Summary of CLIAC Biochemical Genetic Testing Workgroup Input

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SCOPE AND APPLICABILITY

CLIA Requirements	WG Input	
	Key Points	**Clarifications**
Genetic testing is not defined under CLIA (The CLIA regulations define laboratory testing to which the regulations apply, but do not contain definitions of specific testing specialties and subspecialties. CLIA provides specialty requirements for clinical cytogenetic testing but not for other genetic testing, which is subject to quality system requirements for nonwaived testing and personnel requirements for high complexity testing as applicable.)	1. Recommendations for good laboratory practices should be developed to provide guidance for laboratories performing biochemical genetic testing (BGT) and newborn screening for inherited metabolic diseases in meeting applicable CLIA requirements and in applying additional quality assurance measures needed for these tests. These recommendations should be useful for improving the quality of BGT in general, which should improve the quality of patient care associated with diagnosis and management (including monitoring) of inborn errors of metabolism (IEMs) (see Clarification #1). 2. The workgroup (WG) did not see an existing definition that uniquely defines BGT. It should be recognized that any definition will be imperfect and will need to have exceptions defined. For example, the CLIAC 2001 definition suggested that congenital adrenal hyperplasia (CAH) testing and hemoglobin electrophoresis be considered BGTs (See Clarification #2). 3. The recommendations should apply to testing for diagnosis and monitoring of IEMs to include the following: a. Testing performed by BGT laboratories b. BGT even if performed outside of a BGT laboratory, but not necessarily including routine chemistry and other testing performed in general laboratories that would not require BGT interpretation (see Clarification #3a-b and #4). c. Newborn screening (NBS) for inborn errors of metabolism (excluding congenital hyperthyroidism or thyroid profiles, hemoglobinopathies, infectious diseases, and other non-heritable diseases) d. The BGT aspects of those tests that encompass BGT and other areas (See Clarification #5). 4. The recommendations should not apply to testing performed for purposes other than diagnosis or monitoring of inherited metabolic diseases, but should apply to those tests performed in any laboratories that meet Key point	1. The field of BGT is diverse and includes testing for different types of IEMs, different types of testing (e.g. testing of metabolites such as organic acids and amino acids, functional testing, and enzyme assays), and on different specimen types (e.g. blood, urine, cerebrospinal fluid (CSF), skin fibroblasts, muscle, liver, etc). Guidance for good laboratory practices is needed to address the quality assurance measures needed for these tests. 2. Definitions with exclusions (as examples): a. CLIAC 2001 definition included tests that are predominantly used to detect IEMs, heritable genotypes, or gene products of genetic variations, or mutations for clinical purposes. Exclusions were stated that "Tests that are used primarily for other purposes, but may contribute to diagnosing a genetic disease would NOT be covered by this definition." b. The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) provided an example of what might or might not be covered: "For example, amino acid analysis to detect metabolic disorders such as PKU is considered a genetic test, but use of this analysis to monitor general nutritional status is NOT." 3. Examples of tests that are and are not covered by the expected new guideline include: a. Examples of tests to which the expected guideline should apply include (not exhaustive): Tay-Sachs (diagnostic and carrier testing) and other enzyme assays, acylcarnitine profile, urine organic acid analyses, amino acid analyses, neurotransmitter analysis in CSF, NBS for IEMs, transferrin saturation immunoelectrophoresis for carbohydrate deficient glycoprotein syndromes, and other analyses requiring interpretation regarding the patient's heritable conditions when reporting test results (i.e. the ordering physician and/or other users of the test results may need the assistance in interpreting test

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	#3b (also see clarification #6). 5. If testing performed for diagnosis and monitoring of IEMs involves nucleic acid testing, the CLIAC good laboratory practice recommendations for molecular genetic testing should apply to the molecular aspects. 6. For "questionable" or "situational" tests – i.e., diseases that involve chemistry or hematology testing that is usually not considered biochemical genetic tests but in certain situations may indicate genetic conditions, the need for genetics interpretation in these specific situations should be addressed in the test report section (See clarification #4). For these tests, clarification should be made on the relationship between the purpose of the test and the need for its interpretation in relation to a genetic condition. 7. Implementing good laboratory practices will improve test quality. The impact on a non-genetic laboratory (e.g., a chemistry laboratory) that usually performs certain tests that are considered BGTs should be considered. The GLPs should be used where appropriate and should not be mis-applied to general laboratories (see clarification #6). 8. While this document is for the purpose of laboratory guidance, the workgroup looks forward to (once the document is approved with any changes by CLIAC) to the development of an MMWR document to educate other healthcare providers as well. We also see this document as a basis for future educational efforts including education of patients and families.	results for the patient's heritable conditions). b. Examples of tests that are not intended to be covered by the expected guideline include: Lipid profiles, cholesterol, transferrin saturation analysis for hemochromatosis or alcoholic liver disease, glucose, lactate, thyroid profile and other endocrine studies. These tests are not intended to be covered by the expected guideline because they generate analytic results that usually do not need additional interpretation for the requesting physician. This list of examples is not exhaustive c. Whether or not a test is intended to be covered by this expected guideline is not based on whether a test is a multianalyte or single-analyte assay. A single-analyte assay that requires interpretation for diagnosis and management of IEMs would be covered. 4. Examples of tests not covered in this scope when performed in a non-BGT lab but might indicate or monitor genetic conditions: a. Monitoring transferrin for iron overload disease b. Diagnosis and monitoring of clotting disorders c. Diagnosis and monitoring of hemoglobinopathies d. HbA1c for monitoring diabetes mellitus 5. The diagnosis, monitoring and management of IEM usually involves a combination of BGT and other laboratory testing (e.g. monitoring glucose and electrolytes in glycogen storage disease); this does not mean that all the tests used to diagnose and manage IEM are BGT. 6. In New York state the state requirements for genetic testing apply to genetic laboratories. For BGT, the WG intends that the GLPs should apply to the testing regardless of where performed. For this reason, definition of BGT and appropriate application of the GLP scope is critical.

PREANALYTIC PHASE

CLIA Requirements	WG Input	
	Key Points	**Clarifications**
INFORMATION TO BE PROVIDED TO USERS OF LABORATORY SERVICES		
Requirements relating to providing information for patient preparation and test request include: • The laboratory must have written policies and procedures for preparation of patients (§493.1242(a)(1)); • The laboratory must have written policies for test requests (§493.1241); • The clinical consultant must be available to assist the laboratory's clients in ensuring that appropriate tests are ordered to meet the clinical expectations (§493.1457(b)).	1. Laboratories are responsible for providing information regarding the tests they offer to users of their services, to facilitate selection of appropriate tests and test ordering. This role has been increasingly recognized by professional societies representing the laboratory community. 2. Laboratories should provide the following information to their users: a. Information necessary for selecting appropriate testing – i. A list of the tests performed; ii. For each test – 1) Intended use (See Clarification #1-2) 2) Indications for testing; 3) When appropriate, information about important performance characteristics and/or limitations of the test that could affect sensitivity and/or specificity (See Clarification #3) 4) Test method and testing procedures to be used, including CPT codes when appropriate; and 5) Whether testing is performed with an FDA-cleared or approved test system, a laboratory-developed test, or investigational under FDA oversight. b. Information on appropriate collection, handling, and submission of samples (to expand in next section) – i. Any necessary patient preparation, when appropriate; ii. Specimen type, amount/volume, and collection container/device; iii. Specimen preparation; iv. Specimen stability and transport conditions; v. Reasons for rejection of specimens. c. Patient information required to perform and interpret the test (including, as applicable, patient consent	1. For BGT, intended use may be described as "The (analyte or panel of analytes) in (sample type), intended for (diagnosis and/or management) of (disorder or group of disorders) in (population). Examples: 1) Amino acid analysis in plasma, intended for diagnosis and management of amino acid disorders in newborns/infants/children/adults; and 2) □nzyme assay for galactose-1-uridyl-transferase in red blood cells, intended for the diagnosis of galactosemia in patients suspected to have the disorder or for carrier testing in family members. 2. In FDA Guidance Document "Newborn Screening Test Systems for Amino Acids, Free Carnitine, and Acylcarnitines Using Tandem Mass Spectrometry", intended use is described as "each amino acid, free carnitine, and acylcarnitine that your device is intended to measure, the specific population (e.g., newborns) for which the test is intended, and the acceptable specimen type (e.g., whole blood on filter paper)". 3. Test limitations could be related to the assay or the physiology of the biological condition and include: a. Sources of assay interference, inappropriate sample types for analysis (e.g., plasma sample for evaluating a renal transport defect), and other factors such as whether the patient is fasting or fed, transfused, on medications, sick or well that might influence test performance or interpretation of many biochemical tests and all newborn screening, and the specimen collection time. b. Variability in expression of biochemical phenotypes (e.g., low excretor variants of glutaric aciduria type 1, intermittent findings of fatty acid oxidation disorders, or normal analyte levels in intermittent maple syrup urine disease (MSUD)). 4. Since biochemical genetic tests primarily evaluate phenotypes, informed consent should not generally be necessary unless required by law or regulations. 5. Since biochemical genetic tests primarily evaluate phenotypes, this statement may not always need to be provided.

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	information in compliance with federal, state, and local requirements) (Also see clarification #4) d. Availability of consultation and discussion from the laboratory; e. When indicated, implications of test results for relatives or family members (See clarification #5). 3. Laboratories should ensure the information provided in this preanalytic phase is consistent with information included on test reports. 4. Laboratories should determine effective ways to provide the preanalytic information to their clients. There may not be a "one-size-fits-all" approach for all laboratories. At a minimum, laboratories should ensure the information is available, on websites, in-service directories, or information sheets (the passive mode); but laboratories may also wish to be more proactive in providing the information and should determine the situations when the proactive approach is necessary.	

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INFORMED CONSENT		
No requirements for laboratories to document informed consent.	1. While informed consent is required in at least 12 states for genetic tests in general and recommended for many (mostly molecular and cytogenetic tests), the WG is not aware of any professional practice guideline specifically recommending informed consent for biochemical genetic tests. 2. Biochemical genetic tests typically analyze phenotypes, rather than genotypes. It was suggested that informed consent is not generally needed except where required by state and local requirements. When informed consent is required, unless documentation of signed informed consent is mandated, attestation to informed consent by submitting healthcare providers should be adequate (refer also to Clarification #1). 3. Regarding consent issues related to NBS for heritable conditions, the WG reviewed the document "Parental Consent in Public Health Newborn Screening Programs" by the Association of Public Health Laboratories (APHL) and agrees with their recommendations regarding communications with parents regarding NBS. The WG felt one of the recommendations could be construed as an	1. The following clarification is provided in MGT MMWR and applies also to BGT: a. All laboratory testing should be based on informed decision-making. The laboratory should be responsible for providing its users with information necessary for making informed decisions, and should be available to assist in determining the appropriate level of informed consent. b. Informed consent is in the purview of the practice of medicine. The individual ordering a laboratory test should be responsible for obtaining the appropriate level of informed consent. It is not the laboratory's responsibility to obtain or require informed consent before performing the test, unless state or local law mandates it. c. When informed consent for testing is recommended or required by law or other applicable requirements, documentation of the informed consent should be included with the test request, before the test can be performed (However, the patient specimen can be

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	endorsement of written informed consent for all routine screening and therefore clarifies that – a. Explicit parental consent is not necessary for mandated public health newborn screening using assays that are fully analytically and clinically validated, have known clinical utility, and are performed for conditions that are treatable with limited medical consequences. Parental and provider education must be an integral part of the program even where documentation of consent is not required. b. Where programs elect to include new assays or conditions for which the above conditions cannot be met, explicit consent may be required under state statutes and policies and should be required in the spirit of informed participation in medical procedures of limited or unproven benefit. c. Any research use of NBS specimens must be done only with review of appropriate human research subjects' protection procedures (See Clarification #2).	stabilized until informed consent is obtained.). d. The level and nature of the consent needed for specific tests should consider the purpose and implications of the test. e. Laboratories should refer to existing professional guidance for further considerations of informed consent issues related to the molecular genetic tests they perform. f. When written consent is required, laboratories should consider available templates and models in developing the content, format, and the means for documenting the patient consent. 2. Currently few states require explicit parental consent in mandated public health NBS programs. Most other states allow parental dissent on at least religious grounds. The WG would not support language that could be read as recommending states to use informed consent for newborn screening or encouraging the use of written informed consent for validated NBS tests. However the new guideline should 1) remind laboratories and programs that consent and IRB approval are needed for all research testing and 2) remind all stakeholders that education of providers and families is essential to assure optimal experience and outcomes of screening.

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TEST REQUEST		
§493.1241 Test request (c) The test requisition must solicit the following information: (1) The name and address or other suitable identifiers of the authorized person requesting the test and, if appropriate, the individual responsible for using the test results; (2) The patient's name or unique patient identifier; (3) The sex and age or date of birth of the patient; (4) The test(s) to be performed; (5) The source of the specimen, when	1. The following additional or more specific information (relative to CLIA requirements) should be solicited for biochemical genetic test requisitions: a. Patient name <u>and</u> any other unique identifiers needed for testing b. Date of birth; c. <u>Date and time</u> of specimen collection (relative to symptoms and initiation of treatment when appropriate); d. The reason for referral, and information on the clinical, medication, and nutritional status of the patient (see Clarification #1) e. For newborn screening testing, gestational age, birth	1. The additional elements recommended for BGT requisition have incorporated the content from the American College of Medical Genetics Standards and Guidelines for Clinical Genetics Laboratories (ACMG S&G), section F4.1, which might also be used to help laboratories to meet the CLIA requirements at §493.1241(c)(7). (Note: ACMG S&G section F4.1: Whenever possible, specimens for biochemical genetic testing should be accompanied by a reason for referral and information on the clinical, medication and nutritional status of the patient, so that results can be most meaningfully interpreted. The time relative to initiation of treatment should be noted when appropriate.) The test request also includes where appropriate information about any special patient preparation.

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appropriate; (6) The date and, if appropriate, time of specimen collection; and (7) Any additional information relevant and necessary for a specific test to ensure accurate and timely testing and reporting of results, including interpretation, if applicable.	weight, and any additional information required by the state program; f. Patient's race/ethnicity, if applicable; g. Family history and/or pedigree, if applicable; h. Appropriate International Classification of Diseases (ICD) codes or other codes indicating the diseases or conditions to be tested for; i. When required by state law, a check-off box or other means to indicate that appropriate level of informed consent has been obtained in compliance with federal, state and local requirements; j. Emergency contact information for responsible clinician (for additional information or abnormal results). 2. Laboratory electronic information systems (current and in development) should support the collection and transmission of the test request information and ensure that critical information is obtained and retained. Recommended practices include making critical information elements "required" for test requisition submission. (Note: This is also addressed in the preanalytic quality assessment section.) 3. Indicating all the recommended information elements to be solicited upon test request is good laboratory practice and should encourage test requestors to cooperate. Laboratories may also include "Not Available" as an option for certain information fields, and laboratories may perform the test even is some elements of clinical information are lacking, but the laboratory needs to request all pertinent information. 4. The laboratory must follow federal, state and local requirements regarding informed consent and may include check-off boxes or other means on the test request forms to meet these requirements (also serve to remind test requestors of their responsibility to provide patient consent information to the laboratory). 5. The WG does not support including a check-off box on test requisitions to indicate whether the patient has declined having residual samples used anonymously for quality assurance (QA) or quality control (QC) purposes.	2. Guidance should be provided (with examples as needed) for following the CLIA test request requirements and the recommended additional information elements to be solicited on test requisitions.

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SPECIMEN SUBMISSION, HANDLING, AND REFERRAL		
§493.1242 Standard: Specimen submission, handling, and referral (a) The laboratory must establish and follow written policies and procedures for each of the following, if applicable: (1) Patient preparation. (2) Specimen collection. (3) Specimen labeling, including patient name or unique patient identifier and, when appropriate, specimen source. (4) Specimen storage and preservation. (5) Conditions for specimen transportation. (6) Specimen processing. (7) Specimen acceptability and rejection. (8) Specimen referral. (b) The laboratory must document the date and time it receives a specimen. (c) The laboratory must refer a specimen for testing only to a CLIA-certified laboratory or a laboratory meeting equivalent requirements as determined by CMS. (d) If the laboratory accepts a referral specimen, written instructions must be available to the laboratory's clients and must include, as appropriate, the information specified in paragraphs (a)(1) through (a)(7) of this section. **§493.1291 Standard: Test report** (c) The test report must indicate the following: (1) For positive patient identification, either the patient's name and identification number, or a unique patient identifier and identification number. (2) The name and address of the laboratory location where the test was performed. (3) The test report date. (4) The test performed. (5) Specimen source, when appropriate. (6) The test result and, if applicable, the units of measurement or interpretation, or both. (7) Any information regarding the condition and disposition of specimens that do not meet the laboratory's criteria for acceptability.	1. It is the laboratory's responsibility to provide, and assure that users have, information or specific instructions for the proper identification, collection, handling and referral of patient specimens. This information should be part of the information that laboratories provide to their users as specified in the section "Role of laboratories in providing information to users of their services". 2. Guidance should be provided to address patient preparation, when appropriate. If patient preparation information is needed, that information should be specifically solicited on the test request form and communicated to the laboratory users (see Clarification #1). 3. The laboratory should have procedures for handling specific issues in BGT, such as time-sensitive testing, rapid or short turnaround time, critical specimens, and labile specimens to meet the need for clinical care and patient management (See clarification #2). 4. Laboratories should have written criteria for acceptance and rejection of specimens for the biochemical genetic tests they perform. Specimen acceptance and rejection criteria should include determination and handling of situations such as: a. Improper handling or transport of the specimen; b. Mislabeling, use of inappropriate anticoagulants or media, specimen degradation, or inappropriate specimen type (See clarification #2); c. Commingled or possibly contaminated specimens that may affect results of testing procedures; d. Lack of unique identifiers on the specimen or the requisition form; e. Lack of other information necessary to determine whether the specimen or test requested is appropriate for answering the clinical question; f. Specimen not held at appropriate temperature; g. Insufficient specimen volume or amount. 5. Laboratories should carefully distinguish between unsatisfactory specimens (e.g., NBS dried blood spots (DBS) not filling circles, an unfrozen specimen for urine organic acids) and unacceptable specimens (e.g., an unfrozen muscle specimen; a sample for urine organic acid analysis with bacteria overgrowth). In certain	1. The clinician is responsible for proper patient preparation, especially since some patient preparation involves risk (e.g. fasting some patients). For this and other reasons some samples may be submitted after inadequate patient preparation. It is, however, important that the laboratory receives the information on how the patient was prepared. The goal is to ensure that the test is as accurate as possible. Examples in which patient preparation is critical include certain challenge tests (e.g. fasting) for diagnostic testing. In NBS, feeding is patient preparation however standards for NBS recognize that testing still needs to be carried out if infant is too sick to be fed. 2. The laboratory's procedures for time-sensitive testing and critical specimens should address issues of specimen source and specimen handling, including, where appropriate, the need to communicate with the submitting clinician. In rare circumstances when there is a critical need for testing specimens that are suboptimal but still acceptable, the laboratory should follow established procedures to note the exceptions in the test report. 3. Testing or not testing suboptimal specimens is fraught with liability. Written policies and procedures addressing unsatisfactory specimens should be consistently applied. The following may be examples of the specific situations when testing of suboptimal specimens might be considered: a. Critical samples that should not be rejected, such as when the patient is deceased and no additional specimen can be submitted, if rapid response is required for management, if sample was collected while patient was acutely ill or as part of a timed test or challenge, or if sample was collected invasively (e.g. CSF, muscle biopsy). b. NBS particularly illustrates the tension between preferred and necessary sample, and the issue of time-sensitive testing. If an inadequate specimen is tested and the result is normal, the test result may be reported along with a notification on the inadequate specimen. In such a case it may not be necessary to request another sample. However, if the test result is worrisome or questionable, or is near the cutoff for an abnormal result, a repeat sample should be requested and the clinician should be alerted to the test result. c. Unsatisfactory specimens that still meet the laboratory's criteria for acceptability may be analyzed and then

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(h) When the laboratory cannot report patient test results within its established time frames, the laboratory must determine, based on the urgency of the patient test(s) requested, the need to notify the appropriate individual(s) of the delayed testing.	circumstances a laboratory may test an unsatisfactory sample but the laboratory must have policies and procedures addressing the handling of these specific situations (See Clarification #3) 6. Laboratories should 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, result reporting, and specimen referral. (Note: This is also addressed in the preanalytic quality assessment section.) 7. A number of factors should be considered in selecting laboratories for referred testing, including expertise, turnaround time and cost. Costs should not be the only or primary factor for consideration in selecting referral. 8. Newborn screening has special issues that must be addressed by the laboratory. For example, submitters should be made aware that specimens (dried blood spots) should not be batched before being sent to the laboratory. 9. CLIA regulations at §493.1242(c) require laboratories to refer a specimen for patient testing only to a CLIA-certified laboratory or a laboratory meeting equivalent requirements as determined by CMS. (See Clarification #4-#6). The WG recognizes that certain specialized tests for rare diseases are only performed by foreign laboratories, and emphasizes that for good medical diagnosis and management of biochemical disorders U.S. patients and families need access to international laboratories. But international laboratories are not always motivated to apply for CLIA certification. The WG encourages further discussion on ways to access these laboratories.	followed by requesting a repeat specimen for clarification. A specimen may be unsatisfactory for only some tests but acceptable for other tests. Laboratories should have criteria for this determination. However, analysis of a specimen that is deemed unacceptable by the laboratory's own definition may result in a citation by a laboratory inspector. 4. Laboratories that meet equivalent requirements include Department of Veterans Affairs laboratories, Department of Defense laboratories, and laboratories in CLIA-exempt states (New York and Washington). 5. CMS provided the following clarification: The CMS CLIA website has a new search feature titled "Laboratory Demographics Lookup" that will allow anyone to look up a laboratory. This feature will provide a laboratory's location(s), type of certification, and certificate expiration date. This search includes international laboratories registered/certified/accredited in the CLIA data system. However, if a laboratory has not applied for CLIA, then it would not appear in the system. The CMS CLIA website also has information for international laboratories on how to apply for CLIA certification and the regional office contact information, under "How to Apply for a CLIA Certificate, Including International Laboratories". Any laboratory wishing to perform testing for clinical purposes on human specimens from the United States (U.S.) or one of its territories must be CLIA-certified. No CLIA-laboratory or "authorized personnel", as defined by CLIA federal/state, should send out specimens to non-CLIA laboratories for patient testing. If this is discovered during an inspection, the laboratory will be cited. 6. The WG requests that CLIAC and CMS explore strategies to access international laboratories that use ISO certification, to ensure access to international laboratories performing testing critical for diagnosis and management of U.S. patients..

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PREANALYTIC SYSTEMS ASSESSMENT		
§493.1249 Preanalytic systems assessment (a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and when indicated, correct problems identified in the preanalytic systems specified at §§493.1241 through 493.1242. (b) The preanalytic systems assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of preanalytic systems assessment reviews with appropriate staff. (c) The laboratory must document all preanalytic systems quality assessment activities.	1. Laboratories should have written policies and procedures for preanalytic systems assessment, and when indicated, correcting problems identified in test requests, specimen submission, and other preanalytic steps. This should include, for example, making a good-faith effort to verify and confirm test requests that are unclear or lacking critical information, submitted with inappropriate specimens, or 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. 2. If a laboratory recognizes that the lack of necessary information in test requests results from the information being stripped out during specimen submission or test referral, the laboratory should contact the test requestor or referring laboratory to inform them of the information the laboratory needs, and establish effective procedures to ensure information needed for selection of appropriate test methods, prompt initiation of testing, and accurate result reporting is retained during the specimen submission or test referral process (See Clarification #3). 3. The CMS Interpretive Guidelines for the CLIA requirements at §493.1249(a)-(c) provide good examples for preanalytic quality assessment for biochemical genetic testing (See Clarification #1). Additional examples should be added to include: a. Monitoring the frequency of specimen handling problems (such as the use of an improper blood collection tube, inadequate mixing of blood specimens with anticoagulant after collection, and insufficient amount of blood on spot for newborn screening) b. Monitoring the frequency of delays in specimen transport; c. Identifying clients who repeatedly refer unacceptable specimens or improperly complete requisition forms d. Documentation of the laboratory's efforts to reduce the recurrence of these problems (see Clarification #2).	1. <u>CMS Interpretive Guidelines for §493.1249</u> – a. QA of the Preanalytic System includes assessing practices/issues related to test requests, specimen submission, handling and referral. b. Some examples include: i. Monitoring the frequency of specimen handling problems (such as the use of an improper blood collection tube, inadequate mixing of blood specimens with anticoagulant after collection); ii. Monitoring the frequency of delays in specimen transport; iii. Identifying clients who repeatedly refer unacceptable specimens or improperly complete requisition forms; iv. Documentation of the laboratory's efforts to reduce the recurrence of these problems. 2. Practices have been in place in public health newborn screening laboratories to monitor the extent to which they receive inadequate samples and educate their providers. 3. The WG encourages collaboration of all stakeholders, including vendors, to develop structures that do not omit patient information needed for quality testing and communication of results.

ANALYTIC PHASE

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PERFORMANCE ESTABLISHMENT AND VERIFICATION		
§493.1253 Establishment and verification of performance specifications (a) Applicability. Laboratories are not required to verify or establish performance specifications for any test system used by the laboratory before April 24, 2003. (b)(1) Verification of performance specifications. Each laboratory that introduces an unmodified, FDA-cleared or approved test system must do the following before reporting patient test results: (i) Demonstrate that it can obtain performance specifications comparable to those established by the manufacturer for the following performance characteristics: (A) Accuracy. (B) Precision. (C) Reportable range of test results for the test system. (ii) Verify that the manufacturer's reference intervals (normal values) are appropriate for the laboratory's patient population. (2) Establishment of performance specifications. Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book procedures, Gram stain, or potassium hydroxide preparations), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics,	1. For performance establishment and verification of new biochemical genetic tests, the following steps should be considered as general principles: a. Ensure a review is conducted of available scientific studies and pertinent references; b. Define appropriate patient populations for which the test should be performed (see clarification #1); c. Select appropriate test method(s) for the disease (or condition) or analyte being evaluated; d. Establish or verify performance specifications and determine applicable quality control parameters for the test (see clarification #2 and #3). 2. The number of positive and normal samples that should be included in performance establishment and verification should depend on the assay being established or verified, and the prevalence of the disease (see clarification #3-4). 3. Laboratories should determine specifications of the following performance characteristics for each new test (except when not applicable, for example with some qualitative tests). a. Accuracy; b. Precision; c. Analytical sensitivity, including limits of quantification (LOQ) and limits of detection (LOD); d. Analytical specificity; e. Reportable range of test results for the test system, including critical values; f. Reference range or normal values for the age, gender, race/ethnicity, and physiologic ranges expected for the laboratory's patient population; g. Other performance characteristics required for test performance, such as appropriate cutoff values for newborn screening; and h. When appropriate, comparison to other method (e.g. DNA, enzyme assay, analyte quantification, etc.) 4. In certain circumstances when performance	1. Appropriate population may not apply to certain BGTs such as amino acid and organic acid analysis, but does apply to NBS. 2. Performance specifications for NBS, such as sensitivity and specificity, may be different from other BGTs. Typically for screening, sensitivity should be high so that cases are not missed. The presumptive positive results should then be evaluated by a confirmatory test with high specificity. 3. High volume of samples is needed for performance establishment or verification of NBS tests. However, some rare diseases may not have positive samples available for performance establishment for NBS, and therefore alternative mechanisms are needed. 4. For diagnostic testing for some rare conditions and for testing samples collected invasively a large number of positive and sometimes even normal controls are not available and this needs to be recognized. The intent is not to set a low bar for rare disease testing, but to emphasize that performance establishment or verification should be adequate and as comprehensive as possible, to ensure test results can be interpreted for specific patient conditions and the limitations of the testing and test results are known. 5. Laboratories should inform their clients of the sources of their normal values, e.g., whether these are published values or values established or verified by the laboratory. Whenever possible, laboratories should establish their own normative reference ranges. Laboratories should systematically evaluate and justify any change in reference ranges keeping in mind that samples submitted or obtainable generally are not or may not be not from healthy controls. 6. CMS Interpretive Guidelines for §493.1253(b)(1)(ii) Verify that the manufacturer's reference intervals (normal values) are appropriate for the laboratory's patient population. – The laboratory may use the manufacturer's reference range provided it is appropriate for the laboratory's patient population (i.e., a normal range that reflects the type of

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as applicable: (i) Accuracy. (ii) Precision. (iii) Analytical sensitivity. (iv) Analytical specificity to include interfering substances. (v) Reportable range of test results for the test system. (vi) Reference intervals (normal values). (vii) Any other performance characteristic required for test performance. (3) Determination of calibration and control procedures. The laboratory must determine the test system's calibration procedures and control procedures based upon the performance specifications verified or established under paragraph (b)(1) or (b)(2) of this section. (c) Documentation. The laboratory must document all activities specified in this section.	establishment/verification is performed with clinical samples, if the laboratory does not have available samples representing normal individuals and having the identical sample matrix, the manufacturer's, literature or textbook ranges may be used with disclosure, and with monitoring and adjustment if appropriate (see Clarification #5 for special issues related to BGT and the CMS Interpretive Guidelines provided here as Clarification #6). 5. Pattern recognition and interpretation (in addition to measurement of individual analytes) is essential for multianalyte tests such as acylcarnitine profile and organic acids and should be part of performance establishment or verification. 6. In establishing or verifying test performance, laboratories should review and follow professional guidelines such as those by the Clinical and Laboratory Standards Institute (CLSI), that are applicable and appropriate for the testing to be introduced and ensure the professional guidance is followed consistently through performance establishment/verification and subsequent total patient testing process (including preanalytic, analytic and post analytic phases). 7. Laboratory's responsibility for clinical validity should include: a. At a minimum, documentation of information regarding clinical validity (including clinical sensitivity, clinical specificity, positive predictive value and negative predictive value, if applicable) of the genetic tests the laboratory performs from available information sources, such as literature references; b. Establishment of clinical sensitivity, clinical specificity, and predictive values based on internal study results, when appropriate, if information regarding clinical validity is not available from published references (see Clarification #8); c. Laboratories should practice "truth in advertising", which means offering clinically valid tests in the context of clinical biochemical genetic disease and providing the user with the currently known test limitations. d. Specified responsibilities of the laboratory director and the technical supervisor to ensure appropriate documentation and reporting of clinical validity information of the genetic tests their laboratories perform.	specimen and demographic variables such as age and sex, as applicable). If the manufacturer has not provided reference ranges appropriate for the laboratory's patient population, the laboratory may use published reference range(s). The laboratory must evaluate an appropriate number of specimens to verify the manufacturer's claims for normal values or, as applicable, the published reference ranges. Interpretive Guidelines for §493.1253(b)(2)(vi) - Reference Range (Normal Values) – The laboratory must establish a reference range that is appropriate for the laboratory's patient population (i.e., a normal range that reflects the type of specimen and demographic variables such as age and sex, as applicable). 7. Manufacturers often recommend laboratories to use the provided "expected values" only as a guideline and establish their own reference ranges. For example, certain manufacturer's instructions state "The concentration of [analyte] in newborns depends on demographic variations, age, weight, prematurity and twinning. Each laboratory needs to establish validate cut-off levels related to gestational age, infant age and birth weight. The values given should only be used as a guideline." 8. This point applies to all completely novel testing as well as to new newborn screening tests. The laboratory's responsibility should include testing known positives and known negatives in establishing clinical validity; however it is critical to recognize special problems for newly discovered conditions, rare conditions, or conditions with highly variable expression for which it may not be possible to identify clinical sensitivity with certainty. Currently accepted biochemical testing includes many tests for which testing of an affected patient may give normal or abnormal results depending upon the affected individual's state of health, making simple statements of clinical sensitivity unjustifiable. Laboratories should be aware that the collection of clinical sensitivity and specificity information is an ongoing process, especially for rare biochemical disorders.

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TEST SYSTEMS, EQUIPMENT, INSTRUMENTS, REAGENTS, MATERIALS, AND SUPPLIES		
§493.1252 Standard: Test systems, equipment, instruments, reagents, materials, and supplies (a) Test systems must be selected by the laboratory. The testing must be performed following the manufacturer's instructions and in a manner that provides test results within the laboratory's stated performance specifications for each test system as determined under §493.1253. (b) The laboratory must define criteria for those conditions that are essential for proper storage of reagents and specimens, accurate and reliable test system operation, and test result reporting. The criteria must be consistent with the manufacturer's instructions, if provided. These conditions must be monitored and documented and, if applicable, include the following: (1) Water quality. (2) Temperature. (3) Humidity. (4) Protection of equipment and instruments from fluctuations and interruptions in electrical current that adversely affect patient test results and test reports. (c) Reagents, solutions, culture media, control materials, calibration materials, and other supplies, as appropriate, must be labeled to indicate the following: (1) Identity and when significant, titer, strength or concentration. (2) Storage requirements. (3) Preparation and expiration dates. (4) Other pertinent information required for proper use. (d) Reagents, solutions, culture media, control materials, calibration materials, and other supplies must not be used when they have exceeded their expiration date, have deteriorated, or are of substandard quality. (e) Components of reagent kits of different lot numbers must not be interchanged unless	1. CLIA regulations adequately address many key issues. 2. All reagents and supplies that are used during routine testing should be the same as used in performance establishment or verification. 3. New reagent lots and/or shipments must be tested in parallel with old lots before or concurrently with being placed in service to ensure that the calibration of the new lot of reagent has maintained consistent results for patient specimens. 4. Assay modifications should be validated before reporting patient results (see clarification #1). 5. Equipment must be validated to account for basic detection or measurement drift. Re-verification is also necessary when running the same analyte on different analyzers. 6. Professional guidelines, such as CLSI and ACMG S&G, provide additional guidance for specific test methods. 7. Mechanisms for standardizing practices among laboratories for preparing and validating reagents, standards, and reference materials that are not commercially available should be encouraged. Laboratories should be aware that all methods and instruments (including software programs even when shared only through the internet) should be individually validated by each laboratory. When available, FDA-approved reagents should be used for patient testing (see clarification #2).	1. <u>CMS Interpretive Guidelines for §493.1253(b)(2)</u> "Modified by the laboratory," means any change to the assay that could affect its performance specifications for sensitivity, specificity, accuracy, or precision, etc. Laboratory modification of the manufacturer's instructions that could affect performance specification's include but are not limited to: • Change in specimen handling instructions; • Incubation times or temperatures; • Change in specimen or reagent dilution; • Using a different calibration material (or changing the manufacturer's set-points); • Introducing a different antibody (source, monoclonal-vs-polyclonal); • Change or elimination of a procedural step; • Change or addition of detector (conjugate) or substrate; • Change in the solid phase; • Change in the cutoff or method of calculating the cutoff for semi-quantitative assays; • Change in the endpoint or calculation of the endpoint; • Addition of adsorbent; • Change in the strain of antigen in serologic assays; and • Changing the calibrator/reference material. EXCEPTIONS: Use of reagents that are exempt from the premarket notification procedures in 21 CFR 807 for an instrument produced by another manufacturer is not considered a method modification. If the FDA has cleared a manufacturer's reagents and/or calibration materials for use with an instrument produced by another manufacturer, the use of these reagents/materials is not considered a method modification and does not require establishment of performance specifications. However, the laboratory must verify performance specifications as required under §493.1253(b)(1). Verification of performance specifications is required if reagents are changed to those of another manufacturer. "Modified by the laboratory," also means any change in intended use that could affect test system performance specifications for sensitivity, specificity, accuracy, and precision, etc., and the clinical utility of the test system. Changes in intended use are considered "off-label" use of a commercial test system. CAUTION: "Off-label" use is not supported by the manufacturer's clinical data and when identified, must be reported to the FDA.

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otherwise specified by the manufacturer.		Examples of changes in intended use are: • Using a different sample matrix (plasma vs. urine); • Using or promoting the test for another purpose (screening vs. diagnostic); and • Changing the type of analysis (qualitative results reported as quantitative). 2. Laboratories should be aware that regulations require that reagents that are developed or prepared in one laboratory and shipped to another laboratory for use in patient testing require FDA clearance or approval. However, there are special issues in biochemical genetics with lack of availability of certain essential reagents in FDA-approved versions. The lack of FDA-approved reagents increases the responsibility of the laboratory to validate any internally developed or shared reagents, standards or controls.

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CALIBRATION AND CALIBRATION VERIFICATION PROCEDURES		
§493.1255 Standard: Calibration and calibration verification procedures Calibration and calibration verification procedures are required to substantiate the continued accuracy of the test system throughout the laboratory's reportable range of test results for the test system. Unless otherwise specified in this subpart, for each applicable test system the laboratory must do the following: (a) Perform and document calibration procedures– (1) Following the manufacturer's test system instructions, using calibration materials provided or specified, and with at least the frequency recommended by the manufacturer; (2) Using the criteria verified or established by the laboratory as specified in Sec. 493.1253(b)(3)– (i) Using calibration materials appropriate for the test system and, if possible, traceable to a reference method or reference	1. When standards and reference materials for calibration are commercially available, it is good practice to obtain quantities adequate for a reasonable period of testing to minimize variability in these materials (but not to exceed their expiration date). 2. When standards and reference materials for calibration are not commercially available, each laboratory preparing these materials in house should ensure their validation, including verifying each new batch of standards and reference materials against an old batch, and ensure appropriate calibration and calibration verification procedures in place. 3. Not all assays require calibration, but that does not relieve the lab of its responsibility to ensure accuracy. 4. Laboratories should refer to more specific (or method-specific) guidance when these are available, for example, ACMG Standards and Guidelines. 5. CLSI guidelines provide additional references and should be used for further guidance.	

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material of known value; and (ii) Including the number, type, and concentration of calibration materials, as well as acceptable limits for and the frequency of calibration; and (3) Whenever calibration verification fails to meet the laboratory's acceptable limits for calibration verification. (b) Perform and document calibration verification procedures– (1) Following the manufacturer's calibration verification instructions; (2) Using the criteria verified or established by the laboratory under Sec. 493.1253(b)(3)– (i) Including the number, type, and concentration of the materials, as well as acceptable limits for calibration verification; and (ii) Including at least a minimal (or zero) value, a mid-point value, and a maximum value near the upper limit of the range to verify the laboratory's reportable range of test results for the test system; and (3) At least once every 6 months and whenever any of the following occur: (i) A complete change of reagents for a procedure is introduced, unless the laboratory can demonstrate that changing reagent lot numbers does not affect the range used to report patient test results, and control values are not adversely affected by reagent lot number changes. (ii) There is major preventive maintenance or replacement of critical parts that may influence test performance. (iii) Control materials reflect an unusual trend or shift, or are outside of the laboratory's acceptable limits, and other means of assessing and correcting unacceptable control values fail to identify and correct the problem. (iv) The laboratory's established schedule for verifying the reportable		

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range for patient test results requires more frequent calibration verification.		

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CONTROL PROCEDURES		
§493.1256 Standard: Control procedures (a) For each test system, the laboratory is responsible for having control procedures that monitor the accuracy and precision of the complete analytical process. (b) The laboratory must establish the number, type, and frequency of testing control materials using, if applicable, the performance specifications verified or established by the laboratory as specified in Sec. 493.1253(b)(3). (c) The control procedures must– (1) Detect immediate errors that occur due to test system failure, adverse environmental conditions, and operator performance. (2) Monitor over time the accuracy and precision of test performance that may be influenced by changes in test system performance and environmental conditions, and variance in operator performance. (d)(3) At least once each day patient specimens are assayed or examined perform the following for– (i) Each quantitative procedure, include two control materials of different concentrations; (ii) Each qualitative procedure, include a negative and positive control material; (iii) Test procedures producing graded or □ittered results, include a negative control material and a control material with graded or □ittered reactivity, respectively; (iv) Each test system that has an	1. QC procedures should provide adequate monitoring of the quality of the test system's performance and detect immediate errors. 2. Laboratories should validate sampling instruments to ensure there is no carryover between samples on automated instruments. 3. Control procedures should be performed each day of patient testing or with each batch (group of specimens run concurrently or sequentially) of patient testing. However, there are special QC issues with sequential testing in a single-channel analyzer (see clarification #1). 4. Controls should be selected based on patient population and should be as comprehensive as possible, based on the prevalence of the disease and the purpose of the testing. For example, enzyme testing for carrier status should have a normal control and a carrier control if available. 5. Laboratories should use control materials that can monitor the entire analytic process, including the extraction step. 6. For rare diseases for which positive controls are difficult to obtain, laboratories may consider using samples from interlaboratory exchange or other mechanisms. For assays for rare diseases using certain tissue types, such as white blood cells, if it is not practical to have a positive control of the same tissue type, laboratories may consider using a more stable tissue type, such as cultured skin fibroblasts, when available. If the control materials are of a different tissue type that bypass certain preparative analytic steps of the patient testing process (e.g., extraction procedures), the laboratory should have procedures for monitoring the complete analytic process. 7. Control materials are not always practical or available, particularly for rare diseases. Appropriate alternative	1. The following options are acceptable for testing performed with single-channel or single-column instruments with which the run time of each specimen takes a significant portion of a working day on the basis that 1) the laboratory director is responsible for demonstrating that control procedures are adequate for monitoring test system performance and detecting immediate errors, and 2) the laboratory must have performance establishment/verification data to show that control procedures and calibration procedures are appropriate for the laboratory's patient testing. An example of a significant portion of QC testing may be found in the CLSI guideline "Gas Chromatography/Mass Spectrometry Confirmation of Drugs (C43)", which recommends QC samples constitute at least 10% of the samples in an analytic batch. a. Testing a mixed-level control pool (e.g., for amino acid analysis, this control pool may contain the 20 amino acids at various concentrations) once during each day or 24 hours of patient specimen testing and spiking at least one internal control material (e.g., S-2-aminoethyl-1-cysteine (AEC) for amino acid analysis) into each patient specimen. This approach helps to monitor the analytic process for each patient specimen and specimen-to-specimen variability. b. Testing a single-level control pool (e.g., containing all 20 amino acids at the same concentration for amino acid analysis) once during each day or 24 hours of patient specimen testing, together with spiking an internal control material into each patient specimen. c. Testing a previously tested patient specimen that showed abnormal levels of certain amino acids once each day, and spiking an internal standard into each patient specimen. d. If patient specimens are batched into a run exceeding 24 hours, the test run may be bracketed by running one

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extraction phase, include two control materials, including one that is capable of detecting errors in the extraction process; and (v) Each molecular amplification procedure, include two control materials and, if reaction inhibition is a significant source of false negative results, a control material capable of detecting the inhibition. (h) If control materials are not available, the laboratory must have an alternative mechanism to detect immediate errors and monitor test system performance over time. The performance of alternative control procedures must be documented. §493.1101 Standard: Facilities (b) The laboratory must have appropriate and sufficient equipment, instruments, reagents, materials, and supplies for the type and volume of testing it performs.	control procedures should depend on the specific test and control materials needed. For example, spiking or enriching a normal sample with analytes to emulate abnormal samples (See Clarification #2). 8. The above QC recommendations should be considered both in method validation and patient testing.	control sample at the beginning of the run and another control at the end of the run. If the run time is greater than 48 hours, a control should be inserted into the run within each 24-hour span. At least one internal control material should be spiked into each patient specimen. [Note: If the laboratory defines an analytical run this way, the laboratory director is responsible for ensuring and demonstrating the test system has stable accuracy and precision during the defined time period, for both the control samples and patient specimens. The laboratory should also consider the turnaround time needed for reporting patient results in determining the length of a test run.) 2. From MGT MMWR – The CMS Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services provides general guidelines for alternative control procedures and encourages laboratories to use multiple mechanisms for ensuring testing quality. Following are examples of procedures that, when applicable, should be followed by laboratories that perform biochemical genetic testing: a. Split specimens for testing by another method or in another laboratory. b. Include previously tested patient specimens (both positive and negative) as surrogate controls. c. Test each patient specimen in duplicate. d. Test multiple types of specimens from the same patient (e.g., saliva, urine, or serum). e. Perform serial dilutions of positive specimens to confirm positive reactions. f. Conduct an additional supervisory review of results before release.

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PROFICIENCY TESTING (PT) AND ALTERNATIVE PERFORMANCE ASSESSMENT		
Laboratories performing genetic testing must comply with §493.1236(c), to at least twice annually verify the accuracy of any genetic test or procedure they perform, as no genetic tests have been included in the list of regulated analytes. §493.801(b) Standard; Testing of proficiency testing samples. The laboratory must	1. PT is a requirement for all biochemical genetic tests. Laboratories are encouraged to participate in external PT that evaluates both analytic and interpretative elements of the testing (see Clarification #1-3). 2. The frequency of PT must be at a minimum twice per year, and higher frequency is encouraged. To the extent possible there should be PT for each analyte. 3. PT providers and users should be encouraged to support	1. Overall, the WG wishes to recognize the lack of organized PT programs for many of the biochemical genetic tests – a. Lack of comprehensive PT programs that cover all analytes, and assess both quantitative and qualitative approaches and both the analytic and interpretative elements. For example, for the core tests such as amino acid and organic acid analyses, quantitative programs are available from the European group while the CAP program addresses the

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examine or test, as applicable, the proficiency testing samples it receives from the proficiency testing program in the same manner as it tests patient specimens. (1) The samples must be examined or tested with the laboratory's regular patient workload by personnel who routinely perform the testing in the laboratory, using the laboratory's routine methods. The individual testing or examining the samples and the laboratory director must attest to the routine integration of the samples into the patient workload using the laboratory's routine methods. (2) The laboratory must test samples the same number of times that it routinely tests patient samples.	PT programs that examine the entire testing process, encompassing the pre-analytic, analytic, and post-analytic phases. Where possible, PT materials should resemble patient samples. At least for the most common genetic tests, "real" samples or samples mimicking patient specimens should be used for PT. 4. 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 in the laboratory (as required by CLIA for regulated analytes, even though no biochemical genetic test is included on the current list of regulated analytes). 5. Available sources for PT or external quality assessment (EQA), and resources facilitating external sample exchange, should be made available to laboratories in considering meeting PT and alternative performance assessment needs. 6. Alternative performance assessment should be performed at least twice per year, for biochemical genetic tests for which no PT program is available, in meeting the applicable requirements of CLIA, state programs, and accrediting agencies. a. While data are currently unavailable on whether alternative performance assessments are as robust or effective as PT, professional guidelines, such as those developed by CLSI and the College of American Pathologists (CAP), provide guidance on what would be considered acceptable alternative performance assessment approaches (see clarification #4). b. Alternative assessment should ideally be performed by inter-laboratory exchange or using externally derived materials. c. In circumstances when inter-laboratory exchange or externally derived materials are not practical or feasible, such as testing for rare diseases, testing performed by only one laboratory, unstable analytes (e.g. enzymes), laboratories may consider options such as repeat testing of blinded samples, possible exchange with either a research facility or international laboratory, or inter-laboratory data comparison. Examples could also come from laboratories performing testing for ultra-rare genetic disorders. 7. Laboratories should document and track their PT and EQA performance. A quality improvement audit should be	clinical part; however no single program ties it all together. b. There are many single analytes for which PT programs are not available. Residual patient samples may be used in interlaboratory comparison and this may in some cases, according to state and local regulations, involve consent issues. 2. Whenever possible, laboratories performing quantitative assays should enroll in PT programs that provide specific values. Qualitative PT is appropriate for some testing. PT providers should be mindful of the variability in methods and consider development of peer group approaches to PT when different methodology can lead to differences in values. 3. There may be differences in laboratory interpretation in NBS QAP due to different cutoffs. 4. The WG would like data on the effectiveness of alternative PT and regular PT with relation to clinical outcomes. 5. CLSI GP-27 *Using Proficiency Testing to Improve the Clinical Laboratory* provides guidance in using proficiency testing as a quality improvement tool.

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	performed to evaluate performance, investigate any failures or concern, and make corrective action upon disparate results and document outcomes (see Clarification #5).	

POSTANALYTIC PHASE

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TEST REPORT		
§493.1291 Standard: Test report (a) The laboratory must have adequate manual or electronic systems in place to ensure test results and other patient-specific data are accurately and reliably sent from the point of data entry (whether interfaced or entered manually) to final report destination, in a timely manner. This includes the following: (1) Results reported from calculated data. (2) Results and patient-specific data electronically reported to network or interfaced systems. (3) Manually transcribed or electronically transmitted results and patient-specific information reported directly or upon receipt from outside referral laboratories, satellite or point-of-care testing locations. (b) Test report information maintained as part of the patient's chart or medical record must be readily available to the laboratory and to CMS or a CMS agent upon request. (c) The test report must indicate the following: (1) For positive patient identification, either the patient's name and identification number, or a unique patient identifier and identification number. (2) The name and address of the laboratory location where the test was performed. (3) The test report date. (4) The test performed. (5) Specimen source, when appropriate. (6) The test result and, if applicable, the units of measurement or interpretation, or both. (7) Any information regarding the condition and disposition of specimens that do not meet the laboratory's criteria for acceptability. (d) Pertinent ``reference intervals'' or	1. **Content of biochemical genetic test reports**: The following additional elements (in addition to CLIA requirements at §493.1291(c)) should be included on biochemical genetic test reports: a. Patient's name and any other necessary unique identifier(s); b. Patient's date of birth; c. Indication for testing when needed for result interpretation (see clarification #1) d. The date and time of specimen collection and arrival in the laboratory (see clarification #2) e. Name of the referring physician or other authorized individual who ordered the test; f. When appropriate, an interpretive guide (for example a table or reference to literature or to website); g. Analytes tested and/or type of test method, whichever is appropriate; h. Performance specifications, including the normal range or reference intervals appropriate to the individual (e.g. sex, age, and population as appropriate), and, when appropriate, limitations of the test (see clarification #3); i. Test results in appropriate measurement units and current recommended standard nomenclature, which should include clarifications and commonly used terms if different from the current/recommended. j. Result interpretation for complex tests, profiles, and testing for carrier status (see clarification #4) k. Notation if report is preliminary or whether it is an update or revision to previously reported results l. Results of other relevant tests that the laboratory performed for the patient if available (see clarification #5) m. When appropriate, recommendations for additional testing of patient or for family members. n. References to the literature if applicable o. Recommendation for consultation with a genetics professional, when appropriate and indicated (see clarification #6) p. For any in-house developed test using any analyte-specific reagent (ASR), provide the statement	1. Indications for testing are not always provided upon test request and may not reflect the reason for requesting the test specifically or accurately. However including this information on test reports can help users understand the reason for the test request and result interpretation, particularly when a test report is sent to users other than the test requestor. Improving the communications between laboratories and users in the preanalytic phase – such as the recommended preanalytic practices to inform users of the information laboratories need and solicit the needed information on test requisitions – should result in improved result reporting practices. 2. Sample information should include date and time of specimen collection and not the time it was ordered or the time it was accessioned in a referring lab. If correct date and time of sample collection and receipt by laboratory are not known, it might be best to say date and time unknown on test report. For example, normal amino acids when well does not exclude the possibility of intermittent maple syrup urine disease. 3. The test report should include limitations on the test, such as a statement on the intended use and the technical limitation of the test method. 4. Interpretation of test results a. Should be linked to the reason that the test was ordered, and communicated in a clinically relevant manner. b. When appropriate, should explain how technical limitations impact the clinical use of the test results for the person receiving the report. c. Some testing requires interpretation of complex combination of BGT and non-BGT, e.g. allopurinol challenge. This can involve also multiple samples over time d. When appropriate and necessary, may indicate the test results in reference to information on family members, for example information regarding abnormality(ies) previously detected in a relative that was used for

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``normal'' values, as determined by the laboratory performing the tests, must be available to the authorized person who ordered the tests and, if applicable, the individual responsible for using the test results. (e) The laboratory must, upon request, make available to clients a list of test methods employed by the laboratory and, as applicable, the performance specifications established or verified as specified in §493.1253. In addition, information that may affect the interpretation of test results, for example test interferences, must be provided upon request. Pertinent updates on testing information must be provided to clients whenever changes occur that affect the test results or interpretation of test results. (g) The laboratory must immediately alert the individual or entity requesting the test and, if applicable, the individual responsible for using the test results when any test result indicates an imminent life-threatening condition, or panic or alert values. (h) When the laboratory cannot report patient test results within its established time frames, the laboratory must determine, based on the urgency of the patient test(s) requested, the need to notify the appropriate individual(s) of the delayed testing. **§493.1276 Standard: Clinical cytogenetics -** (d) The laboratory report must include a summary and interpretation of the observations, number of cells counted and analyzed, and use the International System for Human Cytogenetic Nomenclature. CMS Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services provide guidance for meeting the test report requirements, including: • Interpretive Guidelines for §493.1291(c) - For genetic tests, laboratories should include the test method(s) employed and any mutations on test reports.	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” (see clarification #7); and q. The date and, when appropriate, time the test report is released. 2. Laboratory reports should be electronic or electronically compatible with electronic medical records. Records of test reports retained in the laboratory should be in same format as reported and all information should be maintained in the original report. The laboratory information system should ensure future software can read electronic reports generated in the past. 3. Laboratories should inform or update their users when test methods change to meet the CLIA requirement at §493.1291(e). 4. Test reports should include signatures, which can be electronic, to indicate the laboratory personnel who reviewed the test results and provided the result interpretation. 5. Test reports should be clinically understandable. The language used in test reports should be understandable by non-geneticist health professionals. Laboratories should determine appropriate language and terms to use in test reports based on the assessment of the needs of specific users. 6. Panic or critical values that indicate the patient may be in crisis should be communicated to the clinician caring for the patient.	selection of the test method, to assure appropriate interpretation of the test results and understanding of their implications e. The name of the laboratory personnel providing the interpretation should be included on the test report. 5. Laboratories should be encouraged to develop systems that allow them to be aware that more than one biochemical test has been sent on a patient so that interpretation can include information on other current or prior tests on the same patient. 6. Genetic consultation a. CLIAC considers genetic consultation as encompassing genetic services, including genetic counseling, provided by trained qualified genetic professionals, such as genetic counselors, clinical geneticists or other qualified professionals, to healthcare providers, patients, or at-risk family members. b. Providing information regarding the need for genetic consultation can also be an educational initiative, to improve understanding of genetic tests in the medical community. 7. For laboratory-developed tests using ASRs, it is not appropriate to additionally state "FDA has determined that this test does not require regulatory clearance or approval". For laboratory-developed tests using no ASR, this “ASR disclaimer” is not required.

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• Interpretive Guidelines for §493.1291(e) - When the laboratory changes methods, establishes a new procedure or refers tests to another laboratory, the laboratory must provide the client with necessary updated information concerning parameters such as patient preparation, preservation of specimens, specimen collection or new "normal" values.		

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RETENTION OF RECORDS AND REPORTS		
Under 493.1105, CLIA requires laboratories to retain records of patient testing, including test requisitions and authorizations, test procedures, analytic systems records, patient test records, proficiency testing records, and quality system assessment records, for no less than 2 years; and test reports for at least 2 years after the date of reporting. Laboratories performing genetic testing are subject to these general retention requirements.	1. For QC, PT, and other records – a. The CLIA-required 2-year retention timeframe is minimum requirement for biochemical genetic testing. b. Laboratories may want to keep some records longer for educational purposes, especially for rare conditions. Records of tests that generated normal results should also be retained. c. Primary data from which reports are generated should be kept along with the reports, preferably electronically. 2. For test reports – a. When the intended purpose of testing is to identify genetic conditions, the test reports indicating genotypes should be retained for the longest possible timeframe, at least 21 years after the date of reporting (see clarification point #1 and 2). b. Retention time frame of newborn screening test reports is subject to state requirements (see clarification #3). 3. Retention policies and procedures should comply with applicable state laws and other requirements, such as those by accrediting organizations. 4. Laboratories should ensure that electronic records and reports are accessible while the technology of electronic storage evolves.	1. Twenty-one years is recommended as an acceptable time frame of one generation. 2. The financial impact of the suggested longer (than required by CLIA) retention timeframe for genetic test reports should be considered, as well as technology and space issues. 3. Certain states require different retention time frames for newborn screening test reports depending on the results. For example, Tennessee requires positive NBS reports be retained for at least 25 years and negative reports a minimum of 2 years.

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	Key Points	**Clarifications**
RETENTION OF SPECIMENS		
§493.1232 requires laboratories to establish and follow written policies and procedures that ensure positive identification and optimum integrity of patient specimens from the time of collection or receipt in the laboratory through completion of testing and reporting of results.	1. Specimens should be retained for the longest possible timeframe as permitted by sample stability and integrity, technology, space, and cost (see clarification #1). 2. At a minimum, but with attention to specimen stability, tested patient specimens should be retained until after the final reporting of result to allow for identification of any problems in patient testing and for corrective actions to be taken, and for adding on another test using the same specimen after results are reported. When possible (for low volume tests) the sample should be retained until the next PT/EQA. (keep highlighted) 3. The retention of specimens, especially NBS residual specimens is subject to federal, state and local requirements (see clarification #2) 4. The laboratory director should be responsible for ensuring the laboratory has and follows their own written policies and procedures for specimen retention that are consistent with the laboratory's quality assessment activities and applicable consent procedures, in compliance with applicable federal, state, and local laws and requirements, including requirements for laboratory accreditation.	1. Sample volume and/or storage capacity may prevent laboratories from keeping samples for a long time. However, abnormal samples should be retained indefinitely or for the longest possible time for laboratory QA and educational purposes, in compliance with applicable federal, state and local requirements. 2. The system of BGT depends on use of residual samples to protect the quality of testing and therefore patient health and safety. The use of residual samples for EQA and QC is appropriate because these activities are not research and that EQA and QC directly affect the quality of laboratory testing and patient safety. a. In context of NBS there is a move to limit use of residual samples for any purpose. Inability to use residual samples for retesting a baby and for EQA/QC places babies at risk. In considering the use and storage of residual NBS samples, research use should always be distinguished from the need to preserve the ability to retest when necessary and to perform EQA/QC to maintain quality. b. Laboratories should always comply with applicable requirements in use of residual patient samples.

CLIA Requirements	WG Input	
	Key Points	**Clarifications**
POSTANALYTIC SYSTEMS ASSESSMENT AND OTHER ISSUES		
Sec. 493.1299 Standard: Postanalytic systems assessment (a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess and, when indicated, correct problems identified in the postanalytic systems specified in Sec. 493.1291. (b) The postanalytic systems assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of postanalytic	1. The CLIA postanalytic systems assessment requirements apply to biochemical genetic testing (see clarification #1). 2. Laboratories should have procedures in place to address the following postanalytic or interpretive issues, which are often unique in biochemical testing: a. When diagnostic testing shows an abnormality, testing of other analytes may be critical to clarify diagnosis (e.g. when MMA is elevated, need homocysteine level); b. Reflex testing on the same sample may be useful and appropriate, and raises questions of test ordering, cost and coverage.	1. <u>CMS Interpretive Guidelines §493.1299(a)-(c):</u> QA of the Postanalytic System includes assessing practices/issues related to test reports. Examples include: ▪ Monitoring and evaluating the accuracy and completeness of the laboratory's test reports (i.e., patient information, test results, normal ranges, and the disposition of unacceptable specimens); ▪ The laboratory's turn-around times; ▪ Procedures for notification of test results e.g., routine tests, STATS, abnormal or panic values. If the laboratory uses an LIS, the laboratory must have a mechanism to periodically verify the accuracy of:

CLIA Requirements	WG Input	
	Key Points	Clarifications
systems assessment reviews with appropriate staff. (c) The laboratory must document all postanalytic systems assessment activities.	c. Additional testing by another method or of another tissue may be important for clarification of diagnosis, for management of the patient, and for the healthcare management of the patient's family. d. Additional samples may be needed when testing unstable analytes to make sure the initial sample was not compromised. 3. All abnormal screening results need further investigation by analysis of a freshly collected second sample, and a comprehensive system should be in place for follow-up of a positive screen.	• Its calculated data; • The results sent to interfaced systems; and • Patient specific data.

CLIA Requirements	WG Input	
	Key Points	Clarifications
CONFIDENTIALITY		
§493.1231 The laboratory must ensure confidentiality of patient information throughout all phases of the total testing process that are under the laboratory's control.	1. While CLIA does not specify that a confidentiality policy is required, all laboratories should have written policies to ensure confidentiality of patient information. 2. Laboratories must ensure confidentiality of genetic test information in the same manner they ensure confidentiality of other laboratory or medical information, in compliance with applicable federal, state, and local requirements. All the recommended confidentiality practices in MGT MMWR should apply to BGT (see Clarification #1).	1. The following are recommended confidentiality practices in MGT MMWR: a. The CLIA regulations provide principles for ensuring confidentiality of patient test information. Laboratories should follow more specific requirements and guidance, such as the HIPAA Privacy Rule, state requirements, accreditation standards, and professional guidelines, to establish procedures and protocols to protect the confidentiality of all patient information, including information related to genetic testing. The procedures and protocols should include defined responsibilities of all employees and agents to ensure appropriate access, documentation, storage, release, and transfer of confidential information and prohibition of unauthorized or unnecessary access or disclosure. b. Electronic records should be under proper access control to ensure patient confidentiality. c. CLIAC recognized the concern about circumstances in which information regarding family member(s) needs to be included in test reports to ensure appropriate result interpretation, and the need to ensure confidentiality of patient information in accord with all applicable federal, state, local requirements and professional standards. CLIAC recommends that laboratories have in place procedures and systems to ensure confidentiality of all patient information, including information on family members when required for test performance and result interpretation, in all testing procedures and reports in

CLIA Requirements	WG Input	
	Key Points	Clarifications
		compliance with CLIA requirements and other applicable federal and state regulations. d. CLIAC provides the following recommendations for situations in which a healthcare provider requests genetic test information of a patient for the purpose of caring for his/her relative (i.e., releasing a patient's genetic test results that are needed or may be useful for health care and management of the patient's family members): i. The requests should be handled in the same manner as requests for other protected patient information. Laboratory should release information only to authorized individuals, such as ordering physicians or other healthcare providers cooperating in the care of the patient who was tested. ii. Even though the HIPAA Privacy Rule permits the communication of patient information between healthcare providers for patient care purposes (per HHS Answer to HIPAA Frequent Questions), laboratories should not share a patient's genetic test results without the patient's authorization to do so. It should be up to the patient to contact the family members or to ask his/her physician or other authorized person to do it. iii. When patient consent is required for the testing, the consent form should address situations in which test results may be requested by healthcare providers caring for the patient's relatives, and should inform the patient of the laboratory's confidentiality policies and procedures. iv. The laboratory director should be responsible for determining and approving the circumstances in which access to confidential information is appropriate, as well as when, how and to whom information is to be released, in compliance with federal, state, and local requirements. Laboratories should recognize that HIPAA and CLIA provide minimum standards for ensuring confidentiality and that state or local requirements may set a higher standard. HIPAA expressly provides that institutions may adopt stricter standards. HIPAA also expressly states that it is not intended to interfere with good medical care, as explained in the Q&A from the HHS Office of Civil Rights. Concerns about privacy and good medical care are occasionally in conflict in biochemical

CLIA Requirements	WG Input	
	Key Points	Clarifications
		genetics.

PERSONNEL QUALIFICATIONS AND RESPONSIBILITIES

CLIA Requirements	WG Input	
	Key Points	**Clarifications**
LABORATORY DIRECTOR QUALIFICATIONS		
§493.1443 Laboratory director qualifications (for high complexity testing; abbreviated) • Be an M.D. or D.O. certified in clinical and/or anatomic pathology; • Be an M.D., D.O., or D.P.M., and have 1 year of laboratory training during residency and two years of supervisory experience in high complexity testing; • Hold a doctoral degree in a chemical, physical, biological, or clinical laboratory science, and be certified and continue to be certified by a board approved by HHS; or • Be grandfathered.	The current CLIA requirements for the qualifications of directors of laboratories performing high complexity testing are adequate for biochemical genetic testing.	

CLIA Requirements	WG Input	
	Key Points	**Clarifications**
LABORATORY DIRECTOR RESPONSIBILITIES		
§493.1445 Laboratory director responsibilities. (Abbreviated) The laboratory director's responsibilities include — • Ensure each test performed in the laboratory provide quality laboratory services for all aspects of test performance; • Ensure physical and environmental conditions of the laboratory are appropriate and safe; • Ensure the test methodologies selected have the capability of providing the quality of results required for patient care; • Ensure adequate performance verification; • Ensure the quality of test performance; • Ensure enrollment in an HHS-approved proficiency testing program;	1. ALL CLIA responsibility requirements for laboratory directors of high complexity testing apply to biochemical genetic testing. In addition, laboratory directors should have the authority for ensuring laboratory testing quality and compliance with all applicable requirements for laboratory operation. 2. For biochemical genetic testing, laboratory directors should ensure the documentation of clinical validity of any biochemical genetic test their laboratories offer (see clarification point #1).	1. Documentation of clinical validity may differ from test to test, and is the responsibility of the laboratory director. Literature references may be a common starting point. Details are outlined in the section "Performance establishment and verification".

CLIA Requirements	WG Input	
	Key Points	Clarifications
• Ensure quality control and quality assessment programs are established and maintained; • Ensure establishment and maintenance of acceptable levels of analytical performance for each test system; • Ensure all necessary remedial actions are taken and documented and patient test results are reported only when the system is functioning properly; • Ensure test reports include pertinent information required for interpretation; • Ensure consultation is available to the laboratory's clients on the quality of test results and their interpretation; • Ensure on-site supervision of high complexity testing by a general supervisor; • Employ a sufficient number of laboratory personnel with appropriate education, experience or training, and ensure all personnel have demonstrated appropriate competency prior to testing patients' specimens,; • Ensure that policies and procedures are established for monitoring personnel competency and for identifying needs for remedial training or continuing education; • Ensure an approved procedure manual is available to all laboratory personnel; • Specify in writing the responsibilities and duties of each consultant, supervisor, and testing personnel.		

CLIA Requirements	WG Input	
	Key Points	Clarifications
TECHNICAL SUPERVISOR QUALIFICATIONS		
§493.1449 (i) Technical supervisor qualifications for chemistry (abbreviated) • Be an MD or DO, and certified in clinical pathology; • Be an MD, DO, or DPM, and have 1 year of laboratory training/experience in high complexity testing in chemistry; • Have a doctoral degree in a chemical, physical, biological or clinical laboratory	1. Technical supervisors for biochemical genetic testing should have the qualifications that are appropriate for the section they are supervising, taking into account the type(s) of testing performed and the purpose for performing the testing. 2. WG suggested technical supervisor qualifications for the following 2 categories of testing:	1. Proposed eligibility for certification as a Technical Supervisor in Public Health Newborn Screening: a. Hold an earned doctoral degree from an accredited institution in a chemical, physical, biological or clinical laboratory science or medical technology and have at least one year of clinical laboratory training or experience on human specimens, or both, in high complexity testing within the specialty. b. Be a doctor of medicine or doctor of osteopathy licensed

CLIA Requirements	WG Input	
	Key Points	**Clarifications**
science from an accredited institution, and have 1 year of laboratory training/experience in high complexity testing in chemistry; • Have a master's degree in a chemical, physical, biological or clinical laboratory science or medical technology from an accredited institution, and have 2 years of laboratory training/experience in high complexity testing in chemistry; or • Have a bachelor's degree in a chemical, physical or biological science or medical technology from an accredited institution, and have 4 years of laboratory training/experience in high complexity testing in chemistry. **§493.1449(p) Technical supervisor qualifications for clinical cytogenetics (abbreviated)** • Be an M.D., D.O. or D.P.M.; and have four years of training or experience in genetics, two of which have been in clinical cytogenetics; or • Hold a doctoral degree in a biological science or clinical laboratory science from an accredited institution; and have four years of training or experience in genetics, two of which have been in clinical cytogenetics.	a. Biochemical genetic testing: i. Be equivalent to the CLIA qualification requirements for clinical cytogenetics technical supervisors, with four years of training or experience in genetics, two of which have been in the area of biochemical genetic testing; or ii. Have current certification in biochemical genetic testing by HHS-approved boards, such as certifications by the American Board of Medical Genetics (ABMG) b. Public health newborn screening: i. The current CLIA requirements for the qualifications of technical supervisor for high complexity testing are appropriate for newborn screening. ii. Have at least four years of laboratory training or experience in newborn screening systems (which include dried blood spot specimen acquisition and handling; relevant biochemical, immunological, hematological, and chemical methods, including tandem mass spectrometry; data processing and quality assurance; report generation; and follow up and referral protocols). iii. If CMS-approved board certification is available, it is highly recommended that NBS technical supervisors pursue such certification (see clarification #1). iv. Meet any additional state requirements that apply.	to practice medicine or osteopathy and have at least one year of clinical laboratory training or experience on human specimens, or both, in high complexity testing within the specialty. c. Hold an earned master's degree from an accredited institution* in a chemical, physical, biological or clinical laboratory science or medical technology and have at least two years of clinical laboratory training or experience on human specimens, or both, in high complexity testing within the specialty. d. Hold an earned bachelor's degree from an accredited institution in a chemical, physical or biological science or medical technology and have at least four years of laboratory training or experience on human specimens, or both, in high complexity testing within the specialty.

CLIA Requirements	WG Input	
	Key Points	**Clarifications**
TECHNICAL SUPERVISOR RESPONSIBILITIES		
§493.1451 Technical supervisor responsibilities (High complexity testing) The technical supervisor is responsible for the technical and scientific oversight of the laboratory. The technical supervisor is not required to be on site at all times testing is performed; however, he or she must be available to the laboratory on an as needed basis to provide supervision as specified in (a) of this section.	1. The CLIA responsibility requirements for technical supervisors of high complexity testing are appropriate for biochemical genetic testing. 2. When determined by the laboratory director, technical supervisors for biochemical genetic testing should have the following additional responsibilities: a. Assess the suitability of any particular test for a particular use.	1. When simple biochemical genetic testing is done in a general laboratory, the technical supervisor of the general laboratory has the responsibility to know when it is appropriate to suggest and/or seek further consultation.

CLIA Requirements	WG Input	
	Key Points	Clarifications
(a) The technical supervisor must be accessible to the laboratory to provide on-site, telephone, or electronic consultation; and (b) The technical supervisor is responsible for— (1) Selection of the test methodology that is appropriate for the clinical use of the test results; (2) Verification of the test procedures performed and establishment of the laboratory's test performance characteristics, including the precision and accuracy of each test and test system; (3) Enrollment and participation in an HHS approved proficiency testing program commensurate with the services offered; (4) Establishing a quality control program appropriate for the testing performed and establishing the parameters for acceptable levels of analytic performance and ensuring that these levels are maintained throughout the entire testing process from the initial receipt of the specimen, through sample analysis and reporting of test results; (5) Resolving technical problems and ensuring that remedial actions are taken whenever test systems deviate from the laboratory's established performance specifications; (6) Ensuring that patient test results are not reported until all corrective actions have been taken and the test system is functioning properly; (7) Identifying training needs and assuring that each individual performing tests receives regular in-service training and education appropriate for the type and complexity of the laboratory services performed; (8) Evaluating the competency of all testing personnel and assuring that the staff maintain their competency to perform test procedures and report test results promptly, accurately and proficiently. The procedures for evaluation of the competency of the staff must include, but	b. Ensure appropriate documentation of clinical validity information on the biochemical genetic tests their laboratories perform. c. Review test results and the interpretation (see clarification #1). d. Review and/or sign test reports. e. Be available to answer questions about the test report. f. Evaluate test results and need to refer to another laboratory. 3. Although CLIA regulations specify that technical supervisors do not need to be on-site, but must be accessible to the laboratory to provide on-site, telephone, or electronic consultation, certain on-site time in the laboratory may be needed for technical supervisors of biochemical genetic testing, as determined by the laboratory director based on the complexity of the tests performed in the laboratory. 4. Technical supervisors for NBS should follow state-specific policies and practices to determine when additional testing is needed.	

CLIA Requirements	WG Input	
	Key Points	Clarifications
are not limited to— (i) Direct observations of routine patient test performance, including patient preparation, if applicable, specimen handling, processing and testing. (ii) Monitoring the recording and reporting of test results. (iii) Review of intermediate test results or worksheets, quality control records, proficiency testing results, and preventive maintenance records (iv) Direct observation of performance of instrument maintenance and function checks; (v) Assessment of test performance through testing previously analyzed specimens, internal blind testing samples, external proficiency testing samples; and (vi) Assessment of problem solving skills. (9) Evaluating and documenting the performance of individuals responsible for high complexity testing at least semiannually during the first year the individual tests patient specimens. Thereafter, evaluations must be performed at least annually unless test methodology or instrumentation changes, in which case, prior to reporting patient test results, the individual's performance must be reevaluated to include the use of the new test methodology or instrumentation.		

CLIA Requirements	WG Input	
	Key Points	Clarifications
CLINICAL CONSULTANT QUALIFICATIONS		
§493.1455 Clinical consultant qualifications (abbreviated) • Be qualified as a laboratory director under §493.1443(b)(1), (2), or (3)(i) or, for the subspecialty of oral pathology, Sec. 493.1443(b)(6); or • Be a doctor of medicine, doctor of osteopathy, doctor of podiatric medicine licensed to practice medicine, osteopathy,	1. The CLIA requirements for clinical consultant qualifications for high complexity testing are minimum qualifications. For biochemical genetic testing and newborn screening for heritable conditions, clinical consultants should have relevant training and/or experience in the testing for which they provide clinical consultation. 2. Clinical consultants for biochemical genetic testing should have the following qualifications:	1. Experience in biochemical genetic testing gained through training should be considered acceptable experience.

CLIA Requirements	WG Input	
	Key Points	Clarifications
or podiatry in the state in which the laboratory is located.	a. Be an M.D., or D.O., and be either board-certified or board-eligible in clinical or clinical biochemical genetics; or b. Be an M.D., or D.O., and have two years of experience in biochemical genetic testing and/or diagnosis and management of IEMs; or c. Hold a Ph.D. degree in a relevant discipline, be board-certified in clinical biochemical genetics, and have two years of experience in biochemical genetic testing (See Clarification #1)	

CLIA Requirements	WG Input	
	Key Points	Clarifications
CLINICAL CONSULTANT RESPONSIBILITIES		
§493.1457 Standard; Clinical consultant responsibilities The clinical consultant provides consultation regarding the appropriateness of the testing ordered and interpretation of test results. The clinical consultant must — (a) Be available to provide consultation to the laboratory's clients; (b) Be available to assist the laboratory's clients in ensuring that appropriate tests are ordered to meet the clinical expectations; (c) Ensure that reports of test results include pertinent information required for specific patient interpretation; and (d) Ensure that consultation is available and communicated to the laboratory's clients on matters related to the quality of the test results reported and their interpretation concerning specific patient conditions.	The CLIA requirements for clinical consultant responsibilities are adequate for biochemical genetic testing.	

CLIA Requirements	WG Input	
	Key Points	Clarifications
GENERAL SUPERVISOR QUALIFICATIONS		
§493.1461 General supervisor qualifications (high complexity testing; abbreviated) • Be qualified as a laboratory director or	1. For biochemical genetic testing general supervisors should have the following qualifications: a. Be qualified as a laboratory director or technical supervisor; or	1. The WG considered the general supervisor qualifications recommended in professional guidelines, such as the ACMG S&G, and felt that it would be more important to emphasize that they have appropriate education and experience in high

CLIA Requirements	WG Input	
	Key Points	Clarifications
technical supervisor; • Be an M.D., D.O., D.P.M.; • Have a doctorate, master, or baccalaureate degree in a chemical, physical, biological or clinical laboratory science, and have one year training or experience in high complexity testing; • Have an associate degree or equivalent in a chemical, physical, biological or clinical laboratory science, and have two years training or experience in high complexity testing; or • Be grandfathered. §493.1463 General supervisor responsibilities (high complexity testing; abbreviated) Responsibilities of the general supervisor include: • Be accessible to testing personnel at all times testing is performed; • Provide day-to-day supervision of high complexity testing • Be onsite to provide direct supervision when high complexity testing is performed by any grandfathered individual; • Monitor test analyses and specimen examinations to ensure that acceptable levels of analytic performance are maintained. • The laboratory director or technical supervisor may delegate to the general supervisor the responsibility for — o Assuring that all remedial actions are taken whenever test systems deviate from the laboratory's established performance specifications; o Ensuring that patient test results are not reported until all corrective actions have been taken and the test system is properly functioning; o Providing orientation to all testing personnel; o Annually evaluating and documenting the performance of all testing personnel.	b. Be an 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 c. Have a 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 d. Have a 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 (see Clarification #1 and #2) 2. The CLIA general supervisor qualification requirements for high complexity testing are adequate for newborn screening. These general supervisors should also meet any additional state or local qualification requirement (see clarification #3).	complexity testing, and demonstrate specific competencies for the biochemical genetic tests the laboratory performs, rather than specifying training/experience specifically in biochemical genetic testing. 2. CLIA requirements are adequate for biochemical tests performed in a general laboratory setting that may indicate genetic conditions (e.g., lipids, cholesterol). 3. Most general supervisors in NBS at the state public health setting have multiple areas of responsibility and not just NBS. Some states have qualification requirements for laboratory general supervisors that are more stringent than the CLIA requirements.

CLIA Requirements	WG Input	
	Key Points	Clarifications
GENERAL SUPERVISOR RESPONSIBILITIES		
§493.1463 General supervisor responsibilities (abbreviated) The general supervisor is responsible for day-to-day supervision or oversight of the laboratory operation and personnel performing testing and reporting test results. Responsibilities include: • providing day-to-day supervision of high complexity test performance by a qualified testing personnel; • providing onsite, direct supervision when high complexity testing is performed by any qualified individuals • providing orientation to all testing personnel • Annually evaluating and documenting the performance of all testing personnel.	The CLIA general supervisor responsibility requirements for high complexity testing are adequate for biochemical genetic testing.	

CLIA Requirements	WG Input	
	Key Points	Clarifications
TESTING PERSONNEL QUALIFICATIONS AND RESPONSIBILITIES		
§493.1489 Testing personnel qualifications (abbreviated) • Be a MD, DO, or DPM; • Have earned a doctoral, master's or bachelor's degree in a chemical, physical, biological or clinical laboratory science, or medical technology from an accredited institution; • Have earned an associate degree in a laboratory science, or medical laboratory technology from an accredited institution; or • Be grandfathered. §493.1495 Standard; Testing personnel responsibilities (high complexity testing) (b) Each individual performing high complexity testing must— (1) Follow the laboratory's procedures for specimen handling and processing, test analyses, reporting and maintaining records of patient test results;	1. The CLIA testing personnel qualification requirements for high complexity testing are appropriate for biochemical genetic tests; testing personnel must receive adequate training and demonstrate competency in high complexity biochemical genetic testing before performing patient testing. 2. Follow state or local requirements. 3. The CLIA testing personnel responsibility requirements for high complexity testing are adequate for biochemical genetic testing.	

CLIA Requirements	WG Input	
	Key Points	Clarifications
(2) Maintain records that demonstrate that proficiency testing samples are tested in the same manner as patient specimens; (3) Adhere to the laboratory's quality control policies, document all quality control activities, instrument and procedural calibrations and maintenance performed; (4) Follow the laboratory's established policies and procedures whenever test systems are not within the laboratory's established acceptable levels of performance; (5) Be capable of identifying problems that may adversely affect test performance or reporting of test results and either must correct the problems or immediately notify the general supervisor, technical supervisor, clinical consultant, or director; (6) Document all corrective actions taken when test systems deviate from the laboratory's established performance specifications; and (7) Except as specified in paragraph (c) of this section, if qualified under §493.1489(b)(5), perform high complexity testing only under the onsite, direct supervision of a general supervisor qualified under §493.1461.		

CLIA Requirements	WG Input	
	Key Points	**Clarifications**
PERSONNEL COMPETENCY ASSESSMENT		
§493.1235 Standard: Personnel competency assessment policies As specified in the personnel requirements in subpart M, the laboratory must establish and follow written policies and procedures to assess employee and, if applicable, consultant competency. CLIA also specifies that competency assessments are the responsibilities of laboratory directors and technical supervisors: • §493.1445(e)(13) requires laboratory directors to ensure that policies and procedures are established for monitoring individuals who conduct preanalytical, analytical, and postanalytical phases of testing, to assure that they are competent and maintain their competency to process specimens, perform test procedures, and report test results promptly and proficiently, and whenever necessary, identify needs for remedial training or continuing education to improve skills. • §493.1451(b)(8) requires technical supervisor to be responsible for evaluating the competency of all testing personnel and assuring that the staff maintain their competency to perform test procedures and report test results promptly, accurately and proficiently.	1. Regular competency assessment is an important element of assuring all personnel are capable of performing their duties appropriately. The CLIA personnel competency assessment requirements are adequate for biochemical genetic testing. 2. It should be the laboratory director's responsibility to determine specific policies and procedures for assessing and ensuring the competency of the following laboratory personnel: a. Technical supervisor; b. Clinical consultant; c. General supervisor; d. Testing personnel. 3. The laboratory's specific personnel competency assessment policies and procedures must comply with applicable CLIA requirements, including the technical supervisor responsibility requirements at §493.1451(b)(8), and follow the applicable guidelines provided by CMS.	

ADDITIONAL ISSUES

CLIA Requirements	WG Input	
	Key Points	**Clarifications**
CONSIDERATIONS BEFORE INTRODUCING GENETIC TESTING OR OFFERING NEW BIOCHEMICAL GENETIC TESTS		
	1. Considerations before introducing genetic testing or offering new genetic tests should include the following aspects: a. Management responsibilities; b. State and local regulatory requirements; c. Benefits to patient care - test volume should be considered, but patient care needs should be considered even if test volume may be low (see clarification #1 and #2); d. Cost and cost-effectiveness considerations, including new CPT codes for certain specific tests; e. Performance establishment or verification needs (see clarification #3); f. Personnel considerations, including available technical expertise and expertise for interpreting test results and providing consultation (see clarification #4); g. Special issues in newborn screening at the federal and state levels should be considered, including the need for and availability of follow-up tests; the HHS Secretary's Advisory Committee on Heritable Disorders in Newborns and Children operates a systematic evidence-based review process to determine disorders that are recommended for inclusion into newborn screening test panels nationwide. h. Facility and laboratory safety considerations; i. Developing and validating procedures and training personnel. 2. Many considerations elsewhere, such as analytical validity and clinical validity, apply to this section. 3. The following additional thoughts were provided: a. The following 3 scenarios should be considered as reasons to introduce a test: i. Introducing a new genetic test that has not been offered anywhere; ii. Introducing a test in house that has been referred out to another laboratory; iii. Introducing a second test that can compliment	1. This is key in considering not only the introduction of a new test not available elsewhere, but also in considering when a test available elsewhere can and should be done on-site. 2. However, testing volume must be sufficient to maintain proficiency in technical aspects of testing and in interpretation. 3. Includes availability of positive and negative controls, reagents, supplies and (thought not always available) external PT. 4. Especially for rare diseases, consider the benefit of relationship between diagnostic laboratory testing and clinical and laboratory researchers.

CLIA Requirements	WG Input	
	Key Points	**Clarifications**
	the existing test. b. The needs and demands of the new test should be considered and assessed in considering introducing the test. This can be accomplished by consulting with ordering physicians. c. Certain tests may be restricted due to intellectual property issues. 4. Consider appropriate professional guidelines, recommendations, and policy statements in introducing or offering new tests.	

CLIA Requirements	WG Input	
	Key Points	**Clarifications**
QUALITY MANAGEMENT SYSTEM (QMS) FOR BIOCHEMICAL GENETIC TESTING		
CLIA regulations overlap with the QMS model.	1. CLIAC recognized that QMS is not yet a widespread approach in the U.S. and laboratories may not be ready to implement QMS in current practices. However, the QMS approach is described in several CLSI guidelines, and the New York State program and CAP have already included QMS in their laboratory standards. Benefits of QMS in BGT include: a. Helping laboratories to meet CLIA requirements; b. Helping to improve quality, efficiency c. Helping laboratories to improve the delivery of laboratory services to meet the expectations for patient care; d. Helping with international test referrals and global harmonization. e. QMS framework may prompt laboratories to examine the process beyond patient testing such as the research and development (R&D) phase for setting up assays. 2. QMS policies and procedures may be helpful for the following specific areas: a. Determining effective ways to provide information to users of laboratory services based on assessment of user needs; b. Specimen submission; c. Test requisitions; d. Test reports, in determining the media, format, style, and language used in test reports based on assessment of user needs; e. Considerations before introducing genetic testing or	1. Since the majority of clinical laboratories are CAP-accredited and QMS components are included in the CAP checklists, the QMS discussion in the MGT MMWR should also be included in the BGT document. 2. Broad benefits of implementing QMS include: a. Improved quality of products and services. b. Better management and a more effective organization. c. Improved customer service. d. Clarifies tasks, processes and procedures and reduces errors. e. Organization and processes will survive in the event of staff turn-over.

CLIA Requirements	WG Input	
	Key Points	**Clarifications**
	offering new genetic tests. 3. Laboratories can refer to professional guidelines, accreditation standards, and other standards for guidance.	