campbell
Dr. Gwendolyn Delaney
Dr. Keith Kaplan
Dr. Roger Klein
Dr. Elizabeth Marlowe
Ms. Helen Mills
Dr. Elizabeth Palavecino
Dr. Richard Press
Ms. Anita Roberson
Ms. Maureen Rushenberg
Dr. John Sinard
Dr. Hardeep Singh
Ms. Susan Sheridan
Ms. Paula Vagnone
Dr. Qian-Yun Zhang
Mr. Andy Quintenz, AdvaMed (Liaison Representative)

Committee Members Absent

Dr. Monica de Baca
Dr. Ann Gronowski

Ex Officio Members

Dr. Barbara Zehnbauer, CDC
Ms. Karen Dyer, CMS
Dr. Alberto Gutierrez, FDA

Designated Federal Official

Dr. William (Bill) Mac Kenzie, CDC

Executive Secretary

Ms. Nancy Anderson, CDC

Centers for Disease Control and Prevention (CDC)

Ms. Sharon Andrews
Dr. J. Rex Astles
Ms. Diane Bosse
Dr. Roberta Carey
Dr. Alexis Carter
Dr. Bin Chen
Mr. Kevin Clark
Dr. Nancy Cornish
Dr. Marie Earley
Mr. Lin Fan
Ms. Bernita Frazier
Ms. Maribeth Gagnon
Ms. Rachel Greenberg
Ms. Stacy Howard
Dr. Michael Iademarco
Ms. Melissa Jennings
Dr. Lisa Kalman
Mr. Austin Kreisler
Mr. Derrick Lake
Dr. Edward Lockhart
Dr. Ira Lubin
Ms. Allison McAlister
Ms. Laura Martin
Ms. Graylin Mitchell
Mr. Jeffrey O'Kelley
Ms. Rhonda Louise Page
Dr. Jean Patel
Ms. Anne Pollock
Dr. John Ridderhof
Mr. Joseph Rothschild
Mr. Matthew Rubinstein
Dr. Paramjit Sandhu
Ms. Megan Sawchuk
Dr. Shahram Shahangian
Mr. Darshan Singh
Ms. Theresia Snelling
Ms. Heather Stang
Ms. Sonya Strider
Dr. Julie Taylor
Ms. Monica Toles
Mr. H. Eric Thompson
Ms. Pamela Thompson
Dr. Laura Wesolowski
Dr. Brenda Williams
Dr. Laurina Williams
Ms. Karlyn Wilson
Dr. Lyna Zhang
Mr. Jonathan Zhong

Department of Health and Human Services (Agencies other than CDC)

Ms. Amy Zale, CMS
Dr. Steven Gitterman, FDA
Dr. Peter Tobin, FDA

In accordance with the provisions of Public Law 92-463, the meeting was open to the public. Approximately 30 public citizens attended one or both days of the meeting. The meeting was also available by webcast.

CLINICAL LABORATORY IMPROVEMENT ADVISORY COMMITTEE (CLIAC) -BACKGROUND

The Secretary of Health and Human Services is authorized under Section 353 of the Public Health Service Act, as amended, to establish standards to assure 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. In addition, the Committee provides advice and guidance on specific questions related to possible revision of the 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.

The Committee consists of 20 members, including the Chair. Members are selected by the Secretary 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; the Commissioner, Food and Drug Administration; the Administrator, Centers for Medicare & Medicaid Services; and such additional officers of the U.S. Government that the Secretary deems are necessary for the Committee to effectively carry out its functions. CLIAC also includes a non-voting liaison representative who is a member of AdvaMed and such other non-voting liaison representatives that the Secretary deems are necessary for the Committee to effectively carry out its functions.

Due to the diversity of its membership, 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 their advice due to other overriding concerns. Thus, while some of the actions recommended by CLIAC may eventually result in changes to the regulations, the reader should not infer that all of the Committee's recommendations will be automatically accepted and acted upon by the Secretary.

CALL TO ORDER AND COMMITTEE INTRODUCTIONS

Dr. William Mac Kenzie, Designated Federal Official (DFO), Clinical Laboratory Improvement Advisory Committee (CLIAC), and Deputy Director for Science, Center for Surveillance, Epidemiology, and Laboratory Services (CSELS), Office of Public Health Scientific Services (OPHSS), CDC, welcomed the Committee and the members of the public, acknowledging the importance of public participation in the advisory process. Dr. Burton Wilcke, Chair, CLIAC, welcomed the Committee and called the meeting to order. All members then made self-introductions and financial disclosure statements relevant to the meeting topics.

Dr. Wilcke and Dr. Mac Kenzie recognized Mr. Robert Di Tullio, the outgoing CLIAC industry liaison, who received a certificate of appreciation signed by the DFO and Chair for his service on the Committee. Dr. Wilcke welcomed the new members, Dr. Ramy A. Arnaout, Dr. Sheldon M. Campbell, Ms. Helen Mills, Ms. Susan E. Sheridan, and new industry liaison, Mr. Andy Quintenz, to the Committee.

As an update to the April 2015 CLIAC meeting, Dr. Wilcke informed the CLIAC members that two letters were sent to the U.S. Department of Health and Human Services (HHS) on May 6, 2015:

- A letter expressing the Committee's recommendation pertaining to advancing a more connected, interoperable health information technology infrastructure.
- A letter expressing the Committee's recommendation pertaining to clinical laboratory biosafety, especially with regards to emerging infections in the United States.

The letters, along with the response to each letter from HHS, are available under "Presentations & Other Documents" as attachment 18 on the CLIAC website (http://wwwn.cdc.gov/cliac/Default.aspx).

Dr. Wilcke reminded the Committee that CLIAC seeks suggestions for candidates to the Committee at any time. Suggestions for consideration for the 2017 year can be provided by emailing CLIAC@cdc.gov. Each slate of nominees is carefully selected in an effort to assure that the Committee meets the required balance of stakeholders with respect to laboratory medicine, pathology, public health, clinical practice and consumers. The slate of candidates must also maintain the Committee's balance with respect to gender, geographic distribution, and minority representation. Dr. Mac Kenzie informed the Committee that during the past nomination cycle, one member representing physicians/family practitioners had to resign before the term started and a replacement is being sought for the next nomination cycle for submission in December.
Dr. Wilcke conveyed that the agenda topics included updates from the CDC, the Centers for Medicare & Medicaid Services (CMS), and the Food and Drug Administration (FDA). In addition, there would be presentations and discussions on the laboratory interoperability action plan, noninvasive prenatal testing, the FDA CLIA waiver guidance, the Institute of Medicine (IOM) Report: *Improving Diagnosis in Health Care*, and an FDA update on their laboratory developed test guidance. Dr. Wilcke reminded the

Committee of the change in procedure for agency updates indicating that the time allotted for agency updates had been decreased and CLIAC members had been asked to review each agency presentation prior to the start of the meeting.

AGENCY UPDATES AND COMMITTEE DISCUSSION

Revised Charter Overview *Addendum 00*

William Mac Kenzie, MD, Capt. USPHS
Deputy Director
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Office of Public Health Scientific Services (OPHSS)
Centers for Disease Control and Prevention (CDC)

Dr. Mac Kenzie provided a brief overview of the revisions to the CLIAC charter approved on June 30, 2015. The Estimated Number and Frequency of Meetings section of the charter was amended to read, "Meetings will be held at least once per year at the call of the DFO, in consultation with the Chair." In addition, the current Membership and Designation section of the charter was amended to read: "The committee shall also consist of three non-voting ex officio members, or designees: the Director, CDC; the Commissioner, FDA; and the Administrator, CMS; and such additional officers of the United States government that the Secretary deems are necessary for the committee to effectively carry out its functions." Dr. Mac Kenzie assured the Committee that these changes do not shift from historical CLIAC practices.

Centers for Disease Control and Prevention (CDC) Update *Addendum 01*

Barbara Zehnbauer, PhD, FACMG, FACB
Acting Director
Division of Laboratory Systems (DLS)
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Office of Public Health Scientific Services (OPHSS)
Centers for Disease Control and Prevention

Keeping the new agency update format, Dr. Zehnbauer did not provide a formal presentation, but inquired if there were any questions related to the CDC update slides which highlighted the activities and accomplishments of DLS since the last CLIAC meeting.

Committee Discussion

- One member asked for clarification regarding the CLIA-7 and CLIA-4 National Institute of Standards and Technology (NIST) test method categories of the electronic health records (EHR) certification tool as shown on slide number four. Dr. Zehnbauer clarified that DLS' Laboratory Health Information Technology (LabHIT) team is

working to ensure that the CLIA requirements for laboratory test report elements are incorporated into the Meaningful Use rules of EHR certification. She added that some EHRs are focused on physician communications and do not accurately represent all of the requirements that laboratories must meet under CLIA. The LabHIT team has been working to make the Office of the National Coordinator for Health Information Technology (ONC) aware of CLIA regulations.

- Another member asked if guidance would be developed on the appropriate definition for the "patient name and identifiers" laboratory test report elements that are added into the EHR adding that with the different methods for entering a name, patients may be entered multiple times. Dr. Zehnbauer replied this issue is a work in progress and active discussions with ONC to examine the limitations that currently exist in EHRs are ongoing.

Centers for Medicare & Medicaid Services (CMS) Update

Addendum 02

Karen Dyer MT (ASCP) DLM
Director, Division of Laboratory Services
Survey and Certification Group
Centers for Medicare & Medicaid Services (CMS)

Ms. Dyer provided the Committee with a brief overview of the current CLIA statistics and survey deficiencies. She informed the Committee that the CMS document "Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services" was updated in May 2015. She noted the implementation of the Individualized Quality Control Plan (IQCP), effective January 1, 2016, will require additional revisions to the interpretive guidelines. Ms. Dyer informed the Committee that the final rule on fecal occult blood testing has been put on a regulation schedule for publication in 2017. She commented that CMS has continued to provide presentations on the issue of "off-label" use of waived glucose meters in specific patient populations. She indicated the CMS Survey and Certification (S&C) Memorandum 15-11 entitled "Off-Label/Modified Use of Waived Blood Glucose Monitoring Systems (BGMS)" was reissued in March 2015 in draft form to obtain feedback and promote education.

Committee Discussion

- A member asked how CMS will ensure that laboratories are performing IQCP, how the survey process will work, and how CMS will address any problems that are identified. Ms. Dyer explained IQCP is a voluntary quality control (QC) option. She discussed the educational outreach including the development of an IQCP workbook in collaboration with the CDC available at https://wwwn.cdc.gov/clia/Resources/IQCP/ and an IQCP email (IQCP@cms.hhs.gov) for questions. CMS will have more information on how well laboratories are performing IQCP when surveys begin in January 1, 2016. CLIA surveyors will be inspecting laboratories based on the CLIA regulations. During the survey, if a laboratory has chosen to implement IQCP, the risk assessment and QC plan will be reviewed to ensure all stages of the laboratory test process and all five required elements of the IQCP are addressed. As with the standard CLIA QC review,

if problems are identified, they will be cited and the laboratories will need to address the issues.

- The same member asked if there is a way to incentivize the use of IQCP by laboratories. Ms. Dyer responded that CMS does not have a process in place for laboratory incentives. Another member added that in many cases performing QC following the CLIA regulations is very expensive and laborious and IQCP provides an alternative.
- A member commented that with only 48 percent of Certificate of Waiver (CW) sites receiving a letter of congratulations when CMS conducts their educational visits, there must be a number of issues in these sites that need to be addressed. Ms. Dyer reminded the Committee that under the CLIA law, CW sites are not surveyed as are other laboratories. Approximately two percent of the CW sites receive the educational visits by CMS where they are provided the "Ready? Set? Test!" booklet and surveyors assess the site's practices through a series of questions. Another member noted that since physician operated laboratories and private clinics with a CW do not have as much oversight as hospital systems, the member encouraged CMS to include the "Ready? Set? Test!" booklets and other educational products when CWs are mailed out. Ms. Dyer indicated that CMS plans to send the "Ready? Set? Test!" booklet out when testing sites apply for a CW.
- A member provided an example of an emergency department not following the manufacturer's instructions and inquired where the responsibility lies to ensure that the testing is performed correctly. Ms. Dyer suggested that emergency departments should have a point-of-contact or site director who oversees testing. If the site performing the waived test has a CLIA Certificate of Compliance or CLIA Certificate of Accreditation, then the laboratory director is responsible for ensuring the tests are performed correctly. Ms. Dyer added that individuals should notify their CLIA State Agency contact to report problems. Another member added that if the hospital has a Certificate of Accreditation the accreditation agency would oversee laboratory testing in the emergency department. A third member noted that in situations where there is a single CLIA Certificate that encompasses the entire hospital, the laboratory director is responsible for all testing and often performs in-house inspections to ensure compliance.
- One member suggested that manufacturers provide online educational products. Ms. Dyer commented that many manufacturers provide educational products but the issue seems to be compliance with the manufacturer's instructions.
- A member suggested that the topic of reimbursement for laboratory testing be added to the CLIAC agenda for a future meeting. Ms. Dyer reminded the Committee that the CMS Division of Laboratory Services does not oversee reimbursement issues. Another member added that the CMS Advisory Panel on Clinical Diagnostic Tests was chartered in April 2015 to advise the Secretary of Health and Human Services on the establishment of payment rates for new clinical diagnostic laboratory tests and the factors used in determining coverage and payment processes for new clinical tests. Perhaps this Panel could address CLIAC's questions and concerns regarding reimbursement. CDC agreed to investigate.

Food and Drug Administration (FDA) Update *Addendum 03*

Alberto Gutierrez, PhD
Director
Office of In-Vitro Diagnostics and Radiological Health (OIR)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration

Dr. Gutierrez began his presentation with an organizational update of the OIR. He provided a brief update on the status of two presidential initiatives that OIR has been involved in, the national action plan for combating antibiotic-resistant bacteria (CARB) and the Precision Medicine Initiative (PMI). Dr. Gutierrez highlighted two public workshops which occurred in October, "In Vitro Diagnostic Testing for Direct Oral Anticoagulants" and "Non-Microbial Biomarkers of Infection for In Vitro Diagnostic Device Use." He discussed the draft guidance documents developed to distinguish between prescription blood glucose meters intended for use in point-of-care professional healthcare settings and over-the-counter blood glucose meters for consumers. The draft guidance documents were published in January 2014, the comments have been analyzed, and the final guidance documents should be published soon.

Committee Discussion

- A member asked about the next steps with the blood glucose monitoring system for critical care. Dr. Gutierrez replied that the FDA separated the glucose guidance document into two documents; one for the direct-to-consumer glucose meters and the other for glucose meters that are meant to be used on more than one patient. He explained the dichotomy between blood glucose testing for a critically ill patient in an intensive care unit and the routine monitoring of an outpatient's glucose levels and related these are issues that are not being controlled by the manufacturers. He noted that over-the-counter glucose meters are automatically waived by CLIA law and are being used broadly in hospitals by people who do not understand the issues. He stated the FDA requires manufacturers to clearly label the meters to indicate that the meter has not been tested on critically ill populations. Dr. Gutierrez added that CMS has been actively involved in educating users of glucose meters about testing populations and informing the testing sites that any change to the manufacturer's instructions will result in a default to a high complexity category of testing.
- One member requested additional information on the *National Action Plan for Combating Antibiotic-Resistant Bacteria*. Dr. Gutierrez responded that the plan is quite broad with many different goals across many federal government agencies. He commented that the FDA is involved in promoting the development of *in vitro* diagnostic tests that would be of significant clinical and public health utility to combat the development and spread of antibiotic resistant bacteria. Dr. Gutierrez provided examples of projects including the collaboration with the National Institutes of Health (NIH) to promote new research on rapid diagnostics, the development of the Antimicrobial Resistance Isolate Bank, a centralized repository of microbial pathogens with well-characterized resistance profiles that are assembled by CDC in collaboration with the FDA, and the FDA's work in defining databases for next generation sequencing so that regulatory decisions can be made from the databases.

- A member asked if the Class II Special Controls Guideline: Multiplex Nucleic Acid Assay for Identification of Microorganisms and Resistance Markers from Positive Blood Cultures was intended for manufacturers or for clinical laboratories. Dr. Gutierrez replied that the special controls guidance documents are guidelines written for a new device. Manufacturers follow these guidelines when they wish to clear a device by claiming it has substantial equivalence to a predicate device.
- Another member inquired about the review of *in-vitro* diagnostic (IVD) kits and how the FDA would discover issues such as carryover contamination in nucleic acid based tests by looking at the data alone. Dr. Gutierrez responded though the FDA does not perform any laboratory testing there is a thorough review of the submission. He observed that one of the weaknesses of the premarket approval (PMA) review is that it relies solely on data the manufacturer submits. PMA approval is based on a determination by the FDA that the submission contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). Dr. Gutierrez noted that in many cases problematic issues with a device will be reported and the FDA does investigate these claims.

PRESENTATIONS AND COMMITTEE DISCUSSION

ONC Laboratory Interoperability Action Plan

Introduction ***Addendum 04***

William Mac Kenzie, MD, Capt. USPHS
Deputy Director
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Office of Public Health Scientific Services (OPHSS)
Centers for Disease Control and Prevention (CDC)

Dr. Mac Kenzie introduced the topic of laboratory interoperability with a brief overview of its value to the laboratory, patients, providers, and the nation. He briefly discussed the challenges being encountered. Finally, he presented three questions for CLIAC to address during their discussion of this topic.

Promoting Semantic Interoperability of Laboratory Data; Public Workshop Update

Steven Gitterman, MD ***Addendum 05***
Medical Officer
Center for Devices and Radiological Health (CDRH)
Office of Medical Products and Tobacco (OMPT)
Center for Devices and Radiological Health (CDRH)
Office of In Vitro Diagnostics and Radiological Health (OIR)
Division of Microbiology Devices (DMD) (BAC1)
Food and Drug Administration (FDA)

Dr. Gitterman opened his talk with a review of the workgroup's agenda and noted the meeting's focus was on Logical Observation Identifiers Names and Codes (LOINC), Systematized Nomenclature of Medicine/ Unified Code for Units of Measure (SNOMED/UCUM), and unique device identifiers (UDI). He acknowledged that staff from the National Library of Medicine (NLM), Regenstrief, CDC, and FDA met regularly to plan this public workshop and will continue meeting to address coding issues. Dr. Gitterman presented some comments received after the meeting, and briefly reviewed the background and key issues discussed at the meeting. He stated the workgroup concurred that the focus should remain on LOINC which currently remains the most pivotal coding scheme for supporting laboratory data interoperability.
Dr. Gitterman ended with a review of the FDA's ongoing considerations including how to integrate industry into the workgroup and piloting possible technical solutions.

The video, slides and transcript from the workgroup meeting are available at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm453897.htm.

Committee Discussion

- One member asked whether there are any data that demonstrate how the lack of interoperability impacts patient outcomes. Dr. Gitterman responded there are no supporting data, however, good decision support depends on interoperability. The member agreed and asked if there will be an opportunity in the future to include consumers and patient organizations in the ongoing workgroup's endeavors. Dr. Gitterman agreed it is a good idea.
- One member noted that although we understand the benefits of interoperability, others who are involved may not. Therefore, it is important to be able to produce data showing the benefits. Dr. Gitterman agreed.
- Another member asked if the workgroup discussed the ramifications of LOINC and SNOMED on the consumer's/patient's experience when accessing their health records. Dr. Gitterman replied no, this issue is beyond the workgroup's current scope.
- A member commented on the difficulty in finding units when researching laboratory tests in the Regenstrief LOINC Mapping Assistant (RELMA). Dr. Gitterman agreed and explained the units would be coded within the structured product labeling (SPL).
- A member remarked that LOINC codes are important for unifying and creating reference ranges and standards. However, there are other issues that need to be addressed. A universal platform is needed for result reporting and patient identifiers must be standardized.

Laboratory Interoperability Update ***Addendum 06***

MariBeth Gagnon, MS CT(ASCP)HTL
Health Scientist
Division of Laboratory Systems (DLS)
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Office of Public Health Scientific Services (OPHSS)
Centers for Disease Control and Prevention (CDC)

Ms. Gagnon began by reminding the Committee of Ms. Dyer's high level review of the ONC laboratory interoperability action plan presented during the April 2015 CLIAC meeting. She said the three agencies (CDC, CMS, and FDA) have identified five areas (noted on her slides as five bullets) from the action plan where they may be able to promote interoperability. These were presented to the ONC and have been published (Connecting Health and Care for the Nation: A Shared Nationwide Interoperability Roadmap, Final version 1.0, published October 2015; https://www.healthit.gov/policy-researchers-implementers/interoperability) in the current version of the roadmap.
Ms. Gagnon remarked that the notes in the parentheses on each slide identify where the bullet is found in the ONC roadmap. Ms. Gagnon said bullet one addresses coding and standardizing of coding and value sets. This is being addressed through the ongoing work of the FDA/CDC/NLM task force mentioned by Dr. Gitterman. She reported the three agencies believe if manufacturers are involved in the coding it will simplify the process and noted that some manufacturers have already begun this process. She noted the second and third bullets relate to CDC's work with NIST to develop use cases which include the data elements that were listed in Dr. Zehnbauer's slides. These use cases were also included in Health Level Seven International's (HL7) Implementation Guides (IGs) for Laboratory Orders Interface (LOI), Laboratory Results Interface (LRI) and electronic Directory of Service (eDOS). Ms. Gagnon noted the laboratory community and vendors invested a lot of time and effort in the development of the IGs, ensuring they include data elements to help laboratories meet the CLIA requirements and anticipated this would save laboratories a lot of time when validating the sending and receiving of laboratory results between the laboratory information system (LIS) and multiple EHRs.
Unfortunately, she said, none of this work was recognized by the most recently published CMS Incentive Rule and thus could not be recognized in ONC's Certification Rule. She related the fourth bullet is a joint effort between CMS and CDC to develop training aids, particularly around LOINC. The fifth area, she said, deals with identity management and is more of a challenge for the laboratory than for the providers. The data elements included in the above mentioned IGs for patient identification, if required, would direct EHR and LIS vendors to use the same elements. This would help with patient identity between systems.

Committee Discussion

- A member asked if multiple LOINC codes map to the same CPT reimbursement code. Ms. Gagnon replied there is not a one-to-one mapping of CPT codes to LOINC codes. They are coding systems for two different types of processes. If there could be a one-to-one mapping of CPT and LOINC codes it might make reimbursement easier to implement and be profitable to the providers and laboratories.
- Another member observed that CPT codes are generally codes for classes of tests. There could be several different methodologies, but each would be in the same test class and have the same CPT code reimbursement. Therefore, multiple LOINC codes could map to a single CPT code category.
- A member noted that test costs can very extensively and grouping multiple methodologies into one category for payment will cause a problem.

- One member noted that the NIH website mentions a CMS project mapping LOINC codes to CPT codes. The member asked whether that information is going to be incorporated into the standardization of LOINC codes.
- Commenting on industry providing the LOINC codes or performing most of the background work for the laboratories, the AdvaMed liaison cautioned that it is not just a straightforward one-for-one LOINC code for tests on a certain platform, there are a lot of variables. He said manufacturers struggle to provide as much value-added customer service as possible, however, providing a comprehensive guide for LOINC codes on a specific instrument is a daunting task because laboratories perform so many manipulations on their own, whether in the pre-analytical phase or elsewhere, that could cause a LOINC code to change. So the laboratory cannot solely rely on manufacturers to provide LOINC codes to them. The laboratories will have to examine their practice and determine whether a LOINC code is applicable.
- A member commented that it is disappointing to hear that the CLIA requirements are not going to be included in the ONC's Certification Rule as one of the laboratories' continuing issues is assuring accurate transmission of comments included in the test report, which may be necessary for the interpretation of results. Without a standard, the healthcare provider may not realize there are comments included with the report. Ms. Gagnon replied the IGs, which are voluntary, do have a standard for including comments. She agreed having a comment presented in a standardized way will make it easier for the provider to know where to look.
- A member asked for the top three next steps that would move the laboratory interoperability agenda forward. Ms. Gagnon replied the first step would be the semantic interoperability coding efforts the FDA/CDC/NLM task force is working on. This could solve a lot of problems in how the information is presented to a patient. If the coding can be standardized and the clinical decision support tools created it may be possible to display test results from multiple years in one graphic. This would also decrease the amount of material a patient would need to see. Semantic interoperability, though, only helps with making sure the boxes are like boxes. The second step would be to determine how the boxes are connected. That is the issue of the interfaces where the LOI/LRI/eDOS IGs will help. Though the IGs were not specifically written into the current regulations, ONC has been working with the developers of the IGs to promote pilot testing that will demonstrate if the implementation of these guides saves time and/or money. It will also help if the laboratories write about their challenges and issues during implementation as a comparison of the issues could lead to a one-time solution. The third major step is patient identification. Congress has not mandated a unique patient identifier, therefore voluntary standards for patient identification are needed.
- One member asked if there would be any action from HHS regarding the CLIAC recommendation on health IT made during the April 2015 meeting. Ms. Gagnon replied CDC has had conversations with ONC since the April meeting. ONC has assigned a laboratory liaison who has been in communication with the different groups working on laboratory interoperability. ONC was involved with the FDA meeting and following it, there was a federal meeting to discuss next steps. She stressed progress is being made.

- One member noted the goal, to be able to take similar results from multiple institutions and aggregate them in some way, is admirable. However, the difficulty with using LOINC is that LOINC is an incredibly granular coding system. The member voiced the opinion that there will need to be another layer because the LOINC coding system is not hierarchical, so there is no way one can determine subtle differences between code numbers. The member asked if this plurality of code numbers is being addressed. Ms. Gagnon replied that a representative from Regenstrief is on the workgroup, and the workgroup anticipates addressing this issue through FDA's interaction with the manufacturers. The member noted that to yield the benefit from this, one needs to know which of the codes can be grouped together, so code group sets are needed. Ms. Gagnon agreed and added that multiple manufacturers might have the same test. Regenstrief involvement is to make sure that if two manufacturers are offering a test for the same analyte or organism, that it has the same code. The member responded they may have different codes and still be an aggregable test result. For example, there may be differences in the procedure that nonetheless yield comparable results that could then be aggregated to benefit the patient's understanding. Ms. Gagnon agreed, and responded that NLM is actively looking at this issue.
- A member commented that there are similar coding issues in SNOMED as in LOINC, For example, hepatitis B surface antigen might be coded as a substance and hepatitis B as an organism, but there is nothing in SNOMED that links the two. The member asked if this was a recognized problem that is being addressed in the current undertaking. Dr. Gitterman replied it is not being addressed through this activity.
- Another member noted that each instrument may have a different reference range and asked how the reference ranges were being handled and if every result has a reference range attached to it. Dr. Gitterman responded the workgroup is currently focused on aggregating test systems and has not begun to consider including reference ranges.

The Chair introduced the discussion questions for the Committee to consider.

Addendum 07

What are the semantic interoperability challenges for currently marketed in vitro diagnostic devices? How can FDA, CDC, CMS, and other agencies help to address the challenges?

- A member said semantic interoperability is laboratory specific, therefore laboratory professionals need to solve this issue and provide solutions to be incorporated in the EHR.

What needs to happen to bring about widespread exchange of laboratory data among providers? What should be the role of CMS, CDC, and FDA and other agencies in this process?

- Several members suggested that laboratories cannot determine if there is benefit to being interoperable with other healthcare systems. It was suggested that if CMS offered incentives to laboratories and showed them the benefits of information exchange, then interoperability would happen.
- A member agreed that the effort must be incentivized and added there is legislation that was recently proposed called the "Trust IT Act" that proposes to create a three

star rating for electronic health records in terms of usability, security, and interoperability.

- Another member responded that while legislation on those lines sounds great, if done incorrectly the result could be worse than what now exists.
- A member commented that laboratory professionals need to be included in the discussions. Another member remarked that consumer and patient organizations need to be involved, noting they would be valuable in envisioning outcomes.
- One member commented interoperability requires standardizations across multiple platforms. The member suggested utilizing systems already in place through CMS and through CLIA, e.g., standardized reporting and regulatory requirements. If these were incorporated in EHRs we would be much further along. This should be the basis for the beginning of interoperability. Ms. Dyer responded CMS worked with the developers of the IGs with the idea that standardization would help and acknowledged this was a huge effort that included laboratory professionals, the American Clinical Laboratory Association, and vendors.
- A member asked if there are other disciplines that have already encountered and solved such interoperability issues that we could learn from.

What educational information needs to be provided to laboratory professionals to promote interoperability of laboratory systems with the EHRs and other health IT systems?

- A member commented that in the presentations, statements were made that laboratory professionals have not engaged in the process and that there is a need for education. The member remarked that education is not the issue. Instead, the issue has been that laboratory professionals were not invited into the process and have not been given any financial incentives, so decisions have been made without input from them. This is being corrected.

- After deliberating on the interoperability challenges and the need for bringing about widespread exchange of laboratory data in EHRs and other health IT systems, the Committee voted to provide the following recommendation to HHS.

HHS should ensure the following next steps:

- EHR content display related to laboratory data (including graphs) should be standardized such that all CLIA-required test report elements are on every laboratory display/graph.
- National Institute of Standards and Technology (NIST) should create use cases for testing transmission and display of laboratory data in the pre- and post-implementation stages of EHR use in order to maintain semantic interoperability in various laboratory (clinical/anatomic pathology) settings. Use cases should start at the laboratory system and involve sending data across the interface for display in multiple EHRs. This would test the interoperability of comments, units, reference ranges, etc. (sometimes the reference ranges in the EHR are different than in the laboratory information system).
- Consider the incorporation of CLIA use cases in next certification cycle.

- CMS should consider identifying activities considered as 'information blocking' and place multifaceted strategies to discourage such activities. For example, incentives could be built for offsetting the current high fees for laboratory/EHR interfaces.

In addition to the recommendation above, HHS should consider following next steps to drive interoperability:

*Drive semantic interoperability through incentives (perhaps from CMS) and establish some measure thereof and leverage existing standards in CLIA.

*Engage laboratory professionals and consumers in all discussion regarding global issues of interoperability and its related outcomes.

*Use information from Standards & Interoperability guides to address patient ID issues. For example, HHS should require laboratories to collect and send key patient identifying characteristics such as first name, last name, date of birth, and gender, and optional items such as cell phone number, email address, and physical address. This would help ensure accurate patient matching across systems.

Non-Invasive Prenatal Testing

Introduction

Addendum 08

Barbara Zehnbauer, PhD, FACMG, FACB
Acting Director
Division of Laboratory Systems (DLS)
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Office of Public Health Scientific Services (OPHSS)
Centers for Disease Control and Prevention (CDC)

Dr. Zehnbauer began an overview of non-invasive prenatal testing (NIPT) with a comparison of non-invasive and invasive methods. She explained that NIPT uses maternal peripheral blood specimens taken as early as ten weeks gestation to test for circulating cell-free fetal DNA (cfDNA). Dr. Zehnbauer listed four companies that detect aneuploidies (abnormal numbers of chromosomes) and fetal sex by using either massively parallel sequencing, also referred to as Next-Gen sequencing, or by comparing differences in single nucleotide polymorphisms (SNPs) between the DNA of the mother and the fetus. She explained that these tests were initially validated as screening tests for high-risk pregnancies and abnormal results were expected to be confirmed by a diagnostic test such as chorionic villus sampling or amniocentesis before any discussion of pregnancy termination. She also emphasized that these tests would not detect other genetic disorders. She said concerns have been expressed by patients, physicians, laboratory professionals, regulators, and stakeholders who deal with ethical, legal, and social implications. Dr. Zehnbauer briefly described the recently published "Non-invasive Examination of Trisomy (NEXT)" study and discussed possible solutions to concerns that have been raised about NIPT. She concluded by reviewing the questions to be discussed by the Committee following the presentations.

Prenatal Screening for Down Syndrome Using Cell Free (cf)DNA: Current Issues

Glenn E. Palomaki, PhD
Associate Professor
Department of Pathology and Laboratory Medicine
Women & Infants Hospital
Alpert Medical School at Brown University
Providence, Rhode Island

Addendum 09

Dr. Palomaki began his presentation by discussing terminology and concepts stressing that placental DNA is tested, not fetal DNA. He provided an overview of the methods used and explained the differences between them. Using data from different studies, he discussed the sensitivity and limitations of the NIPT tests compared to the traditional tests, addressing various parameters including time of specimen collection, failure rate, maternal mosaicism, and confined placental mosaicism. He emphasized that the high failure rates observed in some studies or laboratories were usually due to method failure and rarely due to true false positives. In these cases some part of the process did not pass quality control criteria or there was an insufficient quantity of DNA. Dr. Palomaki concluded his presentation by briefly discussing positive predictive values and how this can be misleading for NIPT.

Committee Discussion

- A member asked if test samples were independently analyzed or results from other samples combined for the data shown on slide 10. Dr. Palomaki responded that the observations are not combined.
- Another member asked what the turnaround time was for the test. Dr. Palomaki responded that it can vary but the average turnaround time is eight to nine days.
- A member asked how often other chromosomal variances are found. Dr. Palomaki answered that additional disorders have been added over time. The tests originally detected one trisomy and now at least one laboratory has added a crude whole genome test.
- One member asked how the performance of these tests compares to other screening tests. Dr. Palomaki answered that the most common screening test, the quadruple test, has an 80% detection rate and a 5% false positive rate. The NIPT tests have approximately a 97-98% detection rate and 2% false positive rate. He stated, although test failures need to be handled differently, the NIPT tests are much better screening tests with much higher predictive values than what is currently available for serum and ultrasound, however, they are not diagnostic tests.
- A member asked what information a woman should be given when considering NIPT. Dr. Palomaki replied three options could be offered. If the woman wants to know everything that could be wrong with the fetus, an amniocentesis or chorionic villus sampling (CVS) that is tested by a chromosomal microarray would be the best option. If the woman wants to know more before deciding if she wants amniocentesis or CVS, NIPT is the best option. The final option is not to test at all.

Non-invasive Prenatal Screening: The Clinical Perspective ***Addendum 10***

Cecelia Bellcross, PhD, MS, CGC
Assistant Professor
Director, Genetic Counseling Training Program
Emory University School of Medicine
Department of Human Genetics

Dr. Bellcross provided an overview of NIPT and the concerns from the clinician's perspective. She compared the characteristics of invasive and non-invasive prenatal testing including costs and sensitivity. She discussed NIPT's challenges and common reasons false positives occur. Dr. Bellcross described the lower positive predictive value (PPV) based on several recent studies compared to marketing materials and previous studies and pointed out a free website that would calculate the PPV for Trisomy 21, Trisomy 18, and Trisomy 13 based on maternal age, gestational age, and the test being used. As some of the tests have been expanded to detect microdeletion syndromes not associated with maternal age, Dr. Bellcross illustrated the low PPV for each disorder and listed some of the limitations of NIPT tests for microdeletion syndromes. She briefly reviewed the recommendations of some professional organizations and stressed that NIPT is not comprehensive prenatal screening but many patients do not understand that screening is very different from diagnostic testing. Before conducting the test, Dr. Bellcross suggested a number of limitations and issues that should be discussed with the patient as well as the benefits of NIPT and concluded with concerns and limitations to be kept in mind during counseling after the test.

Committee Discussion ***Addendum 11***

- A member asked if women were terminating pregnancies based solely on NIPT without going to a physician or receiving an elective abortion for non-medical reasons. Dr. Bellcross clarified that the study found women electing to terminate the pregnancy on the basis of the NIPT results. The member stated that if a physician performed an abortion without understanding the test it would be a medical malpractice issue as the patient did not receive a proper explanation of the test results. Dr. Bellcross stated that is part of the issue.

The Chair introduced the discussion questions for the Committee to consider.

- What should labs performing NIPT disclose
    - Assay validation for different patient populations? (high-prevalence of genetic disorders vs general population)
    - Performance specifications for aneuploidy detection?
    - Regarding risk interpretation in result reporting?
    - About confirmatory diagnostic testing?
- How can laboratories help physicians and patients be better informed about the limitations and appropriate use of NIPT?
- Is there a role for FDA/CMS/CDC in providing that information?

The Committee did not respond to the questions individually but offered the following comments.

- Dr. Gutierrez recounted that the topic of NIPT was selected because of legislation introduced this year. HR3441 proposes that CDC establish educational programs for patients and healthcare providers regarding NIPT. Dr. Zehnbauer added that while CDC was named, it was unclear which part of CDC would be responsible. Dr. Bellcross stated that the National Society of Genetic Counselors would be happy to assist in this endeavor.
- Several members agreed that the CLIA regulations regarding clinical consultant responsibilities should be followed and enforced rather than developing a new process. It should be made clear that a screening test is different from a diagnostic test.
- A member commented that if the experts on the Committee do not agree or have questions about what information needs to be understood by physicians and patients, then they should recommend that materials be developed by unbiased bodies and endorsed.
- Another member suggested that parallel tracks for education, one for physicians and one for patients, be endorsed and, at least for the patient materials, CDC should be involved in some way because parents find CDC to be a trustworthy resource.
- One member asked why CLIAC is discussing this because the main issues are misrepresentation in marketing and whether the data used for approval are consistent with more recent data. Dr. Gutierrez responded that FDA reviews evidence and information of tests but only when the manufacturer applies for FDA approval. These are currently laboratory developed tests (LDT) so no review occurred. Also, laboratories are adding rarer disorders to the testing performed with no evidence to support the testing because huge studies would be required. Concerns have been communicated, however, until there are new LDT regulations nothing can be done.
- Another member asked if there is a process or a barrier stopping the FDA from using its enforcement discretion available for LDTs to inspect the laboratories that perform this testing. Dr. Gutierrez replied that the concern is practices surrounding the use of the tests, not the tests themselves. To determine these practices, the FDA would have to inspect the laboratories which could be seen as FDA overreach.
- A member questioned the validity of the tests for Trisomies 13 and 18. Dr. Gutierrez replied this is an unusual case because these are very precise tests but they still need a second confirmatory test. Patients and physicians need to understand that validity for some disorders is an issue.
- One member questioned the cost effectiveness and value for a patient, especially for patients who do not plan to terminate regardless of the screening result or who is considered high risk and will already be tested later in the pregnancy. General practitioners need education too because their patients are asking them about these tests that the doctors are not familiar with and information about them are not readily available.
- A member stated that as everyone agrees that providers and patients need to be informed and laboratories need to disclose all information, the recommendation should be that this should be moved forward.
- Dr. Palomaki read the test limitation statement from one laboratory's report and two Committee members addressed the clarity and ability to change the limitation statement. Dr. Bellcross suggested providing the positive predictive value and a clear

statement of risk for the disorder is helpful. A member asked if a statement that positive and negative predictive values depend on prevalence would be a sufficient improvement. Dr. Bellcross replied no because maternal age is also important.

- Two members and Ms. Dyer addressed where laboratory communications with the patient are mentioned in the CLIA regulations and if CMS has rulemaking authority regarding marketing information. Ms. Dyer replied that CLIA addresses patient access to laboratory test results, but CMS does not have rulemaking authority regarding test marketing.
- One member commented that physicians usually turn to laboratories for information about tests and their results but genetic testing is sometimes different because ordering physicians may send the testing directly to a specialty laboratory and the hospital laboratory is unware that the test was ordered. When the hospital laboratory is later asked to interpret the results, they do not have the expertise to help so the burden should be on the laboratory performing the test.
- Dr. Wilcke, the CLIAC chair, called for formal recommendations.

The Committee made the following recommendation to be sent to HHS:

- HHS and CDC should support the development of NIPT-related enduring educational materials accessible to patients and health care providers. In order to support effective patient care decisions, these materials should include simple language and visual graphics to effectively convey information about risks, benefits, and limitations of different types of prenatal testing.
- HHS should require that ordering providers requesting non-invasive prenatal screening tests (of cell-free fetal DNA) should perform and document a pre-test discussion to inform the patient of risks, benefits, and limitations.
- HHS should recommend labs performing NIPT to disclose information regarding test limitations and positive predictive values (likelihood that the fetus has a genetic condition) that is directly comparable to conventional techniques (e.g., by maternal age) while reporting results as well as risk interpretation and appropriate indications for confirmatory diagnostic testing.

CLIA Waiver Guidance

FDA Report on CLIA Waiver Guidance

Addendum 12

Peter Tobin, PhD
Office of In-Vitro Diagnostics and Radiological Health (OIR)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration

Dr. Tobin began his presentation by reviewing the definition of a waived test as stated in the CLIA law and describing the available pathways for waiver approval. He provided a brief CLIA waiver history leading up to the 2008 FDA guidance document: "Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA)

Waiver Applications for Manufacturers of In Vitro Diagnostic Devices" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070890.pdf). Dr. Tobin reviewed the process to determine if a test system meets the 2008 CLIA waiver guidance criteria and provided the number of CLIA waivers by application. He discussed the recent concerns regarding the interpretation of "accuracy" in the guidance document. He provided the scientific definition of "accurate" emphasizing the importance of measurement traceability in providing accurate information for medical decision-making in laboratory medicine. A review of accuracy interpretations for waiver studies was provided showing that in 1995 waived method performance was compared to a reference method which changed with the 2001 FDA draft guidance in which the waived method performance was compared between trained and untrained users to determine accuracy. Dr. Tobin discussed the current 2008 guidance document, where there must be a demonstration of insignificant risk of erroneous results by comparison of waived method performance by untrained users to a traceable method. Dr. Tobin reviewed different accuracy study designs emphasizing the clinically relevant flexibility of the current CLIA waiver guidance document and discussed the decision by FDA to reopen the 2008 CLIA waiver guidance to expand and clarify areas in the guidance. He reviewed the dual 510(k) and CLIA waiver application pathway as established as part of Medical Device User Fee Act (MDUFA) III, which offers the simultaneous review for a CLIA waiver approval along with a 510(k) clearance. This option offers a potentially significant time and cost savings due to combined study designs. Dr. Tobin concluded his presentation by introducing two discussion questions for the Committee to consider:

1. Are there any issues you see with the interpretation of "Accuracy" in the 2008 CW Guidance that should be addressed in revisions?
2. Are there any other aspects of the CW guidance that FDA should address in revisions?

Committee Discussion

The Committee did not respond to the questions individually but offered the following comments.

- Dr. Gutierrez clarified that part of the proposed 21st Century Cures Act includes a requirement for FDA to issue guidance clarifying the CLIA waiver study design. As a result of this proposal, they are starting with clarification of the issues regarding accuracy determination for waived tests.
- The Chair noted that the waived testing statutory language includes statements on test simplicity and accuracy which can be assessed before the test is approved for use, but that the other component in the language stating "…as to render the likelihood of erroneous results by the user negligible…" can only be determined after approval. Dr. Tobin replied that the FDA addresses the issue by requiring flex studies, risk analysis, validation of failure alerts and failsafe mechanisms as part of the waiver approval process. He added that in addition to tests approved for home use, there are also nine tests that are waived by inclusion in the CLIA regulations.
- A member stated that there is a possibility of significant risk with many waived tests such as hemoglobin, glucose, *Streptococcus* antigen, and influenza, if they are performed incorrectly.

- A member noted that the 2001 FDA draft guidance allowed a comparison of the waived method between untrained users and trained users and if both users reached the same wrong value, the test was considered accurate. The member agreed with the comparison being between untrained users with the reference or the traceable method in the hands of professional users as noted in the 2008 FDA guidance. Dr. Gutierrez reiterated that the 2008 guidance states that if there is a gold standard, then the comparison must be made to the gold standard. If there isn't a gold standard, then the comparison is to a traceable standard, followed by a comparison to the best available method.
- Mr. Quintenz, the AdvaMed liaison, noted that from an industry perspective if a test that could be approved for moderate complexity is performing the same between untrained and trained users, then that test should be eligible for waiver. He asked if the FDA is proposing a three tier system in which you start with a reference method if available then move to a traceable method, and then, only if either of those are not available, you reflex to untrained users versus trained users. Dr. Gutierrez replied that is the intention and the FDA has had some cases where this was demonstrated.
- A member asked about how the accuracy of the predicate method is determined if there is not a gold standard available. For example, the predicate test for an influenza waiver approval was viral culture which is not considered a gold standard test for influenza. Dr. Gutierrez clarified that influenza tests must reach predetermined performance levels using a specimen panel with predetermined limits for detection and determination before waiver status is determined. He added that if the predicate method has a wide coefficient of variation, it is very difficult to compare and you may need to perform a comparison with a reference method that is traceable.
- Several members asked how the FDA addresses waived tests that are performing poorly but are still commercially available. Dr. Gutierrez explained that the process to discontinue a poor performing waived test is legally complex since the test has been shown to be equivalent to tests available at the time of waiver determination. The process can be performed and the FDA does address this with influenza, requiring the manufacturers of waived influenza tests to successfully perform annual testing.
- A member asked if there are any processes in place to assess continued test performance after CLIA waiver approval. Dr. Gutierrez replied that unlike moderate or high complexity tests, waived tests do not have any requirements such as proficiency testing or surveys to assess continued test performance. Since currently there are not any post-market requirements for data collection for waived tests, the FDA will only investigate a test if there are complaints submitted to the FDA. If the investigation produces evidence of poor performance, recalls may be issued or manufacturers may be required to change the product labeling. Dr. Gutierrez added that complaints can be made anonymously to protect whistle blowers.
- Another member asked about waived HIV tests in which the method is not simple and erroneous results are significant. Dr. Gutierrez replied that the studies for HIV waiver were extensive and the tests were determined to perform as indicated. He added that the FDA Center for Biologics Evaluation and Research is responsible for HIV waivers.
- A member commented on the finding that test performance between clinics and hospitals within a health system varied. The health system performed a complete

evaluation of all test methods and/or kits and selected the one that performed the best. Since implementation, the hospital sends blind studies to assess the clinics' performance using the selected kits to compare results with those of the hospital. The member then suggested conducting a yearly review on waived test performance in comparison to the other waived tests in this particular category. Another member suggested the involvement of manufacturers to provide documentation of continued test accuracy and reliability.

- One member suggested that manufacturers be required to provide educational material for each specific test when they submit their test application for CLIA waiver to ensure that the proper information is provided to users. Dr. Gutierrez replied that as the guidance is revised the FDA could request that manufacturers prepare training materials.
- A member asked if the FDA performs oversight of waived testing personnel. The Chair and Ms. Dyer reminded the Committee that under CLIA, the agencies have limited oversight with respect to CW sites. CMS performs limited educational surveys on approximately two percent of the CW sites annually.
- Another member asked if there is a product, such as a consumer report, detailing waived test issues, costs, accuracy, and other items that would assist physicians and other testing personnel. A member commented that the College of American Pathologists' publication CAP Today will sometimes provide articles on the topic. Dr. Gutierrez added that *Consumer Reports* provides ratings and reviews on home use tests such as glucose meters. Several members commented that a product similar to a consumer report for waived tests would be beneficial but funding the work would be challenging.
- One member commented that in 2009 the CDC published a Morbidity and Mortality Weekly Report evaluating rapid influenza diagnostic tests (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5830a2.htm) which helped physicians determine which influenza test to utilize. Another member asked if it would be possible for CDC to provide funding for an independent group to evaluate different waived tests. Dr. Zehnbauer commented that the evaluations would involve collaborations with the pathogen or disease specific Centers at the CDC. It would not be the purview of DLS to charge other centers with those analyses, but DLS could inform them of the laboratory testing community's concerns with underperforming tests. She provided an example of a DLS collaboration with the Joint Commission to produce an online training and a series of specimen collection videos designed to improve rapid influenza testing and treatment in ambulatory settings (http://www.jointcommission.org/siras.aspx).
- One member suggested that with increasing tests being performed at the point-of-care, funding studies of waived test performance in the post-market context should be a priority. Dr. Mac Kenzie noted that several Committee members commented on the involvement of a third party to provide a periodic post-marketing assessments of test accuracy for priority waived tests.
- A member asked if there would be opportunities to develop educational products to address waived testing in point-of-care sites. Ms. Dyer commented that the "Ready? Set? Test!" booklet includes recommended practices for CW sites and added that the booklet will be mailed with each CW. Ms. Anderson added that the CDC is

developing a non-punitive and non-regulatory self-assessment checklist tool that waived sites can use to assess recommended practices based on the "Ready? Set? Test!" booklet.

- Another member commented on the need of clinical decision support even with waived testing. Dr. Zehnbauer replied that effort is needed to involve the laboratory as well as physicians in communication of test results for clinical decisions. She added that the Clinical Laboratory Integration and Healthcare Collaborative (CLIHC™) developed an iPhone application to help physicians walk through the proper selection of tests for coagulation monitoring based on the patient's presentation and there is active collaboration with Georgia Tech Biomedical Engineering colleagues to make the application more comprehensive. Dr. Zehnbauer commented that clinical decision support tools do not replace the role of the laboratory professional for providing consultative services.
- Dr. Zehnbauer also commented that CLIHC™ has discovered that medical students and residents receive very little education on the use of common medical laboratory tests and addressing this issue will require interfacing with educational institutions and accrediting bodies.
- Mr. Quintenz commented that industry's concern is that the FDA continue to look for ways that new tests can be waived. He indicated that there have not been many new analytes added to the portfolio of tests that are available and industry hopes that the agencies will continue to enable physician operated laboratories and other waived sites to have access to tests that benefit the public health, as opposed to creating a number of additional oversight mechanisms that make it either burdensome for manufacturers or burdensome for physician operated laboratories and other waived sites to remain in operation.
- A member added patient safety risks associated with increased waived test development should also be addressed and that the FDA should consider developing a post-marketing surveillance type of program for waived tests. Dr. Gutierrez noted that new technologies are constantly emerging that will lead to simpler and more accurate testing which could ease the CLIA waiver process for manufacturers.

Institute of Medicine (IOM) Report: *Improving Diagnosis in Health Care*

IOM: *Improving Diagnosis in Health Care* *Addendum 13*

Mark Graber, MD, FACP
Senior Fellow - RTI International
Founder and President
Society to Improve Diagnosis in Medicine (SIDM)

Dr. Graber provided the Committee with a brief overview of diagnostic error and the Institute of Medicine (IOM) report "*Improving Diagnosis in Health Care*," published in September 2015. He primarily focused on issues relevant to the CDC. He briefly

reviewed some of the data from the report noting that it is gleaned from research and that diagnostic error in actual practice is not known. Dr. Graber discussed where diagnostic errors are encountered and why they happen and noted that patient variables, physician variables, and system complexity all contribute to diagnostic errors. Dr. Graber then discussed the laboratory total testing process. He noted though error rates in the analytical phase of testing are very low, error rates in pre- and post- testing are of great concern. He said pre- and post- testing error rates are not currently being addressed and questioned whether it was up to the laboratory to address this part of the problem. He reviewed the IOM definition of diagnostic error and the background information that led to each of the Society to Improve Diagnosis in Medicine's (SIDM) four recommendations. In summary, Dr. Graber said SIDM recommends that CDC should support failsafe communication of laboratory test results, funded clinical liaison pathologists in every hospital, funded autopsies at special centers, and second opinions on surgical pathology.

Committee Discussion

- A member observed that the presentation showed that the majority of errors are in the pre-analytic phase, almost double the number in the post-analytic phase. The member asked Dr. Graber if he had recommendations for addressing the error in the pre-analytic phase of testing. Dr. Graber responded the four SIDM recommendations were the top priorities. The member noted that the first SIDM recommendation was that laboratories should take responsibility for failsafe communication of all test results and asked what types of solutions SIDM is looking for. Dr. Graber responded the solutions will vary depending on the hospital and the electronic medical record system being used.
- Another member expressed the belief that the majority of error is in test selection and results interpretation. The member asked if there was an economic argument that would encourage the laboratory to address pre- and post- testing errors. Dr. Graber responded there is a quality argument which could drive the quest for additional funding. The IOM report states that HHS should consider how to provide remuneration for both the autopsies and the clinical consultation that SIDM is requesting. The member asked if there was an actual cost assigned to this effort. Another member replied that the average malpractice claim for a diagnostic error is about $300,000 and diagnostic error is the most common reason why physicians get sued in the outpatient setting.
- Ms. Dyer noted that laboratory professionals would like to be able to regain the one-on-one relationship they once had with physicians. She said in her experience, laboratories are dedicated to getting the results to the physician or the appropriate person. She expressed the opinion that the laboratories should not be made ultimately responsible for failsafe communication.

CDC CLIA-Related Initiatives to Improve Laboratory Practice
A Key Component of Quality Health Care ***Addendum 14***

Ira Lubin, PhD, FACMG
Acting Branch Chief
Laboratory Research Evaluation Branch (LREB)

Division of Laboratory Systems (DLS)
Center for Surveillance, Epidemiology, and Laboratory Services (CSELS)
Office of Public Health Scientific Services (OPHSS)
Centers for Disease Control and Prevention (CDC)

Dr. Lubin began his presentation with a diagram of the IOM diagnostic model noting the laboratory is rooted in the diagnostic process and integrated with the other processes. He listed the IOM goals for improving diagnosis and reducing diagnostic error and commented that the DLS CLIA initiatives intersect with many of these goals. He discussed the five DLS initiatives (interface between laboratory and clinical professionals; development, implementation, and evaluation of practice guidelines; education and training; health information technology; and new and evolving technologies and practices) and their current status. Dr. Lubin finished by again emphasizing that much of the work in DLS can be fit into the IOM model.

Committee Discussion

- A member expressed interest in the concept of multiple stakeholders providing input on and recommendations for appropriate test ordering but wondered how this would be feasible considering the explosion of tests available. Dr. Lubin agreed this is no longer a feasible means to promulgate guidance. We need to consider how guidance is going to move into the clinical decision support systems, how to monitor the utility of the guidance, how to disseminate guidance, and how to develop education.

The Chair introduced the discussion questions for the Committee to consider.

Addendum 15

What are the opportunities and challenges for empowering laboratory professionals to participate in efforts to improve diagnoses?

- A member agreed that improving diagnosis in healthcare and making the laboratory part of the diagnostic team is a very complex and challenging endeavor and stated decision support is incredibly challenging. The member suggested that EHR software could be used to assist with ordering. The member noted that when popups or hard stops are used, physicians get popup fatigue and asked how to solve that problem. The member also remarked that metrics are very important, however getting to those metrics is very challenging.
- Dr. Wilcke responded laboratories are paid for testing, not necessarily for educating the requesting parties.
- Another member commented experience has shown that the laboratory can utilize algorithms and interact with the clinician when dealing with a small institution, however, it is difficult and there is no financial remuneration. The difficulty is magnified when the laboratory must interact with multiple clients.
- A member commented there seems to be a movement away from in-house laboratories that physicians can interact with toward the consolidation of laboratories which decreases the opportunity for the laboratory to offer consultation. This consolidation seems to be fueled by the belief that centralization of laboratory testing is less expensive. The member contended that reimbursement policies and regulations

are the drivers of laboratory testing being consolidated. In terms of reimbursement, this is part of a larger policy issue that ought to attempt to preserve local testing and create environments where there is freedom of choice rather than set policies that encourage centralizing testing.

What metrics can reasonably be generated that can link laboratory practices (not necessarily specific to a defined test) to patient outcomes?

- Another member stated there are two big issues, information and economics. The member observed that laboratories do not require the physician to indicate why a laboratory test is being ordered. However, knowing why a test is ordered would be a first step towards building a database and evaluating the utility of the test. The member continued that it is also important to link why a test is ordered with the outcome for the patient in terms of the dollar value.

How can the federal government, particularly CMS, FDA, and CDC, be involved in helping laboratories contribute to improved diagnoses?

- A member commented that laboratories do not have enough personnel to respond to all of the physicians that have questions. It would be helpful to utilize some of the platforms that are already in place, including websites such as *Lab Tests Online* (https://labtestsonline.org/). Even simple algorithms incorporated in electronic apps could provide guidance to physicians. The member suggested such a platform be developed and established on the CDC website.
- Another member said the federal government could investigate alternative payment methods that embrace the concept of healthcare teams and reimburse the pathologist as part of that team, ensuring that the patient gets the best outcome and treatment.
- Following discussion pertaining to whether a recommendation related to information in the IOM report should be submitted to HHS, the Committee voted not to put forward a recommendation at this time. However, Dr. Wilcke noted that the Committee had requested that a workgroup be formed to further discuss the issues surrounding the topic of improving diagnosis in health care.

Proposed Regulatory Framework for Laboratory Developed Tests Update

Alberto Gutierrez, PhD ***Addendum 16***
Director
Office of In-Vitro Diagnostics and Radiological Health (OIR)
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration

Dr. Gutierrez provided an update on the proposed regulatory framework for laboratory developed tests (LDTs). He described the benefits of FDA oversight of LDTs, which includes independent premarket reviews, clinical validation, post market surveillance and controls, and oversight of investigational stage devices. Dr. Gutierrez next discussed the FDA's LDT draft guidance process to date and briefly discussed the current proposal which includes the collection of information on all LDTs through a new notification process, use of advisory panels to obtain input on risk and priority for regulation, a

phased-in regulatory framework over approximately nine years beginning with the highest-risk LDTs, and continued enforcement discretion for specific categories determined by the FDA to be in the best interest of public health. He provided an overview of the public comments received during the 90-day public comment period on the LDT guidance and highlighted some concerns. Dr. Gutierrez noted two collaborations, the first being the FDA and CMS Task Force on LDT Quality Requirements formed to ensure effective and efficient oversight of LDTs and the second being a multi-partner collaboration between FDA, CMS, CDC, and NIH which includes senior leadership from all agencies tasked with identifying similarities in regulations under CMS and FDA and streamlining requirements for laboratories regulated by both agencies. Next, he provided a brief overview of the Diagnostic Test Working Group (DTWG) alternative proposal to FDA's LDT framework and mentioned a couple of additional proposals. Dr. Gutierrez concluded the presentation with an overview of the next steps needed including modification of the guidance based on public comments, development of responses to public comments, and issuing the final guidance in 2016 followed by ongoing education and training.

Committee Discussion

- One member commented on the report entitled "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies" published November 2015 by the FDA (http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm472773.htm). The member noted one of the bullets demonstrating the need for FDA oversight discusses the uneven playing field when laboratories and other IVD manufacturers that go through the premarket review process are placed at a disadvantage when their LDT competitors do not follow the same standards to support claims of the safety and efficacy of their device. The member added that the statement seems to indicate the FDA is protecting competitors rather than protecting patients. The member did not see a correlation between a hospital that develops an LDT, knows their patients and monitors the use of the LDT with those patients versus a company that manufacturers, packages, labels, and sells a kit to users. The member added that many hospitals and academic centers are not for profit and have very different goals than vendors. Dr. Gutierrez responded by citing an example of an IVD that a company spent time and money developing and obtaining FDA approval to market, but comments were received from a laboratory that LDTs would still be used because they were cheaper. This resulted in an uneven playing field between the company that developed the IVD and the laboratory using the LDT without performing the necessary steps to obtain FDA approval. He added that he had observed laboratories with LDTs that decided to start marketing the tests they perform, advertising and acquiring a sales force, which in turn created the appearance of a private company rather than a testing laboratory.
- Another member asked why the FDA decided to publish the LDT case study report focusing only on 20 problematic assays when there are numerous beneficial LDT assays available. Dr. Gutierrez replied that there were many problematic LDTs and FDA focused on the assays that had impacted many patients.
- A member asked how the agencies ensure oversight of companies performing inappropriate or inaccurate tests. Ms. Dyer responded that every non-waived CLIA

laboratory is surveyed every two years and if problems are identified, the laboratories are cited and corrective action must be taken and documented. She added that in the case of LDTs, CMS inspects a representative sample of those performed by the laboratory. They review the accuracy, precision, and performance of the tests emphasizing that the CMS inspection is not as detailed as the FDA review of data and other test information.

- Several members commented that the current system of CMS and accreditation agency review is satisfactory as a system for LDT oversight adding that proficiency testing data from the College of American Pathologists does not indicate a difference in test performance between IVDs and LDTs. The member emphasized that a new FDA regulatory system does not need to be created to address LDTs, but rather that CLIA should be expanded and improved to monitor LDT performance.
- A member commented that often in the pursuit of quality, cost and access can be negatively impacted and asked how those trade-offs have been addressed by the FDA. Dr. Gutierrez replied that there are costs incurred by the patient and the system is affected by misdiagnoses due to poorly performing LDTs. He added that the FDA has not performed a cost assessment of all of the LDTs being offered and how they are being used, due to many unknowns that would be encountered in attempting to perform such an analysis. He added that the FDA approach to LDT oversight is intended to be a flexible approach.
- Another member commented that it would be beneficial to perform a cost analysis on the potential impact of the proposed FDA LDT guidance.

Committee Discussion on Proposed Procedural Changes

- A member commented that a lot of the meeting time is spent wordsmithing recommendations and asked if there is a process by which recommendations could be discussed and vetted before the official CLIAC meeting. Dr. Mac Kenzie reminded the Committee that they must adhere to the requirements established by the Federal Advisory Committee Act to provide meetings that are open to the public and provide the public with the opportunity to comment.
- Dr. Gutierrez noted that in his experience with FDA committees often topics are split between two meetings. In the first meeting, the topic is introduced and workgroups are formed to discuss and develop advice to be provided to the full committee at the next meeting. The Chair commented this would be a change in practice, but one that could be considered.
- One member questioned the requirement for a public forum for recommendation development. Dr. Mac Kenzie clarified that a workgroup cannot make formal recommendations, but one can be formed to discuss issues and develop advice to present to CLIAC for consideration and discussion. The Chair added that CDC will need to review the proposal that members work to develop recommendations prior to the official CLIAC meeting with their legal counsel and the CDC Advisory Committee Management Office.
- A member asked if a workgroup could suggest a draft of a possible recommendation on a topic. Ms. Anderson replied that workgroups are formed to include people with different perspectives to collect information and provide a report containing the various perspectives to CLIAC. It is then the Committee's role to discuss the

information provided and decide what recommendations to make. Dr. Zehnbauer cited the November 2014 CLIAC meeting where the Virtual Crossmatch Workgroup provided a report to the Committee as an example of how a workgroup can provide advice to CLIAC on a topic that requires more research and discussion than the typical meeting allowed.

- The Chair suggested fewer topics for future meetings and that topics for discussion be clearly defined so that discussions are productive. A member suggested allowing more time for discussion of the topics.
- One member suggested a possible CLIAC recommendation for process improvement. After a brief discussion the Committee passed the following recommendation:
    - CDC should review the process by which CLIAC creates, reviews, and edits official Committee recommendations to allow a public forum for shared development and drafting of proposed recommendations prior to the meeting to facilitate more effective Committee discussion.

The Chair summarized the meeting discussion highlights and recommendations:

❖ Discussion around the laboratory interoperability issue resulted in a recommendation that:

HHS should ensure the following next steps:

- EHR content display related to laboratory data (including graphs) should be standardized such that all CLIA-required test report elements are on every laboratory display/graph.
- National Institute of Standards and Technology (NIST) should create use cases for testing transmission and display of laboratory data in the pre- and post-implementation stages of EHR use in order to maintain semantic interoperability in various laboratory (clinical/anatomic pathology) settings. Use cases should start at the laboratory system and involve sending data across the interface for display in multiple EHRs. This would test the interoperability of comments, units, reference ranges, etc. (sometimes the reference ranges in the EHR are different than in the laboratory information system).
- Consider the incorporation of CLIA use cases in next certification cycle.
- CMS should consider identifying activities considered as ‘information blocking’ and place multifaceted strategies to discourage such activities. For example, incentives could be built for offsetting the current high fees for laboratory/EHR interfaces.

In addition to the recommendation above, HHS should consider following next steps to drive interoperability:

*Drive semantic interoperability through incentives (perhaps from CMS) and establish some measure thereof and leverage existing standards in CLIA.

*Engage laboratory professionals and consumers in all discussion regarding global issues of interoperability and its related outcomes.

*Use information from Standards & Interoperability guides to address patient ID issues. For example, HHS should require laboratories to collect and send key patient identifying characteristics such as first name, last name, date of birth, and gender, and

optional items such as cell phone number, email address, and physical address. This would help ensure accurate patient matching across systems.

❖ Discussion around the issue of non-invasive prenatal testing resulted in a recommendation that:

- HHS and CDC should support the development of NIPT-related enduring educational materials accessible to patients and health care providers. In order to support effective patient care decisions, these materials should include simple language and visual graphics to effectively convey information about risks, benefits, and limitations of different types of prenatal testing.
- HHS should require that ordering providers requesting non-invasive prenatal screening tests (of cell-free fetal DNA) should perform and document a pre-test discussion to inform the patient of risks, benefits, and limitations.
- HHS should recommend labs performing NIPT to disclose information regarding test limitations and positive predictive values (likelihood that the fetus has a genetic condition) that is directly comparable to conventional techniques (e.g., by maternal age) while reporting results as well as risk interpretation and appropriate indications for confirmatory diagnostic testing.

❖ Although not a formal recommendation, discussion around the IOM Report: *Improving Diagnosis in Health Care* resulted in the suggestion that a workgroup be considered to discuss the topic and report back to CLIAC during the April 2016 meeting.

❖ Discussion on CLIAC proposed procedural changes resulted in a recommendation that:

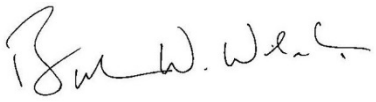
- CDC should review the process by which CLIAC creates, reviews, and edits official committee recommendations to allow a public forum for shared development and drafting of proposed recommendations prior to the meeting to facilitate more effective committee discussion.

ADJOURN

Dr. Wilcke and Dr. Mac Kenzie acknowledged the staff that assembled the meeting agenda and thanked the CLIAC members and partner agencies for their support and participation.

Dr. Wilcke and Dr. Mac Kenzie announced the spring 2016 CLIAC meeting dates as April 13-14, 2016, and adjourned the Committee meeting.

I certify this summary report of the *November 18-19, 2015*, meeting of the Clinical Laboratory Improvement Advisory Committee is an accurate and correct representation of the meeting.



Dated: 2/01/2016

Burton Wilcke, Jr., Ph.D., CLIAC Chair