CDC Advisory Committee to the Director (ACD) Laboratory Workgroup (LW)

Testing of Specimens not Meeting Routine Acceptance Criteria Report of the Laboratory Workgroup of the Advisory Committee to the Director

ADOPTED BY ACD VOTE ON May 11, 2023

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ISSUE

As the national reference laboratory for infectious disease (ID) diagnostics, the Centers for Disease Control and Prevention (CDC) is sometimes the laboratory of last resort for testing specimens that may have been stored in less-than-acceptable conditions, may be an unusual specimen type, or may contain less-than-acceptable volume. These specimens would not meet requirements for acceptable specimens and, adhering to the Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulations, CDC would have to reject them. In so doing, rare or difficult-to-obtain specimens can be rejected, whose results could have a meaningful impact on public health, including identifying pathogens responsible for rare or novel diseases.

Questions:

1. Considering CLIA requirements, should CDC support investigation of unknown infectious agents or diseases using less-than-acceptable specimens when acceptable specimens are not available?
2. If so, how should an appropriate disclaimer be worded regarding result interpretation that acknowledges the specimens are outside validated parameters (e.g., "Not a CLIA-compliant analysis, results should be interpreted with caution and in consultation with CDC laboratories.")?

REVIEW

The Laboratory Workgroup (LW) of the Advisory Committee to the Director (ACD) met virtually on Tuesday April 4, 2023. The members heard a presentation from Dr. Elizabeth Berkow with examples of where CDC declined to test samples outside of usual parameters, such as different fluids or temperatures. CDC staff present for the subsequent discussion were:

- Elizabeth Berkow, PhD, MS, Deputy Senior Advisor for Infectious Diseases Laboratory Science, OLSS
- Atis Muehlenbachs, MD, PhD, Clinical Laboratory Improvement Amendments (CLIA) Laboratory
  Director, Atlanta Infectious Diseases Laboratories/OLSS
- Brandi Limbago, PhD, Associate Director for Laboratory Science/National Center for Immunization and Respiratory Diseases
- Wendi Kuhnert, PhD, Senior Advisor for Infectious Diseases Laboratory Science and Director, Laboratory Quality Office/OLSS and Acting Deputy Director of National Center for Emerging and
  Zoonotic Infectious Diseases
- Triona Henderson, MD, MPH, Deputy Clinical Laboratory Improvement Amendments (CLIA) Laboratory Director

The LW also met virtually on Tuesday, April 11 to discuss the response to be provided to the ACD.

OVERVIEW

The CDC should offer laboratory testing for unknown, rare, important, and/or difficult to diagnose infectious agents, even under less-than-ideal circumstances. Public health laboratories, and especially CDC, are often the laboratories of last resort when it comes to testing for rare pathogens or unusual specimen types. It is not uncommon for specimens not meeting routine acceptance criteria to provide the only opportunity to assess the presence of a rare or potentially emerging pathogen of clinical and public health significance. Maintaining this capability at CDC is a critical responsibility, both for the

health of the individual patient from whom the sample is obtained, and for the health of the population.

The LW believes that it should be possible to address key scenarios of concern and still meet the regulatory requirements of CLIA. Doing so will require some changes to the CDC's processes. It will also require policy discussions with the Centers for Medicare & Medicaid Services (CMS). It is important that CMS understands the significant public health value of this issue, and that both Agencies are aligned in the interpretation of the CLIA regulations.

NOTE: In this report, we use the term "specimens not meeting routine acceptance criteria," to refer to specimens that do not meet usual, defined criteria for such issues as sample volume, storage or shipping temperature, specimen collection device, sample matrix, and duration of storage.

RECOMMENDATIONS

Based on best practices from large clinical/reference laboratories, we recommend that the CDC adopt a plan for clinical diagnostic testing that includes the following.

1. The CDC should develop and validate pathogen detection and quantification assays, using multiple specimen types, to the fullest extent possible. The impact of multiple pre-analytic variables, which can affect the accuracy of the assay, should be evaluated broadly, beyond the ideal state, so the laboratory director has experience with specimens that do not meet routine acceptance criteria.

   To accomplish this goal, the CDC should validate the test using authentic positive or contrived samples. The validation of laboratory-developed tests should be performed to support specimen acceptance for specimens of varying volume, temperature, time in transit, matrix, and collection device. This validation process and resulting data should be well documented.

2. Standard operating procedures for CDC clinical laboratories should describe routine specimen acceptance criteria, as well as the conditions, within the validation for the test, for which specimens will be referred to a qualified laboratory director for review before acceptance. These routine acceptance criteria and conditions should also be included in the test catalogue.

3. Each clinical laboratory at CDC should have a process, defined in the standard operating procedure, for escalation of specimens not meeting the routine acceptance criteria, to a CLIA-qualified laboratory director for evaluation. The laboratory director will determine whether the test's validation can reasonably be understood to mean that technically accurate and clinically useful results can be obtained from testing such specimens. This judgment should also consider the clinical situation of the potentially infected individual, relevant epidemiologic information, and the public health significance of the test result.

4. Each CDC clinical laboratory should develop a written policy on additional interpretive comments that may be appropriate to include on the laboratory report, based on the specific context of the specimen being tested.

5. If a CDC clinical laboratory director determines that the laboratory cannot test a particular specimen accurately, but another laboratory is able to do so, the agency should have a procedure for sending the specimen to the outside laboratory for testing.

6. As part of continuous quality improvement, each CDC clinical laboratory should review its records regularly to determine the main reasons for rejection of specimens received and use this information to improve their validation criteria or processes.

7. Specific CLIA-qualified laboratory directors, with expertise in the specific areas involved, should oversee this process of performing broad validations, specific standard operating procedures, and escalation procedures. The roles of the CLIA-qualified laboratory directors should be included in the Clinical Laboratory Director's formal Position Description and the Laboratory's Quality Manual.

8. We recommend that the CDC divide its diagnostic testing across multiple CLIA-certified laboratories with an individual CLIA-qualified laboratory director responsible for the diagnostic testing in each Center-level CLIA-certified laboratory.

In addition, we recommend that CDC meet with CMS to review a proposed plan for testing specimens not meeting routine acceptance criteria while still meeting CLIA requirements based on the elements described above. These regulatory policy discussions should happen at the leadership level, and the final plan should be shared with accrediting bodies and inspectors. The Association of Public Health Laboratories may be a valuable partner in these discussions.

We believe that CMS should recognize the unique role that public health laboratories, including the CDC's CLIA-certified laboratories, play in testing for pathogens of public health significance and the potential for negative impact on patient care and public health if specimens not meeting routine acceptance criteria are not eligible for testing.

If inter-Agency alignment on the interpretation of CLIA regulations proves difficult, the LW recommends that CDC engage with HHS and CMS executive leadership. It is essential that an acceptable solution is found, so that CDC can perform this critical function.

APPENDIX: LIST OF WORKGROUP MEMBERS

Laboratory Workgroup Co-chairs (alphabetical order)

- Joshua Sharfstein, MD, Johns Hopkins Bloomberg School of Public Health, Professor
- Jill Taylor, PhD, Association of Public Health Laboratories, Senior Advisor for Scientific Affairs

Laboratory Workgroup Members (alphabetical order)

- Angela M. Caliendo, MD, PhD, FIDSA, FAAM, Brown University, Executive Vice Chair, Department of Medicine, Alpert Medical School
- David Fleming, MD, University of Washington School of Public Health, Clinical Associate Professor
- Alberto Gutierrez, PhD, NDA Partners, LLC, Partner
- Paul B. Kimsey, PhD, MA, California Department of Health, Deputy Director; Director, State Public Health Laboratory
- Grace Kubin, PhD, Texas Department of State Health Services, Director, Laboratory Services Section
- Ruth Lynfield, MD, Minnesota Department of Health, State Epidemiologist, Medical Director
- Robin Patel, MD(CM), D(ABMM), FIDSA, FACP, F(AAM), Mayo Clinic, Professor; Director, Infectious Diseases Research Laboratory; Co-Director, Bacteriology Laboratory
- Jennifer L. Rakeman, PhD, Cephid, Senior Director, Medical Affairs, Public Health Programs
- Daniel D. Rhoads, MD, Cleveland Clinic, Microbiology Section Head
- Tim Southern, PhD, MS, D(ABMM), South Dakota Department of Health, Public Health Laboratory Director
- Denise Toney, PhD (HCLD), Commonwealth of Virginia, Department of General Services, Laboratory Director, Division of Consolidated Laboratory Services
- Jay K. Varma, MD, Weill Cornell Medical School, Director, Cornell Center for Pandemic Prevention and Response
- Scott Zimmerman, DrPH, MPH, HCLD (ABB), Lab Corp, Vice President, Department of Science & Technology