Introduction:

CLIAC Biochemical Genetic Testing Workgroup – Good Laboratory Practices for Biochemical Genetic Testing and Newborn Screening for Heritable Diseases

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Background-
Current Oversight for Genetic Testing

- CLIA regulations
  - 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
- FDA requirements for IVD products
- State requirements (e.g., New York and Washington state programs)
- Voluntary professional practice and accreditation guidelines (e.g., ACMG, CAP, CLSI)
- Good laboratory practices

Background-
Addressing Biochemical Genetic Testing

- 2007: CMS action plan to enhance oversight of genetic testing
  - Providing guidance rather than prescriptive regulations
  - Training, education, data collection, collaboration
- Sept. 2007: CLIAC reviewed quality assurance (QA) concerns in genetic testing; suggested developing document to clarify CLIA and provide specific guidance
- 2008: CLIAC Genetics Workgroup 3 focused on molecular genetic testing for heritable diseases and conditions
- Sept. 2008: CLIAC provided good laboratory practice recommendations for molecular genetic testing for inclusion in MMWR R&R (published June 2009); recommended forming workgroup on biochemical genetic testing (BGT) to consider similar good laboratory practice issues

CDC Assessment of BGT Landscape and QA Gaps

- **Purposes:**
  - Frame issues for workgroup consideration
  - Assess areas of expertise needed for the workgroup
  - Assess information needed to facilitate workgroup's evaluation of current standards, guidelines, practices
  - Help to gauge guidance's utility and impact on laboratory testing quality and public's health

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
- Review of available information indicating QA concerns, problems/gaps, room for improvement
- Collaboration with CDC Newborn Screening Quality Assurance Program (NBSQAP)

Assessing BGT Landscape and Gaps

- Sources of information/data identified for analysis:
  - Directories/databases
    - GeneTests
    - Society for Inherited Metabolic Disorders (SIMD) directory
    - National Newborn Screening and Genetics Resource Center
  - State laboratory/public health programs
  - Publications, reports
  - PT/EQA programs
  - Information from professional groups

Assessing BGT Landscape

- What tests are considered BGT?
  - Critical for data collection, gap assessment, scope and applicability of recommendations to be developed
  - CLIA – no definition for BGT
  - Available definitions vary depending on purpose and context
    - Consistent: analysis of human gene products, metabolites to detect inborn errors of metabolisms (IEMs), heritable genotypes or disorders
    - Usually have qualifiers and exclusions
  - Most NBS conditions are IEMs/inherited metabolic disorders
    - Screening tests, presumptive positives need to be confirmed with diagnostic testing
    - Public health labs perform NBS for 97% U.S. infants

Assessing BGT Landscape

- Test volume
  - No published information on current BGT volume or trend of growth
  - Increased needs for definitive diagnosis of presumptive positives due to expansion of NBS (expert opinion)
    - More than 4 million infants born in U.S. each year
    - 2005: 38% infants born in states requiring screening for over 21/29 core conditions recommended by ACMG
    - 2009: All states required at least 21; 24 states and DC screen for all 29 disorders on recommended uniform panel

Assessing BGT Landscape

- Number of BGT laboratories
  - No comprehensive data
  - 2003: 162 BGT labs surveyed (McGovern et al, 2003)
  - As of April 2009:
    - GeneTests: 83 in U.S. and 63 foreign
    - SIMD directory: 99 (US and international)
    - CAP BGT survey: 114 participants in 2008; 93 in 2002
    - New York State: 12 in state and 20 out of state in 2009
- 46 state NBS laboratories

Assessment of Expertise Needed for CLIAC Workgroup

- Diverse technology and diagnostic issues
- Diverse laboratory environments (e.g., large/small labs, common/rare disease testing, academic/private/public health, specialized/general labs)
- NBS and public health perspectives
- Expertise in laboratory performance evaluation, laboratory inspection and accreditation
- Perspective of users of laboratory services (healthcare providers, patients, referring labs) and other stakeholders
- Regulatory (federal and state) oversight; voluntary standards and guidelines
- IVD manufacturers and industry
- CLIAC

Gaps Identified / Issues Needing Guidance

- Comprehensive review of literature, reports, documents to identify QA issues and concerns
- Identified QA concerns relating to preanalytic, analytic, postanalytic phases of testing; personnel; quality management
- Comparison of all relevant laboratory standards and guidelines to assess practices/areas needing guidance or clarification
  - Regulatory vs. voluntary
  - National vs. international
  - BGT vs. genetic testing in general and general laboratory
- Provided to workgroup to initiate discussion and elicit additional insights

Preparation of Workgroup Resources

- 19 comprehensive crosswalks addressing each topic area needing guidance for good laboratory practices (see example; complete list of documents reviewed for preparing crosswalks provided in handouts)

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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

CLIAC BGT Workgroup Process

- Workgroup formed: Feb. – March 2009
- Orientation conference call: March 11, 2009
- Atlanta meeting: June 1-2, 2009
  - Reviewed 19 crosswalks prepared by CDC
  - Developed initial input
  - Identified additional issues to be resolved
- 8 follow-up conference calls: June – Nov. 2009
- Workgroup report finalized: Jan. 2010

Expected Next Steps

- Feb. 2010: Receive CLIAC recommendations for good laboratory practices for BGT and NBS for heritable diseases; initiate guideline preparation by CDC in collaboration with CMS and FDA
- Early 2011: Publication of guideline expected
- Prospective guideline will complement the published MMWR guideline for molecular genetic testing
- MGT and BGT guidelines should improve the quality of laboratory genetic services and healthcare outcomes from genetic testing