A Quality System Mapping Tool: Crosswalk of CLIA Requirements and Recommended Practices in Biochemical Genetic Testing Laboratories

For use in laboratories, in conjunction with the Centers for Disease Control and Prevention (CDC) MMWR *Recommendation and Reports: Good Laboratory Practices for Biochemical Genetic Testing and Newborn Screening for Inherited Metabolic Disorders* (MMWR R&R, 2012 61/RR-02).

Introduction

Clinical laboratories conducting Biochemical Genetic Testing (BGT) should have a Quality Management System (QMS) in place. An important part of any QMS plan is meeting applicable regulatory requirements. Since BGT laboratories are subject to the requirements of the Clinical Laboratory Improvement Amendments (CLIA) regulations, this crosswalk between the MMWR R&R and CLIA has been developed to assist laboratories in meeting the regulatory requirements and aligning the best practices they follow with the applicable areas of the CLIA requirements. While CLIA specifies quality control and other requirements for many testing specialties and subspecialties, other areas of testing, such as biochemical genetic testing, are subject to the general CLIA quality systems requirements for non-waived testing and applicable personnel requirements for high complexity testing, therefore procedures and practices for ensuring quality testing must be established in detail for each test of these tests by the laboratory director.

The MMWR R&R provides specific good laboratory practice recommendations for BGT laboratories in certain areas, and this crosswalk outlines those areas. Page numbers with additional details about the corresponding recommendations in the MMWR R&R are provided for each area.

This crosswalk is a summary of information presented in the MMWR R&R and may not have every applicable CLIA requirement listed. It is not designed to replace the Centers for Medicare & Medicaid Services (CMS) CLIA laboratory guidelines, so be sure to consult with your regulatory agency's requirements to ensure compliance with your certification or accrediting organization. As with all clinical testing, the laboratory director is responsible for good laboratory practices and compliance with regulatory program requirements for all phases of laboratory testing.

Good Laboratory Practice Crosswalk for Biochemical Genetic Testing Laboratories

Phase	CLIA Regulation	Laboratory Compliance Requirement	BGT Laboratory MMWR R&R Reference	MMWR R&R Page Ref
Pre-analytic	§493.1241 §493.1242	Laboratories that perform non-waived testing need to develop and follow written policies and procedures for specimen submission and handling, specimen referral and test requests.		See P. 15-16
		Have written policies and procedures for: • Specimen submission and handling • Specimen referral • Tests requests	1) Provide information to submitter for appropriate test selection such as intended use of the test, indications for testing, performance specifications, test method, and whether test is FDA-approved, a laboratory developed test (LDT) or investigational test under FDA oversight. 2) Provide information for specimen collection, handling and submission 3) Request patient information needed to interpret test results 4) Offer availability of consultation 5) Implication of test results for family members	
Pre-analytic	§493.1457	Qualified clinical consultant is available to assist clients with appropriate test ordering to meet clinical expectations		See P. 30
Pre-analytic	N/A	Informed Consent		See P. 16
		No compliance requirements	Follow state laws	
Pre-analytic	§493.1241	Test requisition must solicit specific information		See P. 17
		• Have name and address of person ordering test • Patient name or identifier • Patient sex and age • Tests ordered • Specimen source • Date and time of collection • Other relevant information	In addition to CLIA regulation, the following information is also needed: 1) Date of birth 2) Date and time of specimen collection related to symptoms and initiation of treatment 3) Reason for referral 4) Patient race/ethnicity 5) Family history 6) Informed consent, if needed 7) Emergency contact number for clinician	

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Pre-analytic	§493.1242	Establish written policies for specimen submission, handling and referral		See P. 18
		Have procedures for patient preparation, specimen collection, labeling, storage, preservation, transportation conditions, processing, acceptability, and referral.	In addition, will need to provide information to clinicians on: 1) Patient preparation that may involve risk, e.g. fasting 2) Time-sensitive testing 3) Specific specimen acceptance and rejection criteria 4) Referral of specimens only to CLIA-certified laboratories	
Pre-analytic	§493.1249	Pre-analytical systems assessment		See P. 19
		Have procedures for monitoring, assessing, and correcting problems in pre-analytic systems, including an evaluation process.	1) Verify unclear patient and test request information 2) Maintain information throughout testing, reporting and referral process 3) Request missing necessary information 4) Monitor, document and develop measures to reduce the frequency of unacceptable specimens, delays in transport time, unacceptable specimens and incomplete requisition forms	
Analytic	§493.1253	Establish and verify performance specifications		See P. 12-13
		For each unmodified, FDA-cleared/approved test system, demonstrate test performance specifications comparable to manufacturer for accuracy, precision, and reportable range for test system, and verify manufacturer provided reference intervals are appropriate for the laboratory's patient population. For any laboratory-developed test or FDA-cleared/approved test system that has been modified, establish accuracy, precision, analytical sensitivity, analytical specificity, reportable range of test results, reference intervals, and any other performance characteristic required for test performance. Determine calibration procedures and control procedures for each test or test system.	In addition to the CLIA regulation: 1) Select sample numbers and types 2) Define analytic performance specifications for accuracy, precision, analytical sensitivity and specificity 3) Establish or verify reference range or normal values 4) Determine reportable range 5) Document other performance characteristics 6) Establish ranges for multi-analyte or profile analysis 7) Effects of changes to established performance specifications 8) Determine QC procedures 9) Document clinical validity	

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Analytic	§493.1255	Calibration and calibration verification		See P. 21-22
		Have procedures to perform and document calibration and calibration verification, established either by the manufacturer or the laboratory.	In addition, implement: 1) Obtaining adequate supplies of calibration materials to reduce variation 2) Verify each new batch of laboratory-prepared calibration material in parallel with previous batch 3) Refer to available professional guidelines	
Analytic	§493.1256	Control Procedures		See P. 19-21
		Have procedures to monitor the accuracy and precision of the testing process, including defining the number, type and frequency of control testing for quantitative, qualitative, tiered, extracted and molecular amplification tests. Special considerations for use of control materials include demonstrating effective monitoring and verification of test system performance.	In addition, implement: 1) Monitor and validate sampling instruments to ensure lack of carryover 2) Perform control procedures with each patient specimen or batch of specimens 3) Select controls based on patient population Special considerations for rare disease testing: 1) May use de-identified patient samples for positive controls 2) May use laboratory-prepared, e.g. spiked, material 3) May use combination of duplicate, split or previously tested specimens, serial dilutions, and increased supervisory review Special issues with sequential testing in single-channel analyzers: 1) May use a mixed-level control pool once a day and spike at least one internal control into each patient specimen 2) May use a single-level control pool once a day and spike one internal control into each patient specimen 3) May use a previously tested abnormal patient specimen once a day and spike one internal control into each patient specimen 4) May bracket control testing to cover patient batches that exceed 24 hours	

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Analytic	§493.1236	Proficiency Testing		See P. 22
		Verify testing accuracy by performing proficiency testing at least twice annually, using materials from proficiency testing (PT) programs when available. Conduct alternative performance assessment at least twice per year for each test for which no PT program is available.	In addition, implement: 1) Participate in PT programs that examine pre-analytic, analytic, and post-analytic phases of testing and review development of new PT programs as they become available 2) Enroll in quantitative PT programs if available, otherwise use quantitative PT programs 3) Evaluate disparate PT results to determine possible causes, including results that might indicate bias Special considerations for alternative performance assessment: 1) Follow professional guidelines on acceptable approaches when commercial PT is not available 2) Use inter-laboratory exchange or externally derived materials 3) If #2 above is not available, use repeat testing of blinded samples, exchange with a research facility, or conduct inter-laboratory data comparison	

Phase	CLIA Regulation	Laboratory Compliance Requirement	BGT Laboratory MMWR R&R Reference	MMWR R&R Page Ref
Post-analytic	§493.1291	Post-analytic: Test Report		See P. 24-25
		Have systems in place to ensure accurate and reliable reporting of patient and test data, including patient and laboratory identification, test name, test date, specimen source and condition, test result and normal values, and further information if specimen did not meet acceptability criteria. In addition, have a list of test methods and performance specifications verified; have procedures in place to notify submitter of panic or alert values and of delayed testing.	In addition, need to include: 1) Patient's date of birth 2) Reason for testing 3) Date and time of specimen collection and receipt at laboratory 4) Interpretive guide to results 5) Normal range values appropriate to age and sex of patient and limitations of the test 6) Test results on family members when appropriate 7) Name of laboratory personnel providing the interpretation 8) Notation of report status; preliminary, final, amended, corrected 9) Other relevant test information 10) Recommendations for additional testing 11) Recommendations for additional consultation 12) The date and time of the test report	
Post-analytic	§493.1105	Retention of Records and Reports		See P. 25-26
		Retain all records of patient testing, to include test requests, test system performance specifications, quality control, proficiency testing records and quality system assessment records for at least two years.	In addition, implement: 1) Compliance with applicable state laws and requirements of other accrediting agencies 2) Use minimum of 21-year retention time for reports indicating a disease or condition or longer if required by state law 3) Use of electronic records preferable	
Post-analytic	§493.1232	Retention of Specimens		See P. 26
		Have procedures to ensure specimen identification and integrity through completion of testing and reporting.	In addition, implement: 1) Retain as long as possible to allow for possible additional testing 2) Retain for use in quality assurance activities if allowable by state law.	

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Post-analytic	§493.1299	Post-analytic Systems Assessment		See P. 26
		Have procedures for monitoring, assessing, and correcting problems in post-analytic systems, including accuracy of test reporting, timeliness, submitter notification, accuracy of electronic information system processes, record retention and specimen retention. Use an evaluation process to review post-analytic system monitoring.	In addition, to clarify diagnosis, implement: 1) Test for other analytes when appropriate 2) Reflex testing 3) Test by another method 4) Test additional specimens 5) Monitor pre-analytic information needed for adequate interpretation of test results	
Post-analytic	§493.1231	Confidentiality of Patient Information		See P. 27
		Ensure appropriate access, documentation, storage, release, and transfer of confidential information.	In addition, when family member information is required for diagnosis: 1) Use established procedures for release and transfer of confidential information 2) Request patient's authorization to release information to healthcare provider of a family member 3) Include confidentiality policies on the patient consent form	
	§493.1443-1445	Personnel Qualifications: Laboratory Director		See P. 28
		A laboratory director must be an MD, DO, DPM or PhD with appropriate experience and/or board certification. Responsible for ensuring test quality, safe working conditions, enrolling in PT programs, and employing sufficient and qualified laboratory personnel, establishing personnel competency assessment policies, specifying employee duties, and ensuring compliance with regulations. Laboratory directors must delegate in writing, responsibilities to other staff as appropriate for their position.	In addition, laboratory directors must: 1) Ensure documentation of the clinical validity of testing 2) Determine specific policies and procedures for assessing all laboratory personnel	

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	§493.1449-1451	Personnel Qualifications: Technical Supervisor		See P. 29
		Technical Supervisors must meet minimum qualifications, appropriate to the section supervised, types of testing performed, and purpose for performing the testing. Responsible for selecting suitable test methods, verifying or establishing performance specifications and QC programs for each test or test system, enrolling in PT programs, resolving technical problems and ensuring corrective actions are taken, and implementing personnel competency assessment policies.	Recommended qualifications are: 1) MD, DO, or DPM. with four years of training or experience, with two of those years in BGT 2) PhD in science with four years of training or experience, with two of those years in BGT 3) Have a current certification in BGT by an HHS-approved board Additional responsibilities are: 1) Assessing suitability of test requests for the expected use 2) Before offering new testing, ensuring documentation of clinical validity 3) Before reporting test results, reviewing and signing results and their interpretation 4) Providing explanations regarding test reports 5) Evaluating test results and the need to refer to another laboratory or seek consultation 6) Providing on-site technical supervision	
	§493.1455-1457	Personnel Qualifications: Clinical Consultant		See P. 30
		Be qualified as a laboratory director for high-complexity testing, or be an MD, DO, or DPM. Responsible for providing consultation regarding the appropriateness of the testing ordered and the interpretation of test results.	Recommended qualifications are: 1) MD, DO, or DPM and be either board-certified or board-eligible in clinical genetics or clinical biochemical genetics 2) MD, DO, or DPM and have two years of experience in biochemical genetic testing, diagnosis, and management of inborn errors of metabolism, or both 3) PhD in science, be board-certified, and have two years of training or experience in BGT Be available to provide: 1) Consultation to laboratory clients regarding ordering and discussing appropriate tests to meet clinical expectations 2) Ensure that test reports include pertinent information for interpretation of specific patient conditions	

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	§493.1461-1463	Personnel Qualifications: General Supervisor		See P. 30-31
		Be qualified as a laboratory director or technical supervisor for high-complexity testing, or be an MD, DO, or DPM, or have a PhD, MS, or BS in relevant science and 1 year of training or experience, or have an associate's degree in a relevant science and 2 years of training or experience in high-complexity testing. Responsible for being accessible to testing personnel at all times testing is performed to provide direct supervision, monitor testing procedures to ensure quality of testing, and fulfill other duties as delegated by the laboratory director or technical supervisor.	Recommended qualifications are: 1) Be qualified as laboratory director or technical supervisor as outlined above. 2) MD, DO, or DPM and have one year training or experience in BGT relevant to the tests performed in the laboratory 3) PhD or MS degree in relevant science and one year training and have one year of training or experience in BGT relevant to the tests performed in the laboratory 4) BS degree in relevant science and have two years of training or experience in BGT relevant to the tests performed in the laboratory	
	§493.1489-1495	Personnel Qualifications: Testing Personnel		See P. 31
		Be an MD, DO, or DPM, have a PhD, MS, or BS in a relevant science, or have an associate's degree in a laboratory science. Responsible for following laboratory procedures for test performance, quality control, results reporting, documentation and problem identification and correction.	1) Demonstrate competency in high-complexity biochemical genetic testing. 2) Meet CLIA and any state qualification requirements for high-complexity testing.	
	§493.1235 & §493.1451	Personnel Competency Assessment		See P. 31-32
		Establish and implement personnel competency assessment policies and procedures.	Meet CLIA and any state qualification requirements for high-complexity testing.	

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Association of Public Health Laboratories

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