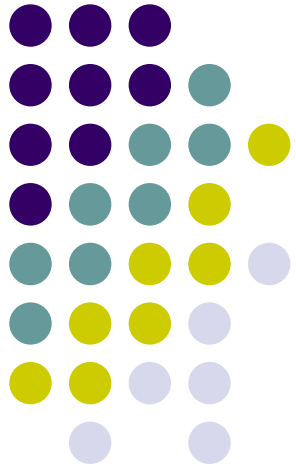
Good Laboratory Practices for Biochemical Genetic Testing and Newborn Screening for Heritable Diseases

Carol Greene, MD, FACMG

Workgroup Chair

CLIAC Meeting February 9-10, 2010



Workgroup Members

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CDC Representatives

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- Diane Bosse
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- Lisa Kalman
- Joanne Mei
- Angela Ragin-Wilson
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- Irene Williams
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CMS Representatives

- Penny Keller
- Ronalda Leneau
- Judith Yost

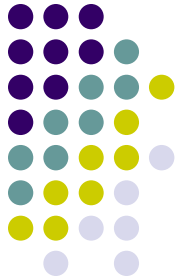
FDA Representatives

- Alberto Gutierrez
- Kellie Kelm

Workgroup Charge and Tasks

- **Workgroup (WG) Charge**
  - Provide input to CLIAC in developing recommendations for good laboratory practices (GLPs) for biochemical genetic testing (BGT)
- **WG Tasks**
  - Suggest the scope of CLIAC consideration for developing GLP recommendations for BGT
  - Recognize and identify issues in BGT that need guidance for quality assurance
  - Identify sources of data and information needed for WG discussion, that are in addition to those provided by CDC
  - Review current guidelines and standards to evaluate GLPs in BGT
  - Consider and suggest strategies for areas in which current standards and practice guidelines are lacking or inconsistent
  - Formulate WG input for CLIAC consideration

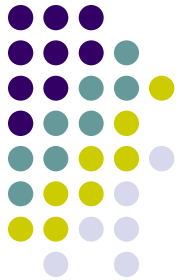
WG Resources



19 comprehensive crosswalks were prepared by CDC staff using information from:

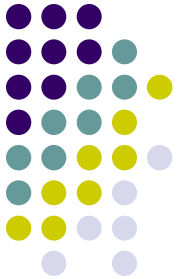
- Accreditation checklists
- Professional guidelines
- Regulatory requirements and guidance documents
- International standards, guidelines and policy documents
- Molecular Genetic Testing MMWR
- Publications/references
- Board certification information
- Industry reports and references

Overview of WG Input



- Consideration on GLPs for BGT and newborn screening (NBS) for heritable diseases
- WG input is based on CLIA requirements
- WG input includes specific guidance for
  - meeting CLIA requirements
  - quality assurance measures in addition to CLIA
- WG suggested GLPs that are more specific or more stringent than CLIA will be shown in **bolded blue text**
- Complete summary of WG input is provided in handouts

Key Areas Addressed by WG



- Scope and applicability
- Preanalytic phase
- Analytic phase
- Postanalytic phase
- Confidentiality
- Personnel requirements
- Personnel competency assessment
- Factors to consider when introducing new tests
- Quality management system (QMS) approach

Scope and Applicability

- No existing definition adequate for intent of CLIAC
- Recommendations should apply to testing for diagnosis and monitoring of inborn errors of metabolism (IEM) to include the following:
  - Testing performed by BGT laboratories
  - BGT performed outside of a BGT laboratory
  - Newborn screening (NBS) for IEMs
  - BGT aspects of tests that encompass BGT and other testing areas
- Provide guidance on CLIA requirements and additional quality assurance measures specific to BGT

Scope and Applicability

Examples of tests for diagnosis and management of inborn errors of metabolism (IEMs) for which the proposed guideline will apply include:

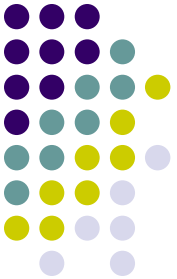
- Enzyme assays for Tay-Sachs and other diseases
- Acylcarnitine profile
- Urine organic acids
- Newborn screening
- Amino acid analysis neurotransmitter analysis in CSF
- Transferrin saturation immunoelectrophoresis for carbohydrate deficient glycoprotein syndromes
- 7-Dehydrocholesterol

Scope and Applicability Exceptions

Examples of tests that are not intended to be covered by the proposed guideline include:

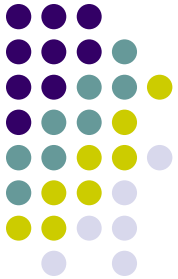
- Testing performed for purposes other than diagnosis or monitoring of IEMs
  - Thyroid function tests
  - Cholesterol and lipid panels
  - Transferrin saturation analysis for monitoring of alcoholic liver disease or hemochromatosis
  - Glucose tests
  - Lactate tests
- Testing nucleic acids for diagnosis of IEMs (covered by MMWR guideline for molecular GT)

Preanalytic Phase Overview



- Information to be provided to users of laboratory services
- Informed consent
- Test request
- Specimen submission, handling and referral
- Preanalytic system assessment

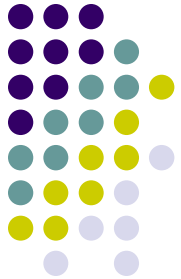
Information to be Provided to Users of Laboratory Services



- Laboratories should provide the appropriate information to their users* to facilitate -
  - Selection of appropriate test(s)
  - Collection, handling and submission of specimens
  - Provision of patient information needed for test performance and result interpretation
- Laboratories should inform users of -
  - Availability of consultation and discussion from the laboratory
  - Implications, when indicated, of test results for relatives and family members

* Under CLIA, laboratories must follow written policies and procedures for these items, but does not require that this information be provided to all users.

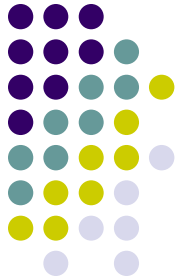
Information to be Provided to Users of Laboratory Services



Laboratories should provide the following information to their users for selection of appropriate testing:

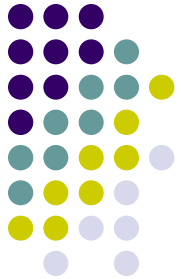
- Tests available
- Intended use
- Indications for testing
- Performance characteristics and/or limitations of the test
- Test method and testing procedures
- CPT codes
- Type of test (FDA-cleared or approved, laboratory-developed test, investigational test under FDA oversight)

Information to be Provided to Users of Laboratory Services



- Information on appropriate collection, handling and submission of specimens
  - Patient preparation
  - Specimen type, amount/volume, and collection container/device
  - Specimen preparation
  - Specimen stability and transport conditions
  - Reasons for rejection of specimens

Information to be Provided to Users of Laboratory Services



Laboratories should:

- Ensure that information provided in the preanalytic phase is consistent with information included on test reports
- Determine effective ways to provide preanalytic information to clients
- Ensure that information is available on websites, in-service directories, or information sheets
- Determine the situations in which a proactive approach is necessary

Informed Consent

- Required in at least 12 states for genetic testing in general
- Recommended mostly for molecular and cytogenetic tests
- BGT typically analyze phenotypes, rather than genotypes, therefore WG does not recommend written informed consent for BGT (except where required by state and local law)
- WG agrees with the molecular GT MMWR that all laboratory testing should be based on informed decision making that involves communication with the clinician

Informed Consent for NBS

- Explicit parental consent is not necessary for mandated public health NBS, if the assay used meets the following criteria—
  - Analytically and clinically validated
  - Clinical utility is documented
  - Treatment is available to prevent or reduce adverse outcome of condition

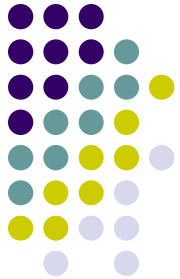
  Parental and provider education must be integral parts of NBS programs regardless of whether informed consent is required
- For new assays, if criteria above are not met, explicit consent should be required in the spirit of informed participation
- Research use of NBS specimens must be done with review of appropriate human subjects protection procedures

Test Request

The following additional or more specific information (relative to CLIA) should be solicited for BGT test requisitions:

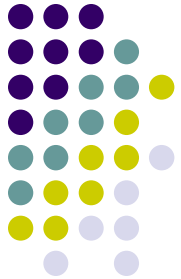
- Patient name **and** any unique identifiers needed for testing
- **Date of birth**
- Date **and** time of specimen collection
- **Test request or referral**
- **Clinical, medication, and nutritional status**
- **NBS -gestational age, birth weight, and state requirements**
- **Race/ethnicity, if applicable**
- **Family history and/or pedigree, if applicable**
- **International Classification of Diseases (ICD) codes**
- **Means for indicating informed consent (when req. by state law)**
- **Emergency contact information for responsible clinician**

Test Request



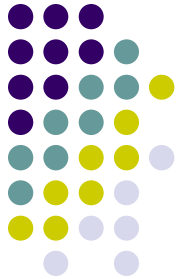
- **Electronic information systems should support and ensure critical information is obtained and retained**
- **Encourage test requestors to submit all the recommended information elements**
- Laboratories must follow federal, state and local requirements regarding informed consent
- **Check-off box may be included to remind test requestors of their responsibility to provide patient consent information**
- **Check-off box is not required to solicit permission for quality assurance (QA) or quality control (QC) use of residual samples**

Specimen Submission, Handling, and Referral



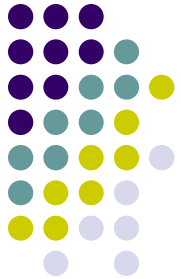
- Laboratories should have policies and procedures to assure pertinent information is provided to users.
- **Laboratories should have procedures for handling specific issues in BGT such as:**
  - **Time sensitive testing**
  - **Turnaround time**
  - **Critical specimen**
  - **Labile specimens**
- **Laboratories should carefully distinguish between unsatisfactory vs. unacceptable specimens**

Specimen Submission, Handling, and Referral



- Have policies and procedures in place to ensure information necessary for selection of appropriate test methods, test performance and result interpretation is retained throughout specimen submission, results reporting, and specimen referral
- Consider expertise, turnaround time in addition to cost when making decisions on test referrals
- For NBS, specimens (dried blood spots) should not be batched before being sent to the laboratory
- WG recognizes that certain specialized tests for rare diseases are only performed by foreign laboratories and encourages further discussion on ways to access these laboratories

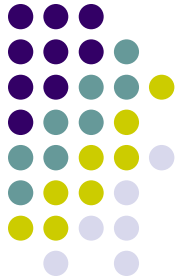
Specimen Submission, Handling, and Referral



Laboratories should have written criteria for acceptance and rejection of specimens, which determine and address:

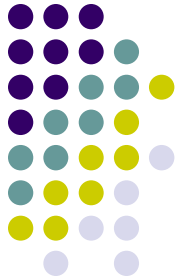
- Improper handling or transport
- Mislabeling
- Inappropriate anticoagulants or media
- Specimen degradation
- Inappropriate specimen type
- Commingled or contaminated specimens
- Lack of unique identifiers on the specimen or the requisition form
- Lack of information necessary to determine if test is appropriate for answering the clinical question
- Specimen not held at appropriate temperature
- Insufficient specimen volume or amount

Preanalytic Systems Assessment



- Preanalytic systems assessment policies and procedures should include making a good-faith effort to verify and confirm test requests that are –
  - Unclear or lacking critical information
  - Submitted with inappropriate specimens
  - Inconsistent with the expected use of test results
- For rapid or time-sensitive testing, the laboratory should have procedures in place for handling situations that require prompt initiation of patient testing
- Contact test requestor or referring laboratory if information the laboratory needs is lacking during specimen submission or test referral

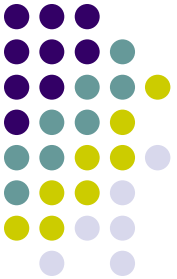
Preanalytic Systems Assessment



- **Establish effective procedures to ensure retention of all needed information throughout the testing process (especially with electronic information systems)**

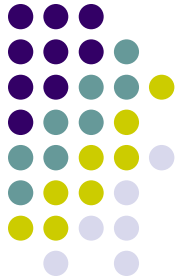
- Follow CMS Interpretive Guidelines, including --
  - Monitoring frequency of specimen handling problems (e.g., insufficient amount of blood on NBS dried blood spots)
  - Monitoring frequency of delays in specimen transport
  - Identifying clients repeatedly referring unacceptable specimens
  - Documenting efforts to reduce recurrence of problems

Analytic Phase Overview



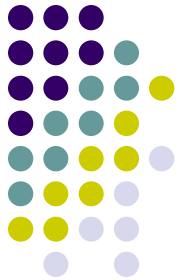
- Performance Establishment and Verification
- Test Systems, Equipment, Instruments, Reagents, Materials, and Supplies
- Calibration and Calibration Verification Procedures
- Control Procedures
- Proficiency Testing and Alternative Performance Assessment

Performance Establishment and Verification



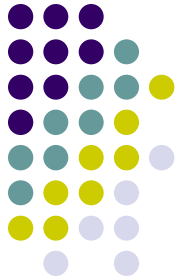
- General Principles for performance establishment and verification
  - Review scientific studies and pertinent references
  - Define appropriate patient populations for which the test should be performed
  - Select appropriate test method for the disease, condition, or analyte
  - Establish or verify performance specifications and determine applicable quality control parameters
- The number of positive and negative normal samples should depend on the assay being established or verified and the prevalence of disease

Performance Establishment and Verification



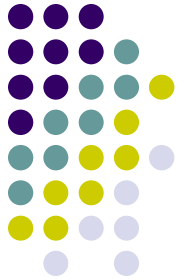
- For **each new test**, determine specifications of the following performance characteristics:
  - Accuracy
  - Precision
  - Analytical sensitivity (**limits of quantification, limits of detection**)
  - Analytical specificity
  - Reportable range of test results, including critical values
  - Reference range or normal values for the patient population
  - Other performance characteristics (**cut-off values for NBS**)
  - **Comparison to other methods when appropriate**

Performance Establishment and Verification



- If samples that represent normal individuals and have the identical sample matrix are not available, the manufacturer's literature or textbook ranges may be used with disclosure, and with monitoring and adjustment if appropriate
- Pattern recognition and interpretation is essential for multi-analyte tests such as acylcarnitine profile and organic acids and should be a part of performance establishment and verification
- Review and follow professional guidelines that are applicable and appropriate for the testing to be introduced and ensure that professional guidelines are followed throughout the total testing process

Performance Establishment and Verification

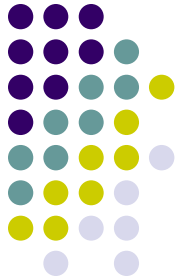


- Laboratory's responsibility for clinical validity should include –
  - Documentation of information regarding clinical validity
  - Establishment of clinical sensitivity, clinical specificity, and predictive values based on internal study results if information regarding clinical validity is not available
  - Providing the user with the currently known test limitations
  - These responsibilities should be specified under the duties of laboratory director and technical supervisor

Test Systems, Equipment, Instruments, Reagents, Materials, and Supplies

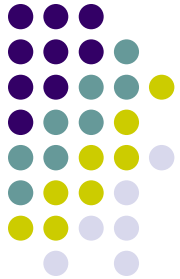
- Reagents and supplies should be the same for routine testing as used in performance establishment or verification
- New reagent lots and/or shipments should be tested in parallel with old lots
- Performance specifications must be established for modified assays before reporting patient results (follow CLIA Interpretive Guidelines)
- **Equipment must be monitored to account for basic detection or measurement drift**
- **Standardizing practice should be encouraged to prepare and validate reagents that are not commercially available**
- **FDA-cleared/approved reagents should be used for patient testing when available**

Calibration and Calibration Verification Procedures



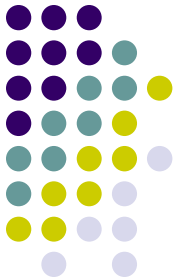
- Obtain adequate quantities of commercially available calibration standards and reference materials for a reasonable period of testing to minimize variability
- When standards and reference materials for calibration are not commercially available, verify each new batch of standards and reference materials against an old batch
- Not all assays require calibration, but that does not relieve the lab of its responsibility to ensure accuracy
- Refer to professional guidelines for specific (or method-specific) guidance

Control Procedures



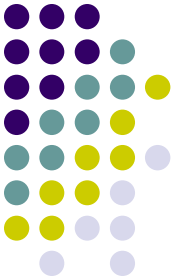
- QC procedures must provide adequate monitoring of the quality of the test system's performance and detect immediate errors
- **Laboratories must validate sampling instruments to ensure there is no carryover between samples on automated instruments**
- Control procedures must be performed each day of patient testing **or with each batch (specific QC issue)**
- **Controls should be comprehensive and based on patient population, prevalence of the disease, and purpose of testing**

Control Procedures



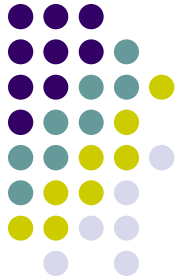
- Control materials must monitor the entire analytic process, including the extraction step
- **For rare diseases for which positive controls are difficult to obtain, laboratories may consider using samples from interlaboratory exchange or other mechanisms, or a more stable specimen type**
- **Alternative control procedures should depend on the specific test and control materials needed**
- **QC recommendations should be considered both in performance establishment/verification and patient testing**

Proficiency Testing and Alternative Performance Assessment



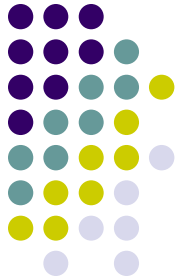
- **PT should be required for all BGT**
- **The frequency of PT must be at a minimum of twice per year, and higher frequency is encourage**
- **Laboratories are encouraged to participate in external PT that evaluates both analytic and interpretive elements of testing**
- **PT providers should develop and users should participate in PT programs that examine the total testing process**
- Where possible, PT materials should resemble patient samples

Proficiency Testing and Alternative Performance Assessment



- **For analyte- or disease-specific PT**, PT samples must be tested with the laboratory's regular patient testing workload by personnel who routinely perform the testing method
- **Available sources for PT or EQA, and resources facilitating external sample exchange, should be made available to laboratories in considering meeting PT and alternative assessment needs**
- Laboratories should document and track their PT and EQA performance, take corrective action for disparate results and document outcomes

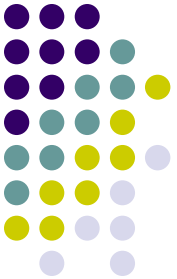
Proficiency Testing and Alternative Performance Assessment



For BGT for which no PT is available, alternative performance assessment must be performed twice a year

- Ideal assessment–
  - Interlaboratory exchange
  - Externally derived materials
- Other options --
  - Repeat testing of blinded samples
  - Exchange with a research facility or international laboratory
  - **Interlaboratory data comparison**
- Refer to professional guidelines

Postanalytic Phase Overview



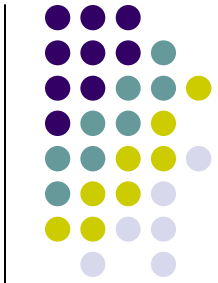
- Test Report
- Retention of Records and Reports
- Retention of Specimens
- Postanalytic Systems Assessment

Test Report

- Content should include:
  - Information required by CLIA
  - 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 (for example a table or reference to literature or to website)**
  - **Analytes tested and/or type of test method**
  - **Performance specifications and limitations when appropriate**

(Cont. on next slide)

Test Report



- Content should include
  - Test results in appropriate measurement units **and current recommended standard nomenclature**
  - Result interpretation **for complex tests, profiles, and testing for carrier status**
  - **Notation if report is preliminary or whether it is an update or revision to previously reported results**
  - **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**

(Cont. on next slide)

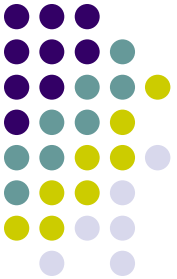
Test Report

- Content should include:
  - **Recommendation for consultation with a genetics 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."**
  - The date **and time** the test report is released
  - **Signature of personnel who reviewed the test results and provided the result interpretation**

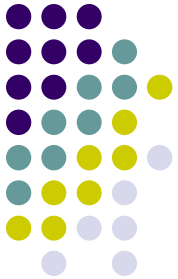
** Required by FDA

Test Report



- **Retain in same format as the original report, includes 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 the patient may be in crisis **to the clinician caring for the patient**

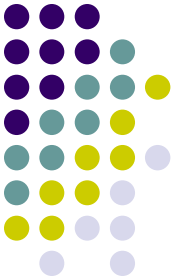
Retention of Records and Reports



For QC, PT and other records

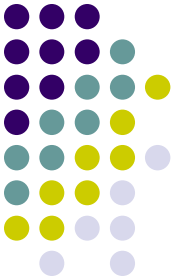
- Retention policies and procedures must comply with applicable state laws and other requirements, such as those by accrediting organizations
- The CLIA-required 2-year retention timeframe is the minimum requirement for BGT
- **Laboratories may want to keep records longer than 2 years for educational purposes**
- **Primary data from which reports are generated should be kept with the reports, preferably electronically**

Retention of Records and Reports



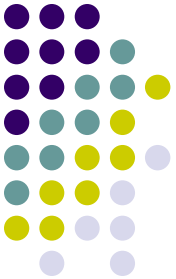
- **Retain reports indicating genotypes for the longest possible timeframe, at least 21 years after the date of reporting**
- NBS reports are subject to state requirements
- **Laboratories should ensure that electronic records and reports are accessible while the technology of electronic storage evolves**
- Retention policies and procedures must comply with applicable state laws

Retention of Specimens



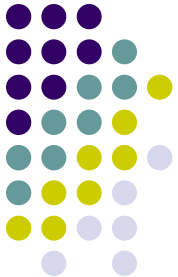
- **Specimens should be retained for the longest possible timeframe as permitted by sample stability and integrity, technology, space, and cost**
- **For low-volume tests, the samples should be retained until the next PT/EQA**
- Tested patient specimens should be retained until after the final reporting of results
- NBS residual specimens are subject to federal, state and local requirements

Postanalytic Systems Assessment



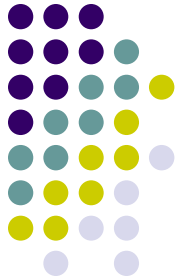
- The CLIA postanalytic systems assessment requirements apply to BGT
- **Abnormal screening results need further investigation by analysis of a freshly collected second sample**
- **Comprehensive systems should be in place for follow-up of a positive screen**

Postanalytic Systems Assessment



- Issues specific to BGT:
  - When an abnormality is detected, testing of other analytes may be critical to clarify diagnosis
  - Reflex testing on the same sample may be useful and appropriate, and raises questions of test ordering, cost and coverage
  - Additional testing by another method or of another tissue may be important for clarification of diagnosis
  - Additional samples may be needed when testing unstable analytes

Personnel Overview



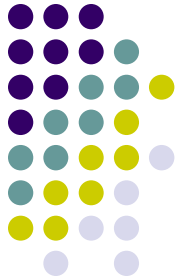
- Laboratory Director
- Technical Supervisor
- Clinical Consultant
- General Supervisor
- Testing Personnel
- Personnel Competency

Laboratory Director

- **Qualifications**: CLIA requirements for high complexity testing adequate

- **Responsibilities**: CLIA responsibility requirements for high complexity testing, plus--
  - Have **authority** for ensuring laboratory testing quality and compliance with all applicable requirements for laboratory operation
  - **Ensure the documentation of clinical validity of any BGT the laboratory offers**

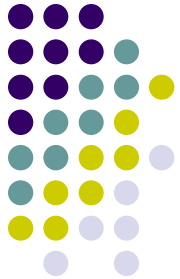
Technical Supervisor - Qualifications



Qualifications should be appropriate for the section they are supervising

- BGT Technical Supervisor qualifications should be equivalent to CLIA qualification requirements for clinical cytogenetic technical supervisor -
  - M.D., D.O., D.P.M., or doctoral degree, with 4 years of training or experience in genetics (2 years in BGT); or
  - Current certification in biochemical genetic testing by HHS- approved boards, such as certification by the American Board of Medical Genetics (ABMG)

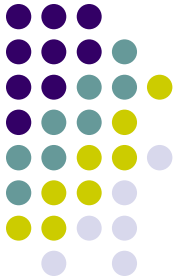
Technical Supervisor - Qualifications



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

Technical Supervisor -Responsibilities



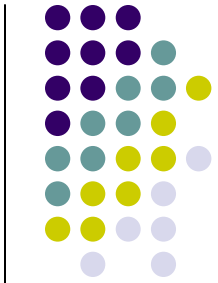
- Follow CLIA responsibility requirements for high complexity testing, and
  - **Assess the suitability of test for use**
  - **Ensure appropriate documentation of clinical validity**
  - **Review test results and the interpretation**
  - **Review and/or sign test reports**
  - **Available to answer test report questions (on-site)**
  - **Evaluate test results and need to refer out**
- **For NBS, knowledge of state policies for additional testing requirements**

Clinical Consultant

- **Qualifications**: CLIA qualifications for high complexity testing, plus relevant training and/or experience -
  - M.D. or D.O., **board certified or eligible in clinical or clinical biochemical genetics**; **or**
  - M.D. or D.O., **with 2 years experience in BGT and/or diagnosis and management of IEMs**; **or**
  - Hold a Ph.D. in a relevant discipline, **be board-certified in biochemical genetics, and have 2 years training/experience in BGT**

- **Responsibilities:** CLIA responsibility requirements for high complexity testing

General Supervisor



- **Qualifications for BGT:**
  - Qualified as a director or technical supervisor; **or**
  - M.D., D.O., D.P.M., and have one year training or experience in high complexity testing relevant to the tests performed by the laboratory; or
  - Doctorate or master degree in a chemical, physical, biological or clinical laboratory science, and have 1 year of training or experience in high complexity testing relevant to the tests performed by the laboratory; **or**
  - Baccalaureate degree in a chemical, physical, biological or clinical laboratory science, **and have 2 years of training or experience in high complexity testing relevant to the tests performed by the laboratory**

General Supervisor

- **Qualifications for NBS**
  - CLIA requirements for high complexity testing **and**
  - Meet state or local requirements

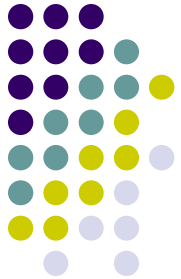
- **Responsibilities**: CLIA general responsibility requirements for high complexity testing

Testing Personnel

- **Qualifications**: CLIA requirements for high complexity testing appropriate
  - Must receive adequate training and **demonstrate competency in high complexity BGT before performing patient testing**
  - Follow state or local requirements

- **Responsibilities**: CLIA responsibility requirements for high complexity testing adequate

Personnel Competency

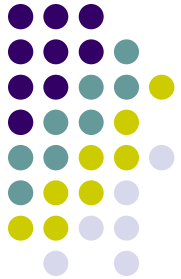


- CLIA requirements are adequate
- Laboratory director is responsible to determine specific policies and procedures for assessing and ensuring the competency of the following laboratory personnel:
  - Technical supervisor
  - Clinical consultant
  - General supervisor
  - Testing personnel
- Follow the applicable guidelines provided by CMS

Confidentiality

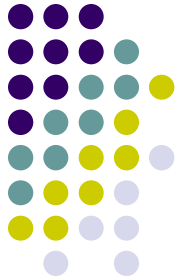
- All laboratories must ensure confidentiality of patient information and **should have a written policy**
- Laboratories must ensure confidentiality of genetic test information in the same manner they ensure confidentiality of other laboratory or medical information
- Electronic records should be under proper access control to ensure patient confidentiality
- **All the recommended confidentiality practices in the MGT MMWR should apply to BGT**

Considerations Before Introducing or Offering New BGT



- Management responsibilities
- State and local regulatory requirements
- Benefits to patient care
- Cost and cost-effectiveness
- Developing and validating procedures
- Personnel considerations
- Special issues in NBS
- Facility and laboratory safety considerations
- Performance establishment or verification needs
- Personnel training

Considerations Before Introducing or Offering New BGT



- Reasons to introduce a test –
  - Introducing a new genetic test that has not been offered anywhere
  - Introducing a test in house that has been referred out to another laboratory
  - Introducing a second test that can compliment the existing test
- Needs and demands of the new test
- Intellectual property restrictions
- Consider appropriate professional guidelines

Quality Management System

- Laboratories can refer to professional guidelines, accreditation standards, and other standards for guidance
- Benefits of QMS in BGT include:
  - Help laboratories meet CLIA requirements
  - Improve quality, efficiency
  - Improve delivery of laboratory services to meet the expectations for patient care
  - Help with international test referrals and global harmonization
  - Prompt laboratories to examine the process beyond patient testing such as the research and development

Quality Management System

- QMS policies and procedures may be helpful for the following specific areas:
  - Determining effective ways to provide information to users of laboratory services
  - Specimen submission
  - Test requisitions
  - Test reports based on assessment of user needs
  - Considerations before introducing genetic testing or offering new genetic tests