

CLIAC Discussion

Good Laboratory Practices for Molecular Genetic Testing

Elissa Passiment

Committee Chair

Workgroup Suggestions for MMWR

- Provide guidance for genetic testing (GT) laboratories to meet CLIA
- Provide guidance for areas needing additional quality assurance (QA) measures
- Provide educational information for:
 - Laboratory community
 - Users of laboratory services

Scope of MMWR



- Clarify the scope and applicability of good laboratory practices (GLPs), but do not need to define GT
- GLP recommendations should improve quality of molecular genetic testing (MGT) in general
- Document would apply to:
 - Molecular/nucleic acid-based
 - Heritable disorders or conditions (including pharmacogenetic testing)
 - Molecular aspects of tests that encompass molecular genetics, such as array-based comparative genomic hybridization
- Future documents should address:
 - Molecular cytogenetic testing
 - Biochemical genetic testing
 - Somatic genetic testing



Committee Discussion

(Scope & Applicability of MMWR)

WG Suggestions for GLPs in MGT (Overview)

- All phases of testing
 - Preanalytic
 - Analytic
 - Postanalytic
- Confidentiality
- Personnel
 - Qualifications
 - Responsibilities
 - Competency Assessment
- Considerations before introducing GT or offering a new GT
- Quality management system (QMS)

Preanalytic Phase of Testing

- Role of Laboratories in Providing Information to Users of Their Services
- Informed Consent
- Test Request
- Specimen Submission, Handling, and Referral
- Individuals Authorized to Order Genetic Tests
- Preanalytic Assessment

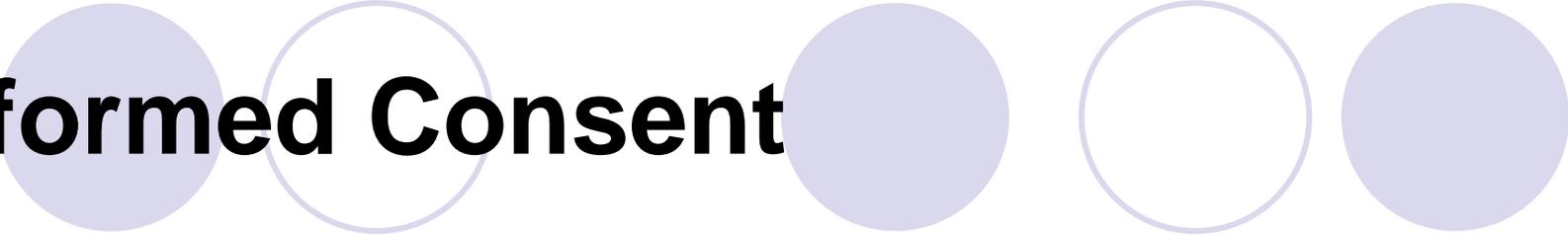
Role of Laboratory in Providing Information to Users of Their Services

- The laboratory has a responsibility to provide information to clients to facilitate selection and ordering of appropriate test(s)
- The laboratory should determine effective ways to provide the information (which may need to be provided through multiple channels – “one-size-fits-all” approach may not work)
- At a minimum laboratories should ensure the information is available, on websites, in-service directories, or information sheets (the passive mode)
- Laboratories should determine situations when they need to be more proactive in providing the information

Laboratories Should Provide the Following Information to Users

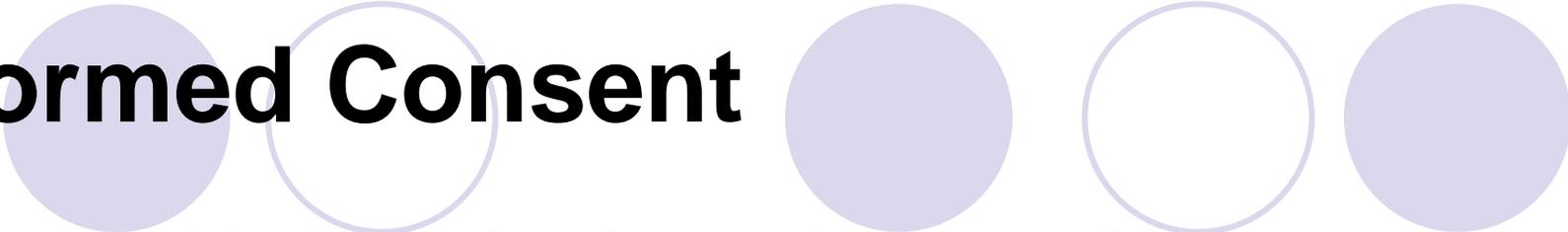
- List of tests performed
- Intended use of the test
- Indications for testing
- Specifications of applicable performance characteristics
- Test methodology and testing procedures (CPT codes if appropriate)
- Limitations of the test
- FDA clearance/approval information
- Information on collection, handling, and submission of specimens, including reasons for rejection of specimens
- Patient information required to perform the test (including patient consent, if required)
- Availability of consultation and discussion from the laboratory
- A statement indicating whether test results may have implications for family members

Informed Consent



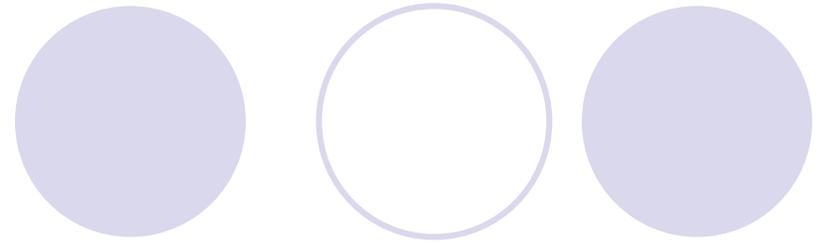
- All laboratory testing should be based on informed decision making
- The laboratory should provide information necessary for making informed decisions
- The laboratory should be available to assist in determining the appropriate level of informed consent

Informed Consent



- The individual ordering the test is responsible for obtaining informed consent if required
 - Informed consent is between the clinician and their patient
 - The laboratory is not responsible for obtaining informed consent before performing the test
 - If required by federal, state or local law, the consent form should be provided to the laboratory with the test request
- The level and nature of consent needed for specific tests should consider the purpose and implications of the test

Test Request



- o In addition to CLIA, solicit the following:
 - Patient name*
 - Date of birth*
 - Indication for testing
 - Relevant clinical or laboratory information, if applicable
 - Patient's race/ethnicity
 - Family history and/or pedigree
 - Appropriate ICD codes or other codes indicating the disease or conditions to be tested
 - Check-off box to indicate informed consent, if appropriate
- Should not need to include a check-off box to indicate whether the patient has declined having residual samples used anonymously for QA/QC purposes

*more specific than CLIA requirements

Specimen Submission, Handling, and Referral

- Ensure users have instructions for identification, collection, handling, and referral of patient specimens.
- Have in place written criteria for acceptance or rejection of specimens, to include:
 - Improper handling or transport
 - Inappropriate anticoagulants or media
 - Inappropriate specimen type
 - Commingled or contaminated specimens
 - Insufficient ID (specimen or requisition form)
 - Insufficient information to determine if test will answer the clinical question
 - Specimen exposure to extremes of temperature
 - Insufficient volume
- Ensure critical information is retained throughout specimen submission, result reporting, and specimen referral

Individuals Authorized to Order GT

- State laws define persons authorized to order GT
- Follow professional guidelines and federal/state /local requirements when deciding which GT could be offered directly to consumers and appropriate circumstances
- Laboratories should ensure qualified personnel are available to assist with test request and result interpretation
- Suggested clarifications to CLIA requirement requiring laboratories to accept test requests from authorized individuals:
 - Initial laboratory is responsible for verifying that the original test request is submitted by authorized individual
 - Referral laboratory should not be responsible for verifying whether the original test requestor is authorized individual

Preanalytic Systems Assessment

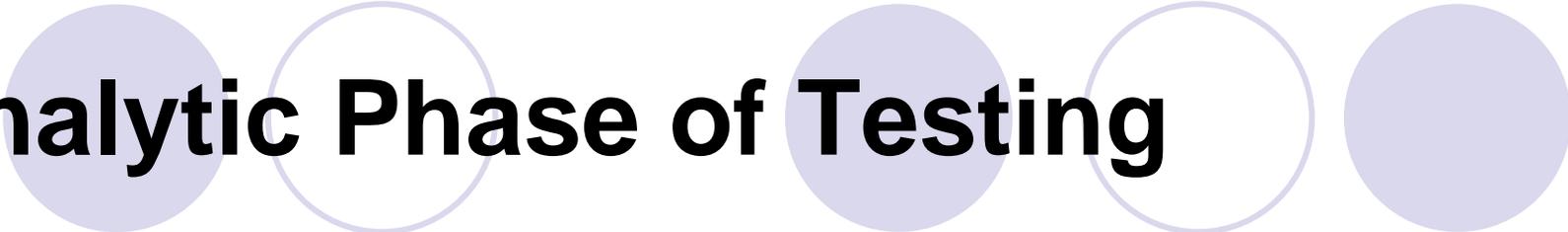
- Laboratories should have written policies and procedures to correct problems identified in the preanalytic steps, including:
 - Unclear request
 - Lack of critical information
 - Inappropriate specimens
 - Inconsistencies with expected use of test
- If necessary information is stripped out during specimen submission or test referral, the laboratory should:
 - Inform test requestor or referring laboratory of the information the laboratory needs on test requisitions
 - Establish effective procedures to ensure information needed is retained during the specimen submission or test referral process



Committee Discussion

(GLPs in Preanalytic Phase of MGT)

Analytic Phase of Testing



- Performance Establishment and Verification
- Control Procedures
- Unidirectional Work flow and Monitoring of Molecular Amplification Procedures
- Proficiency Testing and Alternative Assessments

Performance Establishment and Verification

- Suggested steps before introducing new GT:
 - Review available scientific studies and pertinent references
 - Select appropriate test methodology for the condition
 - Establish or verify the analytical performance and determine applicable quality control parameters for the GT
 - Define appropriate patient populations
 - Ensure test results and their implications can be interpreted for a given individual or family
 - Ensure limitations are defined and reported

Performance Establishment and Verification

- Determine performance specifications before introducing to patient testing:
 - Accuracy
 - Precision
 - Analytical sensitivity
 - Analytical specificity
 - Reportable range of test results
 - Reference range or normal values
 - Other performance characteristics as needed, such as:
 - Robustness
 - Lowest limit of detection (LOD)

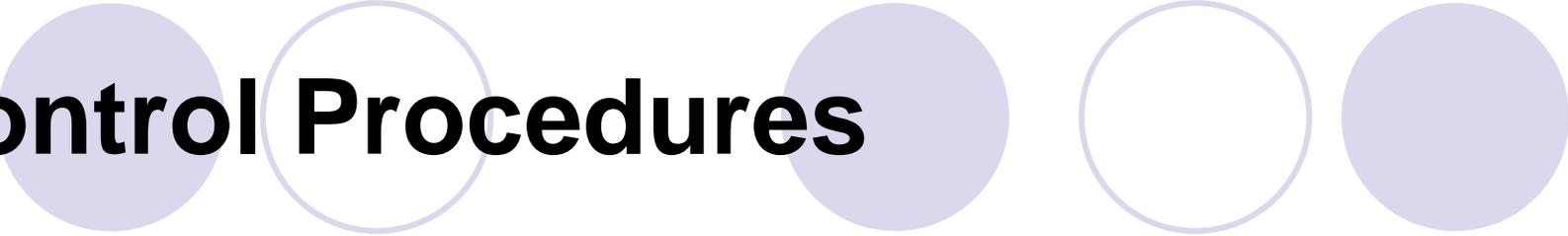
Performance Establishment and Verification

- Validation should be adequate and as comprehensive as possible to ensure interpretable results
- The number of positive and negative samples should depend on:
 - assay being established or verified
 - prevalence of the mutation or variant
 - prevalence of the disease (but not intended to set a low bar for rare disease testing)
- Follow professional guidelines consistently through validation and patient testing
- Include all mutations or variants to be detected for multiplex GT using targeted detection methods (ideally)

Performance Establishment and Verification

- Laboratory director should be responsible for ensuring clinical validity is documented
- Clinical validity documentation should include:
 - Available information (e.g., literature references) on:
 - Clinical sensitivity/specificity
 - Positive/negative predictive values
 - Internal study results, if no published sources
 - Whether clinical claims can be reproduced in the laboratory (truth in advertising)

Control Procedures



- Laboratories should have control procedures in place to monitor and ensure the quality of the entire GT process
 - Include extraction controls to monitor nucleic acid extraction step
 - Validate automated sampling instruments to ensure no carry-over (e.g., checkerboard experiments with nucleic acid samples interspaced with no-template samples)
- Control procedures should be performed with each run of patient testing
- Controls should be selected based on patient population, prevalence of the disease, and the mutation/variant to be detected

Control Procedures

- Appropriate alternative control procedures, when control materials are not available or practical, should depend on the specific test and control materials needed
- Examples of alternative control procedures include:
 - Targeted mutation detection - direct sequencing, or confirming results by a reference laboratory
 - Sequencing – it is important to include a normal control; may use bidirectional sequencing and/or separately extracted nucleic acid sample if positive control is not available
 - Test detecting multiple mutations or variants – if not practical to include all positive controls, rotate positive controls in a reasonable timeframe
- QC suggestions are for **both** validation and patient testing

Unidirectional Workflow & Monitoring Molecular Amplification Procedures

- o Laboratories should monitor and minimize cross-contamination in molecular amplification procedures that are not fully closed with:
 - o Unidirectional workflow
 - o No-template control (NTC)
 - Include at least one NTC in each run or each unit (e.g., 96 well plate).
 - At a minimum, include NTC in amplification and subsequent steps
 - Additional NTC through the extraction step is recommended
 - Determine order of samples, including number and positions of control samples (e.g., NTCs) to ensure adequate monitoring

Unidirectional Workflow & Monitoring Molecular Amplification Procedures

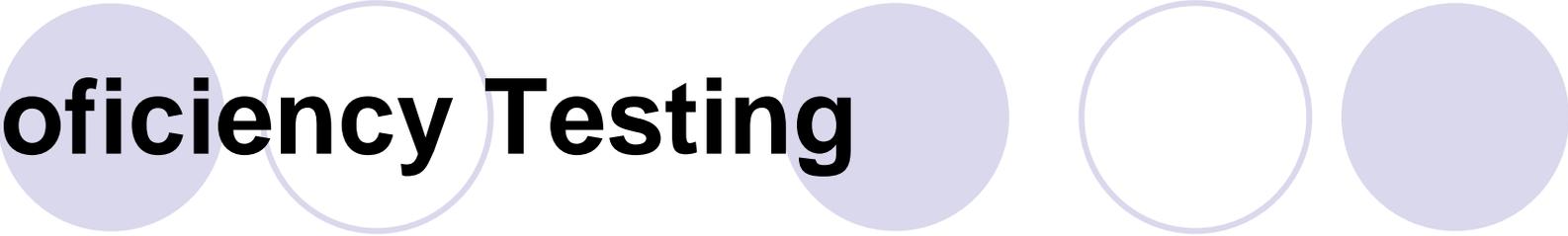
- Specific unidirectional workflow procedures should be implemented if the following is performed:
 - Nested PCR
 - QC materials prepared through PCR, WGA, or subcloning
 - Keep workflow of generating synthetic materials separate from patient testing process
 - Prepare in a well-controlled environment
 - Test control samples to monitor cross-contamination
 - Using purchased amplified materials for controls or competitors

Proficiency Testing



- Should be required for all genetic tests for which a PT program is available
- Minimum frequency is twice a year
- Programs that examine the entire testing process should be encouraged
- PT materials should resemble patient samples where possible, at least for most common GTs
- For analyte- or disease-specific PT, PT materials must be tested with the regular workload by personnel that routinely perform the test
- Laboratories should evaluate their PT results and implement corrective actions for disparate results

Proficiency Testing



- A list of PT/EQA programs and sources that facilitate sample exchange should be made available to help laboratories to meet PT and alternative assessment needs
- Methodology-based PT may be useful for QA and should be explored to supplement disease-specific PT
 - Based on sample type and variables of the testing process
 - Data needs to be collected and evaluated
 - Examples include cytogenetics, FISH assays, and sequencing

Proficiency Testing Alternatives

- Alternative performance assessments should be performed at least twice a year when no PT program exists
- Data unavailable on robustness or effectiveness
- Guidance is provided in professional guidelines on acceptable approaches
- Alternative assessment should ideally be performed by inter-laboratory exchange or using externally derived materials
- If inter-laboratory exchange or externally derived materials are not practical or feasible (e.g., rare disease testing, testing performed by only one laboratory, unstable analytes):
 - Repeat testing of blinded samples
 - Exchange with research or international laboratory
 - Inter-laboratory data comparison



Committee Discussion

(GLPs in Analytic Phase of MGT)

Post Analytic Phase of Testing

- Test Report
- Retention of Records and Reports
- Specimen Retention

Test Report

Should include the following in addition to CLIA :

- Patient's name*
- Patient's date of birth
- Indication for testing
- Date/time specimen collected
- Date/time specimen arrived
- Referring physician or authorized individual
- Test method, including the nucleic acid target the test intended to detect
- Performance specifications and limitations
- Test results in current recommended standard nomenclature
- Result interpretation
- References to the literature
- Recommendation for consultation (if appropriate)
- Implications of test results for relatives or family members (if appropriate)
- Required statement for in-house developed tests using ASR**
- Statement indicating result and interpretation is based on current knowledge and technology

*more specific than CLIA requirements

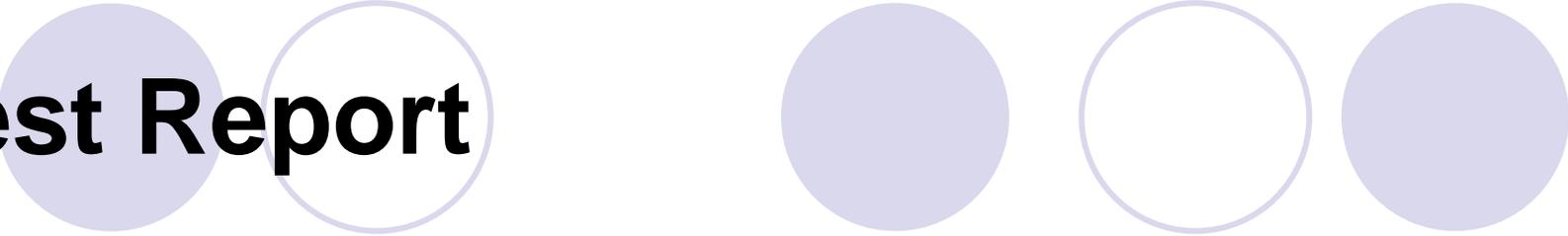
**ASR statement required by 21 CFR 809.30(e): "This test was developed and its performance characteristics determined by (Laboratory Name). It has not been cleared or approved by the U.S. Food and Drug Administration.

Test Report

- Suggested Clarifications to CLIA Requirements:
 - “Normal values”
 - Interpreted as normal alleles for MGT
 - For sequencing assays should be the reference sequence(s)
 - Subject to technology and knowledge advancement
 - Provide updates when changes affect test result/interpretation
 - Keep a database for GTs offered and provide updates to users when knowledge advancement affects performance specifications and/or interpretation of test results
 - Issue a revised report when*:
 - A better interpretation becomes available
 - Knowledge advance changes interpretation of a previous result

*Some WG members disagreed with this point considering the potential burden and difficulty to re-contact clients.

Test Report

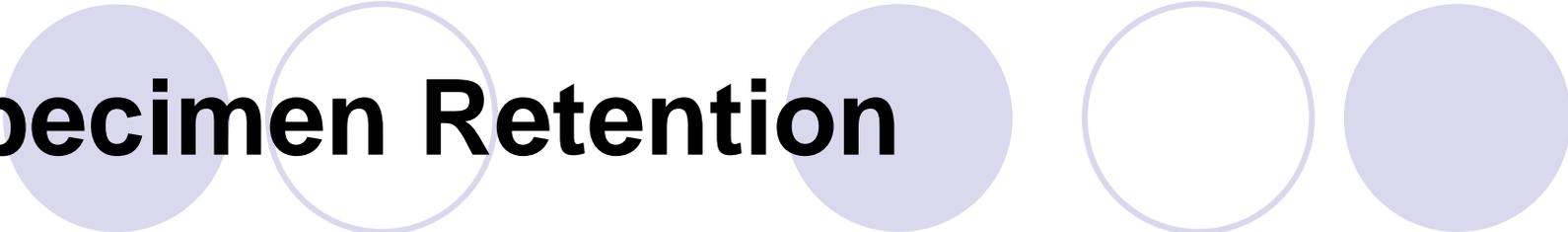


- Qualified personnel should review and sign before release
 - Individual who signs should be linked to personnel competency and responsibilities
 - It may not be practicable for GT reports to include signatures
- Assess needs of users for determining the following:
 - Media
 - Format
 - Style
 - Language
- Informative with all necessary information
- Easy to understand using lay terminology and common terms in interpretation

Retention of Records and Reports

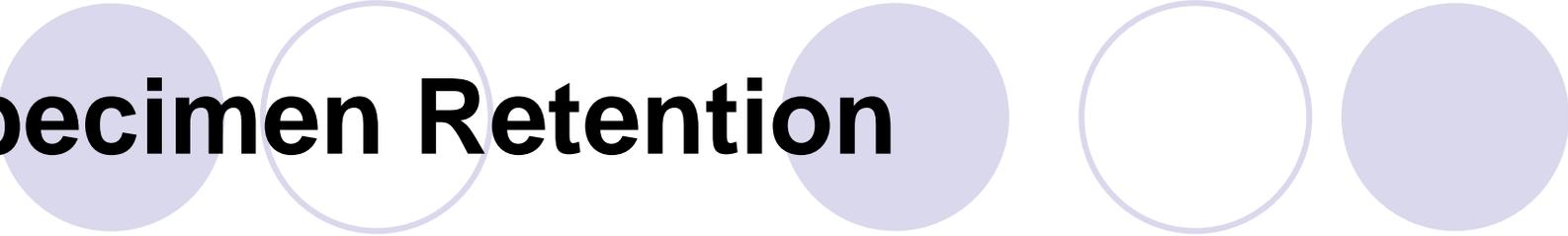
- Retain QC and PT records for at least 2 years as required by CLIA
- Retain test reports for longest possible timeframe, at least for one generation (20 years)
- Comply with state laws and other applicable requirements
- Ensure electronic records and reports are accessible while the technology evolves

Specimen Retention



- Retain specimens for longest possible timeframe as technology, space, and cost permit
- Minimum retention timeframe should be until next PT event or alternative assessment
- If patient consent is needed and is not sent with the specimen, the laboratory should notify the requestor regarding the consent requirement and the timeframe the specimen may be held before it must be rejected or discarded

Specimen Retention



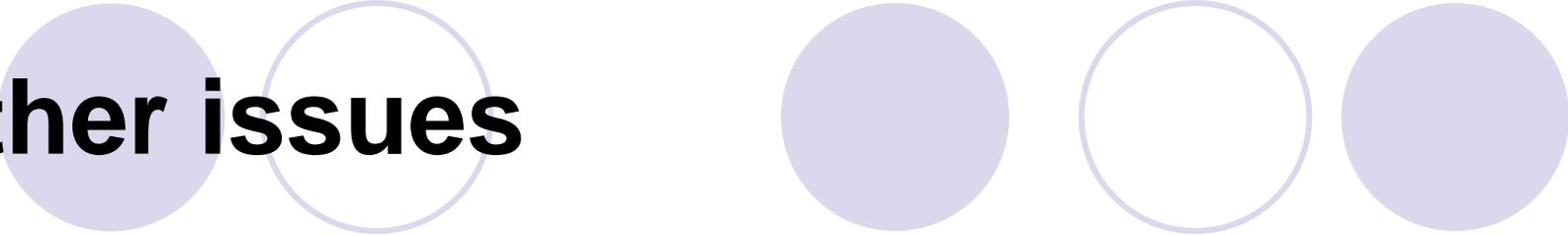
- Laboratory director is responsible for retention policies
- Retention policies should be:
 - Consistent with the laboratory's quality assessment activities
 - Compliant with accreditation requirements and federal, state, and local regulations
 - Based on the following:
 - Type of specimens to be retained
 - Analytes tested
 - Test results (retention of only abnormal samples not recommended considering possible false negatives and bias in performance verification or establishment)
 - Test volume
 - New technologies



Committee Discussion

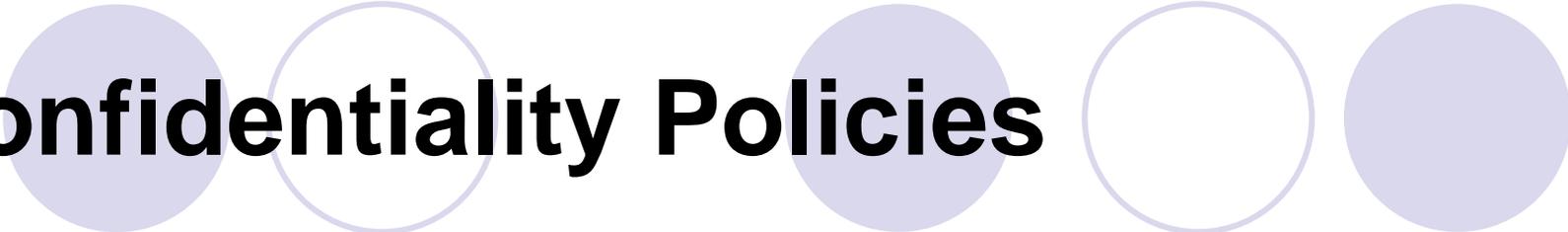
(GLPs in Postanalytic Phase of MGT)

Other issues

A decorative graphic at the top of the slide consists of two overlapping circles on the left and three separate circles on the right. The leftmost circle is solid light purple and overlaps the second circle, which is a light purple outline. The three circles on the right are also light purple, with the first and third being solid and the middle one being an outline.

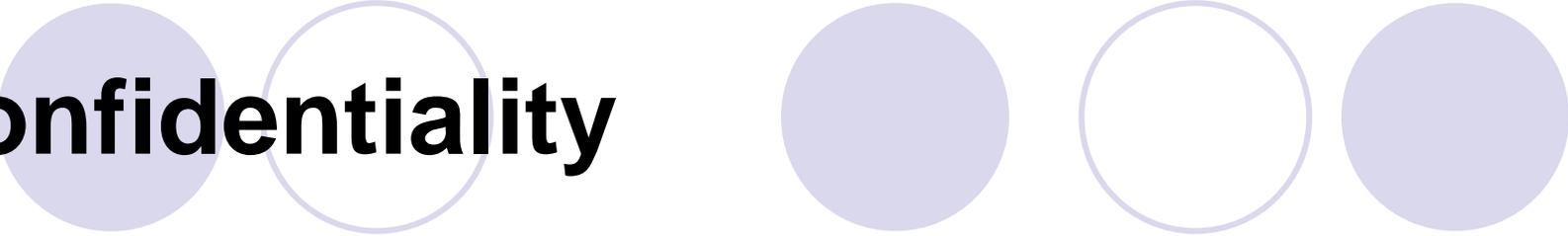
- Confidentiality
- Personnel
 - Qualifications
 - Responsibilities
 - Competency Assessment
- Considerations Before Introducing GT or Offering a New Test
- Quality Management System

Confidentiality Policies



- GT information should be kept confidential in the same manner as other laboratory test or medical information
- In addition to CLIA, more specific practice guidance is provided by:
 - HIPAA Privacy Rule
 - State requirements
 - Accreditation standards
 - Professional guidelines
- The laboratory director is responsible for developing the policy, to include:
 - When access to confidential information is appropriate
 - How and to whom information is to be released

Confidentiality

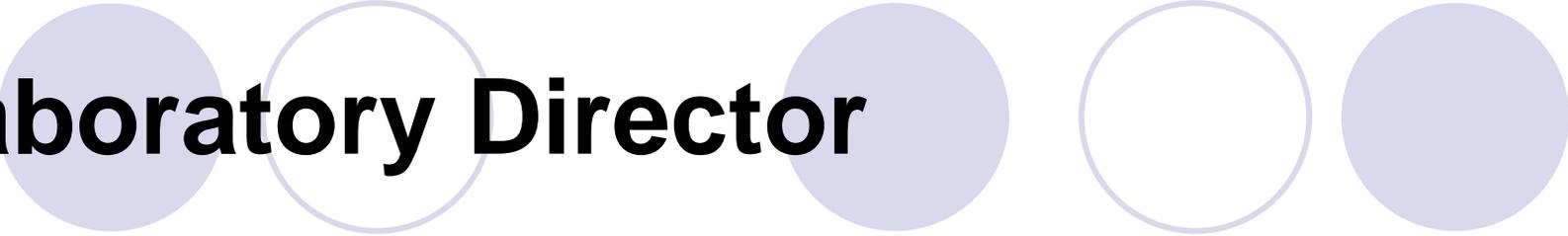


- Responsibilities of all employees should be defined in procedures and protocols that ensure the following:
 - Appropriate access
 - Documentation
 - Storage
 - Release and transfer of confidential information
 - Prohibition of unauthorized or unnecessary access or disclosure.
- Access to electronic records should be properly controlled

Confidentiality and Family Members

- If test results need to reference family members, the laboratory needs to have policies and systems to ensure confidentiality of all patient information, including information on family members
- When a patient's results are needed for management of a family member, the policy should include:
 - Laboratory should release information only to ordering physicians or physicians cooperating in the care of the patient who was tested
 - Results should not be released without the authorization of the patient. It should be up to the patient to contact the family members or to ask his/her physician to do so
 - If patient consent is required for testing, the consent form should address possibility of request from physicians caring for family members and allow the patient to decide whether to authorize the release of information (may be difficult to implement in practice)

Laboratory Director



- Qualifications
 - CLIA requirements are appropriate
- Responsibilities
 - In addition to CLIA requirements, suggested additional responsibilities include:
 - Ensure documentation of the clinical validity of any GT offered
 - Determine specimen retention policy that is consistent with the laboratory's quality assessment activities

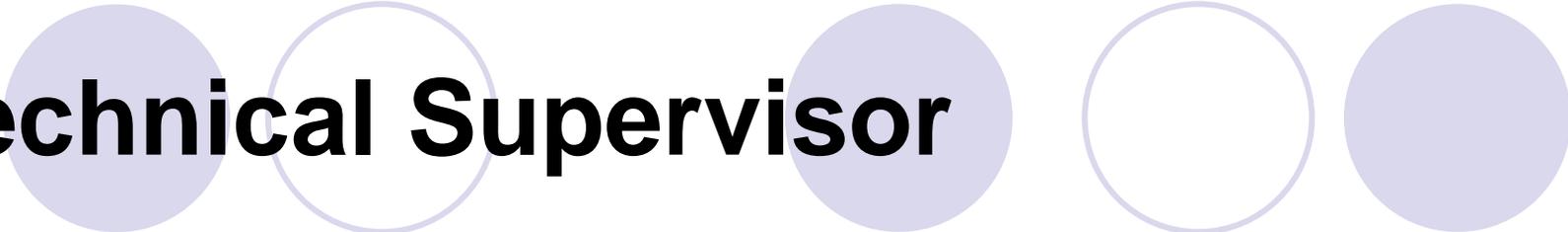
Technical Supervisor

● Qualifications*

- Ideal qualifications
 - Equivalent to the CLIA clinical cytogenetic TS with 4 years training or experience (2 of which are in MGT for heritable conditions) or
 - Certification in MGT by HHS-approved boards
 - ABMG
 - MGP certification jointly administered by ABMG and ABP
 - Tiered qualifications based on test complexity and conditions evaluated were proposed, but not possible to define
 - Current CLIA TS qualifications for high complexity testing are sufficient to avoid restricting access to simple MGT
- Moderate complexity test qualifications would apply if FDA approves moderate complexity MGT
- Tests that include a molecular genetic component should be addressed in suggested additional documents

*Workgroup did not reach agreement on technical supervisor qualifications for MGT.

Technical Supervisor



- Responsibilities

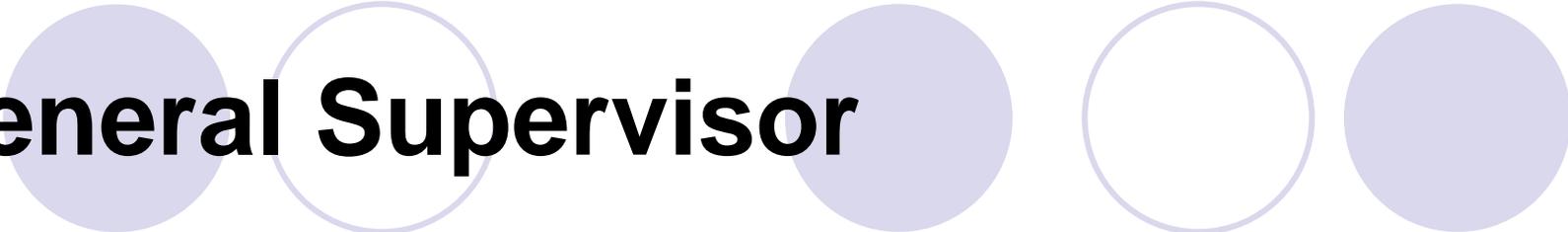
- In addition to CLIA requirements, the following should be included when determined by the laboratory director:

- Assess the suitability of test for a particular use
- Ensure appropriate documentation of clinical validity information
- Review the test results and the interpretation
- Review and/or sign the report
- Be available to answer questions about the test report
- Be on-site or have stipulated on-site time in the laboratory

Clinical Consultant

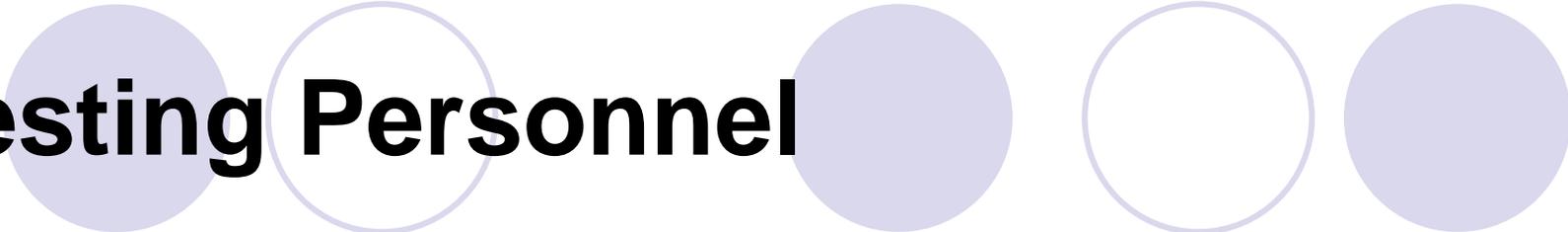
- Qualifications
 - Minimum would be CLIA + training or experience
 - Preferred:
 - MD or DO, with 2 years of training or experience in GT
 - PhD in a relevant discipline, with board certification and 2 years of training or experience in GT
 - MS genetic counselors are not qualified under CLIA to be clinical consultants, but have important role
- Responsibilities
 - CLIA requirements are appropriate

General Supervisor



- Qualifications
 - In addition to CLIA requirements add:
 - Training or experience should include high complexity MGT
- Responsibilities
 - CLIA requirements are appropriate

Testing Personnel



- Qualifications
 - In addition to CLIA requirements add:
 - Training or experience should include MGT
 - Testing personnel who do not have adequate training/experience in molecular genetic testing should go into the trainee category
- Responsibilities
 - CLIA requirements are appropriate

Personnel Competency Assessment



- CLIA requirements are appropriate
- 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

Considerations Before Introducing Genetic Testing or Offering a New Genetic Test

- Management responsibilities
- Regulatory requirements
- Benefit and cost considerations
 - Needs and demands
 - Restricted use due to intellectual property issues
- Personnel considerations
- Facility and laboratory safety considerations
- Developing procedures and training personnel
- Analytical and clinical validity

Considerations Before Introducing Genetic Testing or Offering a New Test

- The following 3 scenarios should be considered
 - New GT not offered anywhere
 - Performing in-house a test that was previously referred out
 - Second test to complement an existing test
- Follow professional guidelines and recommendations

Quality Management System

- GT laboratories may not be ready to implement QMS
- Benefits include:
 - Help meet CLIA requirements
 - Improve quality and efficiency
 - Help with international test referrals and global harmonization
- QMS may be applied to specific areas including:
 - Determine effective ways to provide information to users
 - Specimen submission
 - Test requisitions
 - Assessing the clients needs to determine the media, style and language used for test reports
 - Considerations before introducing GT or offering new GT

The slide features a decorative arrangement of seven circles. In the top row, there is one hollow circle on the left, followed by two solid light-purple circles. In the bottom row, there are two solid light-purple circles on the left and one hollow circle on the right. The text 'Committee Discussion' is centered horizontally across the middle of these circles.

Committee Discussion