CLIAC Recommendations for Development of **Good Laboratory Practice Guidelines for Biochemical Genetic Testing and Newborn Screening**

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Secretary's Advisory Committee for
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Outline

- Development of Clinical Laboratory Improvement Advisory Committee (CLIAC) recommendations for good laboratory practices in biochemical genetic testing and newborn screening for inborn errors of metabolism – **Dr. Bin Chen**
- CLIAC Recommendations for Good Laboratory Practices and Implications for Newborn Screening – **Dr. Carol Greene**
- CDC guideline development and issues for SACHDNC input – **Dr. Bin Chen**

Clinical Laboratory Improvement Advisory Committee (CLIAC)

- Federal advisory committee established under Public Health Service Act [42 USC §217a] in 1992
- Provides scientific and technical advice regarding
  - CLIA regulations
  - Impact on medical and laboratory practice
  - Modifications to accommodate technological advances
- Reports to HHS Secretary/Assistant Secretary for Health, CDC Director, CMS Administrator, FDA Commissioner
- Managed by CDC Division of Laboratory Science and Standards (DLSS)

CLIA Oversight for Genetic Testing

- CLIA regulations
  - Apply to all patient testing performed on U.S. patient specimens
  - General requirements for non-waived testing as applicable
  - Specialty of clinical cytogenetics
    - Specific QC requirements
    - Qualification requirements for technical supervisor
  - Requirements for molecular amplification procedures
  - No specialty for molecular or biochemical genetic testing
  - Emphasize analytic validity rather than clinical validity, no intent to address clinical utility
- Accreditation standards and state programs

Developing Good Laboratory Practice Guidance for Genetic Testing

- 1997: Federal agencies working with advisory committees, other stakeholders to consider quality assurance and oversight for genetic testing
- 2007: CMS developed action plan to enhance oversight of genetic testing
  - Providing guidance rather than prescriptive regulations
  - Training, education, data collection, collaboration
- 2008: CLIAC provided recommendations for
  - Good laboratory practices (GLPs) for molecular genetic testing (MGT)
  - Need for separate guidelines to address biochemical and other areas of genetic testing
- 2009: CDC *Morbidity and Mortality Weekly Report* (MMWR) guideline for MGT

MMWR
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

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Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

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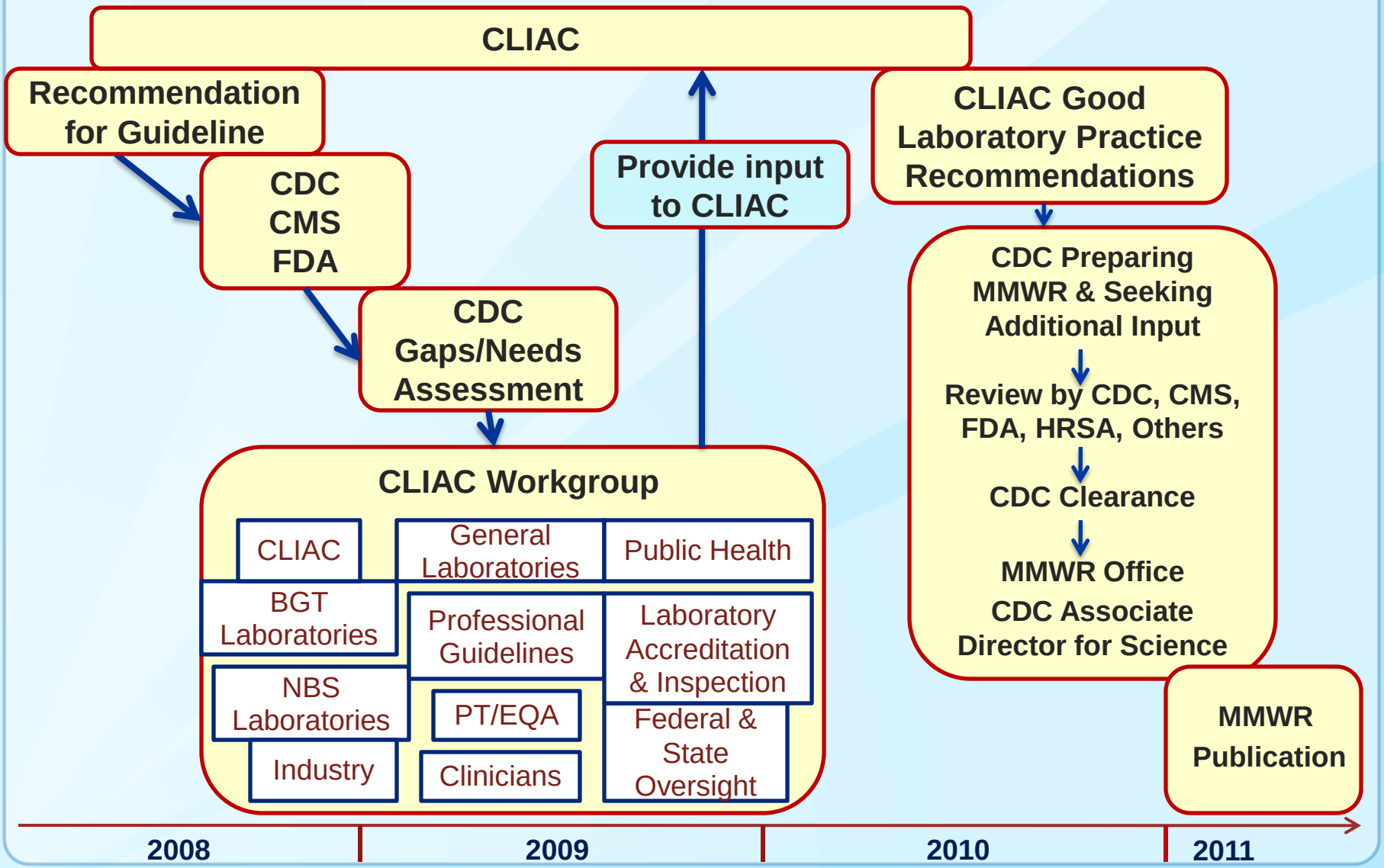
Continuing Education Activity CE-1

Developing MMWR Guideline for Good Laboratory Practices in Biochemical Genetic Testing (BGT) and Newborn Screening (NBS)



Developing Recommendations for Good Laboratory Practices in BGT and NBS

- CDC assessment of BGT landscape and gaps in quality assurance (QA) practices
  - Collection of available information
  - Identification of areas needing QA guidance
  - Assessment of expertise needed for CLIAC workgroup
  - Preparation of information to facilitate workgroup evaluation
- Collaboration with CDC Newborn Screening Quality Assurance Program
- Input from CDC Office of Public Health Genomics

Assessing BGT Landscape and Gaps

- Assessment of current BGT landscape and trends
  - Definitions
  - Number of labs performing BGT
  - Number and type of diseases for which BGT is performed
  - Test volume
  - Test methods and technology
  - Type of services
  - Availability of proficiency testing (PT)/external quality assessment (EQA) programs
  - Growth and trends
- Comprehensive review of available information/data
- QA concerns identified
- Comparison of laboratory standards and guidelines to assess practices/areas needing guidance or clarification

Process of Developing CLIAC-Recommended GLPs for BGT and NBS

- 2009 CLIAC BGT workgroup
  - 13 experts representing key perspectives:
    - BGT laboratories, diverse technology and diagnostic issues
    - NBS/public health
    - Users of laboratory services
    - Federal and state regulatory oversight
    - Laboratory performance evaluation, inspection/accreditation
    - Professional guidelines, voluntary standards
    - IVD manufacturers and industry
  - Workgroup charge: Provide input to CLIAC –
    - Scope of CLIAC consideration
    - Comprehensive evaluation of laboratory standards and guidelines
    - Strategies for identified QA concerns and gaps
    - Additional laboratory practices areas/issues needing guidance

Workgroup Evaluation of Laboratory Standards

- 19 comprehensive crosswalks addressing each topic area needing guidance for good laboratory practices (see example)

For CLIAC BGT Workgroup Review Only. DO NOT REPRODUCE OR DISTRIBUTE. Version 05-27-2009

BGT Crosswalk #7. Performance Establishment and Verification Relating to Genetic Tests

	CLIA Regulations	New York State Clinical Laboratory Standards of Practice	FDA Guidance Documents	ISO 15189:2007	CAP Checklists	ACMG Standards & Guidelines	CLSI Guidelines	MGT MMWR
Analytical performance	Under §493.1253, CLIA requires performance verification on accuracy, precision, reference intervals, and reportable range for each unmodified FDA-cleared/approved test system; and performance establishment for accuracy, precision, analytical sensitivity, analytical specificity, reference intervals, reportable range, and other applicable performance characteristics for each modified FDA-cleared/approved test system or laboratory-developed test. Laboratories also must determine control procedures and calibration procedures based on the performance verification or establishment. **Interpretive Guidelines** §493.1253(b)(1) The laboratory is responsible for verifying the performance specifications of each	**Validation S1:** The laboratory shall use examination procedures, including those for selecting/taking sample portions appropriate for the examination, which meet the needs of the users of the laboratory services. **Validation S2:** The laboratory shall use only validated procedures to confirm that the examination procedures are suitable for the intended use. The validation shall be as extensive as necessary to meet the needs in the given application or field of application; the laboratory shall record the results obtained and the procedure for the validation **Validation S3:** A laboratory that performs the same test using different methods or instruments, or performs the same test at multiple test sites, shall have a system in place that evaluates and defines the relationship between test results every six months **Validation S4:** Documentation of	**NBS Test Systems for AAs, FC/ACs Using MS/MS** Provides guidance for premarket submissions including: • Implications for method validation by laboratories that use these procedures- o Reproducibility (within-run and total imprecision) o Interference (interferents on assay performance) o Functional Sensitivity/ Limit of Detection o Linearity o Calibration and Control Materials o Carry over and drift (evaluate each amino acid, free carnitine, and acylcarnitine for any effects of carry over or drift using referenced material) o Cut-Off(s) / Reference Interval(s) • Method Comparison (compare your device to a predicate device or an acceptable reference Method) o Specimen collection and handling conditions (whether the device can maintain acceptable performance over the recommended storage times and temperatures) o Drift o Sample selection, inclusion, and exclusion	**5.5.1** The laboratory shall use examinations procedures, including those for selecting/taking samples portions, which meet the needs of the users of laboratory services and are appropriate for the examinations. Preferred procedures are those that have been published in established/authoritative textbooks, peer-reviewed texts or journals, or in international, national or regional guidelines. If in-house procedures are used, they shall be appropriately validated for their intended use and fully documented. **5.5.2** The laboratory shall use only validated procedures for confirming that the examination procedures are suitable for the intended use. The validations shall be as extensive as are necessary to meet the needs in the given	**Laboratory General L** Sound laboratory practice requires full characterization of an assay before its use for patient testing, without regard to when the test was first introduced by a given laboratory. The laboratory must have data on each test's accuracy, precision, analytic sensitivity, interferences and reportable range (i.e., **analytic measurement range (AMR) and clinically reportable range (CRR)**) as applicable. Laboratories subject to CLIA 88: For unmodified FDA-cleared or approved tests, the laboratory may use data from manufacturers' information or published reports, but the laboratory must verify outside data on accuracy, precision and reportable range. For tests that are not FDA-cleared or approved, or for FDA-cleared/approved tests modified by the laboratory, the laboratory must establish accuracy, precision, analytic sensitivity, interferences and reportable range, as applicable; data on interferences may be obtained from manufacturers or published literature, as applicable. **GEN.42020** Has the	**C8.4.1** Analytic sensitivity is the proportion of biological samples that have a positive test result or known mutation and that are correctly classified as positive (assumes mutation is tested for). Analytic sensitivity is determined using samples with known test results or mutation status, either by comparison with another methodology or by consensus findings (e.g., proficiency testing samples). Estimates should include confidence intervals. **C8.4.2** Analytic specificity is the proportion of biological samples that have a negative test result or no identified mutation (being tested for) and that are correctly classified as negative. Analytic specificity is also determined using samples with known test results. Alternatively, samples from the target population could be tested with all positive results confirmed by referent method as being true positives.	**EP5-A2** Evaluation of Precision Performance of Quantitative Measurement Methods **EP 17-A** Protocols for Determination of Limits of Detection and Limits of Quantitation **EP6-A** Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach **EP9-A2** Method Comparison and Bias Estimation Using Patient Samples **EP7-A2 (Protocol)** Interference Testing in Clinical Chemistry **C28-A2 (Protocol)** How to Define and Determine Reference Intervals **MM1-A** **14.3.1** Identify and characterize the	1. For performance establishment and verification of new molecular genetic tests, CLIAC recommends the following 5 steps: a. Ensure a review is conducted of available scientific studies and pertinent references; b. Select appropriate test methodology for the disease or condition being evaluated; c. Establish or verify the analytical performance and determine applicable quality control parameters for the genetic test; d. Define appropriate patient populations for which the test should be performed; e. Ensure test results and their implications can be interpreted for a given individual or family, and the limitations of the test are defined and reported. 2. The number of positive and negative samples that should be included in performance establishment and verification should

Process of Developing CLIAC-recommended GLPs for BGT and NBS

- Feb. 2010 CLIAC meeting
  - CLIAC review of workgroup report
  - Recommendations for BGT and NBS for diagnosis and monitoring of inborn errors of metabolism (http://wwwn.cdc.gov/cliac/default.aspx)

- Discussion of CLIAC recommendations and implications for laboratory testing component of newborn screening – **Dr. Carol Greene**

CLIAC Recommendations for Good Laboratory Practices and Implications for Newborn Screening

Carol Greene, MD

President-elect, Society for Inherited Metabolic Disorders
Professor of Pediatrics, University of Maryland School of Medicine
Chair, CLIAC Biochemical Genetic Testing Workgroup

Overview of CLIAC Recommendations

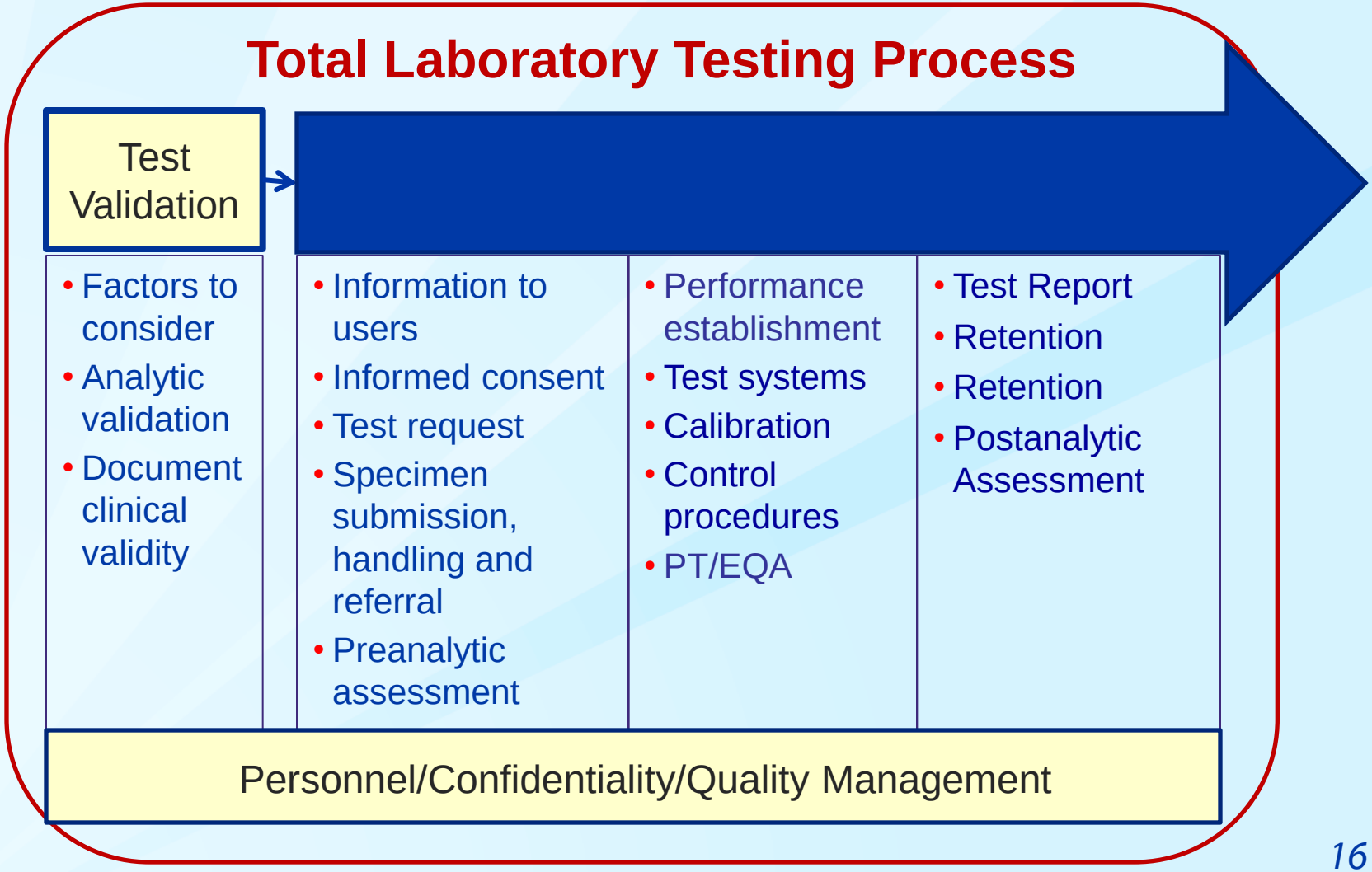
- CLIAC Recommendations for Good Laboratory Practices (GLPs) in Biochemical Genetic Testing (BGT) and Newborn Screening (NBS) for Diagnosis and Monitoring of Inborn Errors of Metabolism (IEM)
  - Scope and applicability
  - Total laboratory testing process (preanalytic, analytic, and postanalytic phases of BGT and NBS)
  - Personnel qualifications, responsibilities, competency
  - Factors to consider when introducing new tests
  - Confidentiality procedures
  - Potential benefits of quality management system approach
- Document available at http://wwwn.cdc.gov/cliac/default.aspx

Highlights of CLIAC Recommendations

Scope and Applicability

- Improve quality of laboratory testing for screening, diagnosis and management of IEMs
- Recommended GLPs should apply to:
  - Testing performed by BGT laboratories
  - BGT performed outside of a BGT laboratory
  - NBS performed for IEMs
  - BGT aspects of tests encompassing BGT and other methods
- Examples are provided for:
  - Tests that should be/should not be covered
  - Clarifications for “situational” tests

Highlights of CLIAC Recommendations



CLIAC Recommendations for Laboratory Preanalytic Phase

- Laboratories should provide test information to users -
  - Information necessary for selecting appropriate testing
  - Information on appropriate collection, handling, and submission of patient samples
  - Types of patient information required to perform testing and report results
  - Availability of laboratory consultation and discussion
  - When indicated, implications of test results for relatives or family members

CLIAC Recommendations for Laboratory Preanalytic Phase

- Information to be provided for each biochemical genetic test:
  - Intended use (e.g., analyte or nucleic acid target, specimen type, purpose of testing, recommended patient population)
  - Indications for testing
  - Test method to be used
  - Analytic performance specifications, clinical validity, limitations
  - FDA approval or clearance
  - Specimen collection, handling, transport, and submission
  - Types of patient information needed by the laboratory for effective testing, accurate laboratory interpretation and result reporting
  - If applicable, potential that test results could have implications for family members
  - Availability of laboratory consultation and discussion
  - Cost information when possible and practical

CLIAC Recommendations for Laboratory Preanalytic Phase

- Informed consent for BGT –
  - Provide users with information necessary to make informed decisions whether informed consent (IC) is required or not
  - Unless mandated, obtaining IC for patient testing generally not a laboratory responsibility
  - When IC is required, assist in determining appropriate level of IC and include method for documentation on test request forms
- Informed consent for NBS -
  - Explicit parental consent not necessary for mandated public health NBS if meeting accepted criteria
  - New tests not meeting criteria should require explicit consent
  - Parental and provider education should be integral to NBS programs regardless of consent requirement
  - Research use of tested specimens should have appropriate human subjects protection procedures

CLIAC Recommendations for Laboratory Preanalytic Phase

- Specimen submission, handling and referral
  - Provide guidance for patient preparation when appropriate
  - Dried blood spot (DBS) specimens should not be batched before being sent to the laboratory
  - Have written criteria for acceptance /rejection of specimens, including handling of non-ideal specimens -
    - Unsatisfactory DBS specimens for NBS
    - If accepting non-ideal specimens, need to document evidence on test performance
    - Use appropriate terminology
  - Refer tests only to CLIA-certified laboratories

CLIAC Recommendations for Laboratory Analytic Phase

- Performance establishment and verification -
  - Ensure adequate establishment/verification of analytic performance
  - Document available information on clinical validity
  - General principles for steps to be taken
  - Performance characteristics to be determined
  - Number of positive and normal samples depends on test and prevalence of disease (but not a low bar for rare disease testing)
  - Use of manufacturer- or literature-provided reference ranges in certain situations (with disclosure and ongoing monitoring/adjustment)
  - “Truth in advertising”

CLIAC Recommendations for Laboratory Analytic Phase

- Control procedures
  - Use control materials to monitor entire analytic process
  - Validate sampling instruments (including automated instruments)
  - Perform control procedures each day or with each batch
  - Controls should be comprehensive, selected based on patient population, prevalence of the disease, and the purpose of testing
  - Acceptable control practices for
    - Time-consuming testing using single-channel/single-column instruments
    - Rare disease assays for which positive controls are difficult to obtain
    - Appropriate alternative control
- Specific analytic issues for BGT and NBS
  - Reagents, standards/reference materials, supplies, equipment
  - Calibration and calibration verification

CLIAC Recommendations for Laboratory Analytic Phase

- Proficiency testing (PT) –
  - Participate in available PT at least twice per year for each test
  - Alternative performance assessments if PT is not available:
    - Interlaboratory exchange
    - Use of externally derived materials
    - Repeat testing of blinded samples
    - Interlaboratory data comparison

CLIAC Recommendations for Laboratory Postanalytic Phase

- Test reports
  - Provide information necessary for accurate understanding and interpretation of test results
  - Comply with CLIA general test report requirements
  - Retain in same format as the original report (including electronic reports generated in the past)
  - Inform or update users when test methods change to meet CLIA requirements*
  - Written in language clinically understandable (by non-geneticist health professionals)
  - Communicate panic or critical values that indicate possible crisis to the clinician caring for the patient*

* Based on CLIA requirements but more specific

CLIAC Recommendations for Laboratory Postanalytic Phase

- Test report contents
  - Include all CLIA-required information
  - Additional information to include -
    - **Patient name and any other unique identifier***, date of birth
    - Indication for testing when needed for result interpretation
    - Date and time of specimen collection and arrival in the laboratory
    - Name of the referring physician or other authorized individual who ordered the test
    - Interpretive guide (e.g., table or reference to literature or website)
    - **Analytes tested and/or type of test method***
    - Performance specifications (including patient-appropriate normal range or reference intervals) and limitations when appropriate
    - **Test results in appropriate measurement units*** and current recommended standard nomenclature
    - **Result interpretation for complex tests, profiles, and testing for carrier status***

(Cont.)

* Based on CLIA requirements but more specific

CLIAC Recommendations for Laboratory Postanalytic Phase

- Test report contents (cont.)
  - **The date and time the test report is released***
  - Notation if preliminary report or update/revision to previous report
  - Results of other relevant tests that the laboratory performed for the patient if available
  - Recommendations for additional testing of patient or for family members where appropriate
  - References to the literature
  - Recommendation for consultation with a genetic professional (when appropriate and indicated)
  - For any in-house developed test using any analyte-specific reagent (ASR), provide the statement required by 21 CFR 809.30(e):
    - "This test was developed and its performance characteristics determined by (Laboratory Name). It has not been cleared or approved by the U.S. Food and Drug Administration."**
  - Signature of personnel who reviewed the test results and provided the result interpretation

* Based on CLIA requirements but more specific

** Required by FDA

CLIAC Recommendations for Laboratory Postanalytic Phase

- Retention of test reports, records, and tested specimens
  - Test reports indicating genotypes: At least 21 years
  - Test records: CLIA and other applicable requirements
  - Tested specimens:
    - Longest possible timeframe as permitted by sample stability/integrity, technology, space, cost
    - BGT: At least until after final result reporting; if possible until next PT or alternative performance assessment
    - NBS: Subject to federal, state, local requirements

CLIAC Recommendations for Laboratory Personnel Qualifications & Responsibilities

- Laboratory directors:
  - Meet CLIA requirements for high complexity testing

- Technical supervisors for BGT:
  - Equivalent qualifications to CLIA requirements for clinical cytogenetics technical supervisors; or
  - Current certification in BGT by an HHS-approved board
  - Equivalent to recommended qualifications in MMWR for molecular genetic testing

CLIAC Recommendations for Laboratory Personnel Qualifications & Responsibilities

- Technical supervisors for public health NBS:
  - CLIA requirements for high complexity testing
  - Four years of laboratory training or experience in NBS
  - Recommend CMS-approved board certification
  - Meet any additional state requirements
- General supervisors for BGT:
  - Baccalaureate degree or above
  - 2 years training/experience
- Clinical consultants & testing personnel:
  - Meet CLIA qualifications
  - Relevant training/experience

Laboratory Considerations Before Introducing New Genetic Tests

- Factors to be considered:
  - All aspects of recommended GLPs
  - Laboratory management issues:
    - Benefits to patient care, needs/demands, cost/cost-effectiveness, (if applicable) intellectual property issues
    - Regulatory compliance
    - Personnel and training
    - Test validation, procedure manual, facility, safety
  - Special issues in NBS at the federal and state levels (including need for and availability of follow-up tests)
- Consider professional guidelines and recommendations

Potential Benefits of Quality Management System (QMS)

- Quality management/quality assessment principles should be stressed throughout the prospective guideline
- QMS policies/procedures may be helpful for:
  - Assess user needs to determine effective ways for providing test information
  - Specimen submission
  - Test requisitions
  - Determine media, format, style, and language for test reports
  - Considerations before introducing or offering new genetic tests
- May help BGT laboratories improve quality and delivery of laboratory services

Development of CDC Guideline for Good Laboratory Practices and Issues for SACHDNC Input

Bin Chen, PhD
Office of Surveillance, Epidemiology and Laboratory Services
Centers for Disease Control and Prevention

CDC Preparation of MMWR Guideline for BGT and NBS

- Provide recommended practices to
  - Clarify applicable CLIA requirements
  - Address need for quality assurance measures in addition to CLIA
- Input solicited to complement CLIAC recommendations
  - Secretary's Advisory Committee for Genetics, Health, and Society (SACGHS)
  - Secretary's Advisory Committee for Heritable Diseases in Newborns and Children (SACHDNC)
  - Association of Public Health Laboratories
- MMWR guidelines intend to –
  - Improve quality of laboratory genetic services
  - Enhance oversight for genetic testing under the current regulatory framework
  - Improve healthcare outcomes from genetic testing

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Topics for SACHDNC Input

- Considering the CLIAC recommendations, are there issues that CDC should explain or clarify for the NBS laboratory community or BGT laboratories in the upcoming MMWR document?
- Are there additional issues that CDC should address in the MMWR guideline pertaining to NBS laboratory practice? If so, can SACHDNC provide recommendations in these areas?
- How should we encourage implementation of the recommended practices once the MMWR guideline is published? What efforts should be taken and who should be reached as partners or collaborators to help with these efforts?

Thank You!

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