

## Summary of CLIAC Genetic Testing Workgroup Input on Good Laboratory Practices for Molecular Genetic Testing

Areas in Which Issues were Recognized	CLIA Requirements	Workgroup Input	
		Key Points	Clarifications
<p><b>Scope of Genetic Testing Good Laboratory Practices that CLIAC Should Consider; Applicability of the MMWR Document</b></p>	<p>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.)</p>	<ol style="list-style-type: none"> <li>1. It is not necessary for the Morbidity and Mortality Weekly Report (MMWR) document to define genetic tests, in light of the complexity and multitude of definitions. Instead, the document should clarify the scope and applicability of recommended good laboratory practices.</li> <li>2. CLIAC-recommended good laboratory practices for genetic testing should focus on molecular (or nucleic acid-based) testing for heritable disorders or conditions (which should explicitly include pharmacogenetic testing) first, because molecular genetic testing is the area that has the greatest immediate need for guidance for good laboratory practices.</li> <li>3. The good laboratory practice recommendations should provide guidance for laboratories performing molecular genetic testing in meeting applicable CLIA requirements and in applying additional quality assurance measures needed to their testing. The recommendations should be useful for improving the quality of molecular genetic testing in general.</li> <li>4. For tests that encompass molecular genetic testing and other areas, such as array-based comparative genomic hybridization (CGH), the recommended good laboratory practices should apply to the molecular aspects of these tests. There is a need for future documents on good laboratory practices for molecular cytogenetic testing and other areas of genetic testing (see clarifications).</li> </ol>	<ol style="list-style-type: none"> <li>1. Additional/future documents should address good laboratory practices for the following areas:               <ol style="list-style-type: none"> <li>a. Molecular cytogenetic testing</li> <li>b. Biochemical genetic testing</li> <li>c. Somatic genetic testing.</li> </ol> </li> </ol>
<p><b>Role of laboratories in providing information to users of their services</b></p>	<p>Requirements relating to providing information for patient preparation and test request include:</p> <ul style="list-style-type: none"> <li>• The laboratory must have written policies and procedures for preparation of patients (§493.1242);</li> <li>• The laboratory must have written policies for test requests (§493.1241);</li> <li>• 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)).</li> </ul>	<ol style="list-style-type: none"> <li>1. Laboratories have a responsibility to provide 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.</li> <li>2. Laboratories should provide the following information to their users:               <ol style="list-style-type: none"> <li>1) Information necessary for selecting appropriate testing -                   <ol style="list-style-type: none"> <li>a. A list of the tests performed;</li> <li>b. Intended use, to include the nucleic acid target (i.e., genes, sequences, mutations, polymorphisms, etc.); purpose of testing and appropriate use of the test; and recommended patient population(s);</li> <li>c. Indications for testing;</li> <li>d. Specifications of applicable performance characteristics;</li> </ol> </li> </ol> </li> </ol>	<ol style="list-style-type: none"> <li>1. The provision of appropriate information to the user will not only help assure selection of the appropriate test and facilitate specimen collection, handling, and submission, it will also prepare users to understand the test report.</li> <li>2. Clarification on specimen information:               <ul style="list-style-type: none"> <li>• “Amount” applies to non-liquid specimens, such as chorionic villus sampling (CVS).</li> <li>• Collection container/device may include vacutainer(s), tube(s) with specific anti-coagulant(s), specific</li> </ul> </li> </ol>

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		<ul style="list-style-type: none"> <li>e. Test methodology and testing procedures to be used, including CPT codes when appropriate;</li> <li>f. Limitations of the test;</li> <li>g. Whether testing is performed with FDA cleared or approved test systems, laboratory-developed tests, or investigational under FDA oversight.</li> </ul> <ol style="list-style-type: none"> <li>2) Information on appropriate collection, handling, and submission of samples (see also clarification #2) -               <ol style="list-style-type: none"> <li>a. Specimen type, amount/volume, and collection container/device;</li> <li>b. Specimen preparation;</li> <li>c. Specimen stability and transport conditions;</li> <li>d. Reasons for rejection of specimens.</li> </ol> </li> <li>3) Patient information required to perform the test (including, when applicable, patient consent information in compliance with federal, state, and local requirements);</li> <li>4) Availability of consultation and discussion from the laboratory;</li> <li>5) A statement indicating that test results may have implications for relatives or family members.</li> </ol> <p>3. Laboratories should ensure the information provided in this preanalytic step is consistent with information included on test reports.</p> <p>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.</p>	<p>cup(s) or tube(s) containing sterile tissue culture media, sputum collection device, etc.</p> <ul style="list-style-type: none"> <li>• Specimen preparation may include dissection for CVS, centrifugation of blood samples where applicable, etc.</li> <li>• Specimen stability information may include the timeframe beyond which the stability and integrity of a specimen or the analyte(s) to be detected in a specimen may be compromised.</li> <li>• Transportation conditions may mean room temperature, frozen, cooling on ice, etc.</li> </ul> <p>3. The Workgroup (WG) discussed whether “costs of genetic tests” should be communicated to users of their services as part of the informed decision making. The WG felt while financial implications for patients and family members should be considered in making informed decisions, it may be very difficult for laboratories or even providers to predict and accurately communicate what charges a particular patient may incur from a given test. Individual laboratories may have different fee schedules for different clients and accept fee schedules from a significant number of payers, with various deductibles, depending upon patient policy selections. Therefore the WG did not suggest “costs” be included in the information to be provided by laboratories to their users.</p>
<b>Informed consent</b>	No requirements for laboratories to document informed consent.	1. All laboratory testing should be based on <u>informed decision-making</u> . The laboratory should be responsible for providing its users with information necessary for making informed decisions, and should be available to assist in determining	1. The WG discussed the 2001 CLIA recommendations and other guidelines and recommendations regarding informed consent for

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		<p>the appropriate level of informed consent (See also clarification point #1).</p> <ol style="list-style-type: none"> <li>2. 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.</li> <li>3. For states, or tests, in which informed consent is recommended or required by law, informed consent should be included with the test request, before the test can be performed (However, the patient specimen can be stabilized until informed consent is obtained. See also Key point #5 in "Retention of specimens" section).</li> <li>4. The level and nature of the consent needed for specific tests should consider the purpose and implications of the test (see clarification point #2).</li> </ol>	<p>genetic testing, including the recommendations in the American College of Medical Genetics (ACMG) Standards and Guidelines for Clinical Genetic Laboratories and the Organisation for Economic Co-operation and Development (OECD) Guidelines for Quality Assurance in Molecular Genetic Testing. The WG suggested "informed decision making", rather than "informed consent", should be considered the "norm" of laboratory testing, including genetic testing. The WG also suggested emphasizing obtaining patient consent is not the responsibility of the laboratory.</p> <ol style="list-style-type: none"> <li>2. The WG agreed that information on costs is helpful for patients and care providers in making informed decisions on genetic testing. However, it may be not feasible for laboratories to provide this information for the same reasons as stated in the previous section "Role of laboratories in providing information to users of their services", at clarification point #3.</li> </ol>
<b>Test request</b>	<p>§493.1241(c) The test requisition must solicit the following information: 1) <u>The name and address or other suitable identifiers of the authorized person requesting the test</u> and, if appropriate, the individual responsible for using the test results; 2) <u>The patient's name or unique patient identifier</u>; 3) <u>The sex and age or date of birth of the patient</u>; 4) The test(s) to be performed; 5) <u>The source of the specimen, when appropriate</u>; 6) <u>The date and, if appropriate, time of specimen collection</u>; and 7) Any additional information relevant and necessary for a specific test to ensure accurate and</p>	<ol style="list-style-type: none"> <li>1. The following additional or more specific information (relative to CLIA requirements) should be solicited for molecular genetic test requisitions (see clarification points #1-3): <ol style="list-style-type: none"> <li>a. Patient name;</li> <li>b. Date of birth;</li> <li>c. Indication for testing and relevant clinical or laboratory information;</li> <li>d. Patient's race/ethnicity, if applicable;</li> <li>e. Family history and/or pedigree, if applicable;</li> <li>f. Appropriate International Classification of Diseases (ICD) codes or other codes indicating the diseases or conditions to be tested for;</li> <li>g. When applicable, 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.</li> </ol> </li> </ol>	<ol style="list-style-type: none"> <li>1. CLIA at §493.1241(c)(2) requires laboratories to solicit the patient's name <u>or</u> unique patient identifier on test requisitions. However, what is considered unique varies among laboratories. Considering heritable mutation testing and implications for family members, laboratories performing molecular genetic testing should solicit the patient's name as one of the unique identifiers when possible. (In situations such as compatibility testing in which donor names are not always provided to the laboratory, an alternative unique identifier should be considered</li> </ol>

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	timely testing and reporting of results, including interpretation, if applicable.	<ol style="list-style-type: none"> <li>2. The MMWR document should provide guidance (and examples as needed) for following CLIA test request requirements and the recommended additional information elements to be solicited on test requisitions.</li> <li>3. 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).</li> <li>4. 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.</li> </ol>	<p>appropriate.)</p> <ol style="list-style-type: none"> <li>2. CLIA at §493.1241(c)(3) requires test requisitions to solicit the patient's age or date of birth. For molecular genetic testing, the patient's date of birth (rather than age) was suggested by the WG as the gold standard.</li> <li>3. Key Points 1-c through g are WG-suggested clarifications to the CLIA requirement at §493.1241(c) (7), which requires test requests to solicit "any additional information relevant and necessary for a specific test to ensure accurate and timely testing and reporting of results", for requests of molecular genetic tests. The WG felt these information elements should be considered essential for test performance and result reporting for molecular genetic tests.</li> </ol>
<b>Specimen submission, handling, and referral</b>	<p>§493.1242 Standard: Specimen submission, handling, and referral</p> <p>(a) The laboratory must establish and follow written policies and procedures for each of the following, if applicable:</p> <ol style="list-style-type: none"> <li>(1) Patient preparation.</li> <li>(2) Specimen collection.</li> <li>(3) Specimen labeling, including patient name or unique patient identifier and, when appropriate, specimen source.</li> <li>(4) Specimen storage and preservation.</li> <li>(5) Conditions for specimen transportation.</li> <li>(6) Specimen processing.</li> <li>(7) Specimen acceptability and rejection.</li> <li>(8) Specimen referral.</li> </ol> <p>(b) The laboratory must document the date and time it receives a specimen.</p> <p>(c) The laboratory must refer a</p>	<ol style="list-style-type: none"> <li>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".</li> <li>2. Laboratories should have written criteria for acceptance or rejection of specimens for the molecular genetic tests they perform. Specimen acceptance and rejection criteria should include determination and handling of situations such as: <ol style="list-style-type: none"> <li>a. Improper handling or transport of the specimen;</li> <li>b. Mislabeling, use of inappropriate anticoagulants or media, specimen degradation, or inappropriate specimen type;</li> <li>c. Commingled or possibly contaminated specimens that may affect results of molecular amplification procedures;</li> <li>d. Lack of unique identifiers on the specimen or the requisition form;</li> <li>e. Lack of other information necessary to determine whether the specimen or test requested is appropriate for answering the clinical question.</li> <li>f. Specimen exposure to temperature extremes.</li> </ol> </li> </ol>	<ol style="list-style-type: none"> <li>1. Problems in specimen handling and patient identification are among major causes of misrepresentation or misidentification of a patient. This is particularly important for genetic tests, because these are often one-time tests.</li> <li>2. These good practices are important for biochemical testing as well.</li> <li>3. Information on test requisitions and test reports is particularly important for the complex communications between the genetic testing laboratories and users. However, sometimes information in test requests and test reports is stripped out during specimen submission, result reporting, and test referral, by electronic or other information systems. This problem affects all testing rather than just genetic</li> </ol>

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	<p>specimen for testing only to a CLIA-certified laboratory or a laboratory meeting equivalent requirements as determined by CMS.</p> <p>(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.</p>	<p>g. Insufficient specimen volume or amount.</p> <p>3. 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 included in the preanalytic quality assessment section.)</p>	<p>testing. Under CLIA, no information on test requisitions or on test reports should be stripped out during specimen submission, specimen referral, or result reporting; the same information should be retained throughout the process.</p>
<p><b>Individuals authorized to order genetic tests</b></p>	<p>§493.2 Definitions - An <u>authorized person</u> means an individual authorized under State law to order tests or receive results, or both.</p> <p>§493.1241 Test request</p> <p>(a) The laboratory must have a written or electronic request for patient testing from an authorized person.</p> <p>(c) The laboratory must ensure the test requisition solicits the following information:</p> <p>(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, or the name and address of the laboratory submitting the specimen, including, as applicable, a contact person to enable the reporting of imminently life threatening laboratory results or panic or alert values.</p> <p>§493.1291 Test report</p> <p>(f) Test results must be released only to authorized persons and, if applicable, the individual responsible for using the test results and the laboratory that initially requested the test.</p>	<p>1. Laboratories cannot decide who can order genetic tests, since authorized persons are defined by state laws.</p> <p>2. Laboratories should follow accepted professional guidelines and must comply with federal, state, and local requirements when deciding which genetic tests may be offered directly to consumers and the circumstances in which providing this service is considered appropriate.</p> <p>3. Laboratories should ensure that qualified personnel with appropriate experience and expertise are available to assist with test requests and result interpretation; and should follow the same guidance as the recommendations for personnel, including training, experience, and other qualifications necessary for technical supervisors and clinical consultants for laboratories performing molecular genetic testing.</p> <p>4. Suggested clarification to §493.1241 (a) requiring laboratories to accept patient test requests from authorized persons, particularly relating to direct-to-consumer (DTC) genetic testing:</p> <p>a. It is the responsibility of the laboratory initially accepting the test request (regardless whether it performs the testing on-site or refers the patient specimen(s) along with the test request to another laboratory) to verify that a test requestor is indeed an authorized individual under applicable state laws and regulations. Laboratories that receive patient specimens from multiple states (or have specimen collection sites in multiple states) should stay up-to-date with, and keep a copy of, the laws of each state regarding authorized persons, and review test requests accordingly.</p> <p>b. Referral laboratories should not (and often are not able to) be responsible for verifying whether the original test requests were submitted by authorized individuals under applicable state laws.</p>	<p>1. The "Consumer Alert" addressing direct-to-consumer genetic testing, developed by the Food and Drug Administration (FDA), the Centers for Disease Control and Prevention (CDC), and the Federal Trade Commission (FTC) in 2006, should be helpful in considering and addressing the laboratory's responsibilities for consumers in DTC genetic testing.</p>

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<b>Preanalytic systems assessment</b>	<p>§493.1249 Preanalytic systems assessment</p> <p>(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.</p> <p>(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.</p> <p>(c) The laboratory must document all preanalytic systems quality assessment activities.</p>	<ol style="list-style-type: none"> <li>1. Laboratories should have written policies and procedures for assessing, and when indicated, correcting problems identified in test requests, specimen submission, and other preanalytic steps of genetic testing. This may 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 (see clarification point #1).</li> <li>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 point #2).</li> </ol>	<ol style="list-style-type: none"> <li>1. The WG discussed whether it should be the responsibility of the laboratory to seek verification from a test requestor when the ICD-9 code does not match the test request. The WG noted that ICD-9 codes do not always directly reflect the reason for test requests, and therefore may be of limited value for verifying appropriate test selection. Thus the WG suggested a more general recommendation be made for laboratories to have procedures in place for ensuring the appropriateness of test requests, to the extent possible with available information.</li> <li>2. The WG recognized the loss (stripping-out) of information during specimen submission and test referral is a particular problem for molecular genetic testing and suggested that laboratories establish written policies and make a good-faith effort to correct this problem and prevent its recurrence.</li> </ol>
<b>Performance establishment and verification</b>	<p>§493.1253 Establishment and verification of performance specifications</p> <p>(a) <i>Applicability.</i> Laboratories are not required to verify or establish performance specifications for any test system used by the laboratory before April 24, 2003.</p> <p>(b)(1) <i>Verification of performance specifications.</i> Each laboratory that introduces an unmodified, FDA-cleared or approved test system must do the following before reporting patient test results:</p> <p>(i) Demonstrate that it can obtain performance specifications comparable to those established by the manufacturer for the</p>	<ol style="list-style-type: none"> <li>1. For performance establishment and verification of new molecular genetic tests, the following 5 steps should be recommended: <ol style="list-style-type: none"> <li>a. Ensure a review is conducted of available scientific studies and pertinent references;</li> <li>b. Select appropriate test methodology for the disease or condition being evaluated;</li> <li>c. Establish or verify the analytical performance and determine applicable quality control parameters for the genetic test;</li> <li>d. Define appropriate patient populations for which the test should be performed;</li> <li>e. Ensure test results and their implications can be interpreted for a given individual or family, and the limitations of the test are defined and reported.</li> </ol> </li> <li>2. The number of positive and negative samples that should be included in performance establishment and verification</li> </ol>	<ol style="list-style-type: none"> <li>1. CLIA does not specifically require laboratories to establish or verify clinical validity of the tests they introduce to patient testing; however, good laboratory practices should go beyond CLIA in this instance. Healthcare professionals need information on clinical validity to be able to select appropriate tests and interpret test results for patient care, especially for one-time tests such as molecular genetic tests. Therefore, laboratories performing molecular genetic testing should ensure that the tests they perform are clinically usable and interpretable for specific patient situations. It should be considered essential that</li> </ol>

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	<p>following performance characteristics:</p> <p>(A) Accuracy.</p> <p>(B) Precision.</p> <p>(C) Reportable range of test results for the test system.</p> <p>(ii) Verify that the manufacturer's reference intervals (normal values) are appropriate for the laboratory's patient population.</p> <p>(2) <i>Establishment of performance specifications.</i> 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, as applicable:</p> <p>(i) Accuracy.</p> <p>(ii) Precision.</p> <p>(iii) Analytical sensitivity.</p> <p>(iv) Analytical specificity to include interfering substances.</p> <p>(v) Reportable range of test results for the test system.</p> <p>(vi) Reference intervals (normal values).</p> <p>(vii) Any other performance characteristic required for test performance.</p> <p>(3) <i>Determination of calibration and control procedures.</i> The laboratory must determine the test system's calibration procedures and control</p>	<p>should depend on the assay being established or verified, the prevalence of the mutation or variant, and the prevalence of the disease. (Note: This point is not intended to set a low bar for rare disease testing; but to clarify that method validation 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.)</p> <p>3. Laboratories should determine specifications of the following performance characteristics for new molecular genetic tests to be introduced to patient testing:</p> <ol style="list-style-type: none"> <li>Accuracy</li> <li>Precision</li> <li>Analytical sensitivity</li> <li>Analytical specificity</li> <li>Reportable range of test results for the test system</li> <li>Reference range or normal values</li> <li>Other performance characteristic required for test performance. For example, robustness and lowest limit of detection (LOD), when necessary as part of performance specifications and if defined separately (or differently) from analytical sensitivity.</li> </ol> <p>4. In establishing or verifying test performance, laboratories should review and follow professional guidelines applicable and appropriate for the testing to be introduced and ensure the professional guidance is followed consistently through method validation and subsequent patient testing.</p> <p>5. When a laboratory verifies or establishes performance specifications of a multiplex genetic test using targeted detection methods, the laboratory should <u>ideally</u> include all the mutations or variants to be detected in the performance verification or establishment.</p> <p>6. Laboratory's responsibility for clinical validity should include (see also clarification point #1):</p> <ol style="list-style-type: none"> <li>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;</li> <li>Inclusion of the clinical validity information as part of the information the laboratory provides to its users;</li> </ol>	<p>laboratories document clinical validity information that is available.</p>

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	<p>procedures based upon the performance specifications verified or established under paragraph (b)(1) or (b)(2) of this section.</p> <p>(c) <i>Documentation</i>. The laboratory must document all activities specified in this section.</p>	<p>c. Establishment of clinical sensitivity, clinical specificity, and predictive values based on internal study results, if information regarding clinical validity is not available from published references;</p> <p>d. “Truth in advertising”, which means documenting whether the clinical claims in the literature could be reproduced in the laboratory, indicating test limitations in all test reports, and informing users of changes in clinical validity values as a result of knowledge advancement.</p> <p>e. 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.</p>	
<b>Control procedures</b>	<p>§493.1256 Standard: Control procedures</p> <p>(a) For each test system, the laboratory is responsible for having control procedures that monitor the accuracy and precision of the complete analytical process.</p> <p>(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).</p> <p>(c) The control procedures must--</p> <p>(1) Detect immediate errors that occur due to test system failure, adverse environmental conditions, and operator performance.</p> <p>(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.</p> <p>(d)(3) At least once each day patient specimens are assayed or examined perform the following for--</p> <p>(i) Each quantitative procedure, include two control materials of different concentrations;</p>	<ol style="list-style-type: none"> <li>Laboratories should have appropriate control procedures in place to monitor and ensure the quality of the entire genetic testing process.</li> <li>Molecular genetic tests are often performed to determine the presence or absence of normal variants, mutations, polymorphisms or allelic variants. A molecular genetic test that has a nucleic acid extraction step should include an extraction control for monitoring this step to help determine the quality and integrity of the specimens, assure the yield of nucleic acid extraction is appropriate for the testing, and detect the presence of inhibitors.</li> <li>Laboratories should validate sampling instruments to ensure there is no carryover between samples on automated instruments. As an example, “checker-board” experiments in which samples containing nucleic acid are interspaced with samples with no template nucleic acid may be considered a good option for detecting carryover.</li> <li>Control procedures should be performed with each run of patient testing rather than once each day patient testing is performed. Controls should be selected based on patient population and should be as comprehensive as possible, based on the prevalence of the disease and the mutation or variant. For example, a heterozygous sample or a normal and a homozygous mutant sample may be considered sufficient for single mutation assays. Cases of rare variants should be verified by bidirectional sequencing or repeat testing of the sample.</li> <li>Ideally, laboratories should use control materials that can monitor the entire testing process, but these control materials</li> </ol>	<ol style="list-style-type: none"> <li>Many of the quality control materials that are currently used are not real full process samples. They are purified DNA that do not provide quality control for the sample preparation step of the testing process.</li> <li>Extraction controls are required by CLIA, but they are often difficult to incorporate into many genetic tests, for example qualitative target mutation testing.</li> <li>Alternative control procedures for the extraction phase should address situations such as rare disease and very rare mutations or variants.</li> <li>Most DNA extraction procedures are now done by an automated system, which has different needs for quality control than manual systems. For example, the positions (or locations) of control matters are important, and require different considerations depending on whether they are used in an automated system or a manual test system.</li> </ol>

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	<p>(ii) Each qualitative procedure, include a negative and positive control material;</p> <p>(iii) Test procedures producing graded or titered results, include a negative control material and a control material with graded or titered reactivity, respectively;</p> <p>(iv) Each test system that has an extraction phase, include two control materials, including one that is capable of detecting errors in the extraction process; and</p> <p>(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.</p> <p>(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.</p>	<p>are not always practical or available. Appropriate alternative control procedures should depend on the specific test and control materials needed. For example -</p> <p>a. For targeted mutation detection: If the positive control material for the specific mutation is not available, alternative control procedures may include direct sequencing, or having the patient sample tested by a reference laboratory to confirm the finding before releasing the result.</p> <p>b. For sequencing: It is important to include a normal control which could be a tested patient sample that has been well characterized to contain the reference sequence, or subcloned sequence segments. If a positive control is not available, alternative control procedures may include bidirectional sequencing, using a separately extracted nucleic acid sample if possible.</p> <p>c. For tests detecting multiple mutations or variants: When it is not practical to include positive controls for each variant or mutation, it is important to rotate all positive controls in a reasonable timeframe. The rotation of control materials is applicable to commercial test systems that provide some of the positive controls needed for testing by rotating positive controls in addition to the control materials provided with the kit.</p> <p>6. The above QC recommendations should be considered both in method validation and patient testing.</p>	
<p><b>Unidirectional workflow and monitoring of molecular amplification procedures</b></p>	<p>§493.1101 (a) The laboratory must be constructed, arranged, and maintained to ensure the following:</p> <p>(2) Contamination of patient specimens, equipment, instruments, reagents, materials, and supplies is minimized.</p> <p>(3) Molecular amplification procedures that are not contained in closed systems have a uni-directional workflow. This must include separate areas for specimen preparation, amplification and product detection, and, as applicable, reagent preparation.</p>	<p>1. Laboratories performing molecular genetic testing must have procedures that monitor and minimize cross-contamination in the testing process, which should include a unidirectional workflow and control samples capable of detecting carry-over contamination, such as a no-template control (NTC), for any test system that is not fully closed.</p> <p>2. For amplification procedures that are not fully closed, at least one NTC must be included each time patient samples are assayed. The NTC should be included at least in the amplification step and carried through the subsequent step(s) detecting test results. It is also good practices to include an extraction blank that goes through the extraction step in addition to the NTC sample for the amplification. If multiple units, such as multiple 96-well plates, are utilized in a run of patient specimen testing, an NTC sample should be included in each unit of the test run if the test system allows it.</p> <p>3. For amplification procedures that are not fully closed,</p>	<p>1. Examples of closed systems provided include specific FDA-cleared or approved test systems that contain amplification and detection steps in sealed tubes that are never opened or re-opened during or after the testing process, and test platforms using particular technology or methodology that need to be used as provided by the manufacturer without user modifications and input. For the purpose of meeting the CLIA requirement at §493.1101 (a)(3), a closed system may be described as a test system designed to be fully integrated and automated to purify, concentrate, amplify, detect and</p>

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		<p>laboratories should determine the order of samples, including the number and positions of the control samples, such as the NTC samples, in order to adequately monitor carryover contamination. The number and positions of NTC samples in each of the multiple units may also be used for unambiguous identification of each unit.</p> <p>4. The WG recognized there are different definitions for closed and not fully closed systems, and provided examples to help laboratories determine appropriate workflow arrangements and QC procedures needed to ensure the quality of their testing (See clarification point #1).</p> <p>5. For nested PCR, if after any amplification procedure the tube is opened for subsequent manipulation with the amplicon(s), the laboratory needs to have specific procedures to ensure unidirectional workflow and prevent cross-contamination.</p> <p>6. Laboratories preparing their own quality control materials through the use of amplification, such as PCR amplification, whole genome amplification (WGA), or subcloning, should recognize that this is a significant potential source of laboratory contamination and have the following specific procedures to monitor, detect, and prevent cross-contamination from this source:</p> <p>a. The workflow of generating synthetic or amplified products for use as control materials should be separated from the patient testing process. The control materials should be prepared and processed in a well-controlled environment to prevent contamination of the laboratory.</p> <p>b. Appropriate control samples should be tested to monitor cross-contamination.</p> <p>c. These practices should also be considered by laboratories that purchase amplified materials and use them as control materials or competitors.</p>	<p>identify targeted nucleic acid sequences. Such a modular system thereby generates test results directly from unprocessed samples without manipulation or handling by the user, and because the tube containing amplicons is sealed and never re-opened, does not pose risks of cross-contamination.</p>
<b>Proficiency testing (PT) and alternatives</b>	<p>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.</p> <p>§493.801(b) Standard; Testing of proficiency testing samples. The laboratory must examine or test, as applicable, the proficiency testing</p>	<p>1. PT should be a requirement for all genetic tests for which a PT program is available (see clarification point #1).</p> <p>2. The frequency of PT should be at a minimum twice per year.</p> <p>3. PT providers and users should be encouraged to support 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 (see clarification point #2).</p>	<p>1. Currently PT is available for most high-volume molecular genetic tests.</p> <p>2. Many PT challenges are provided currently using genomic DNA, thus not requiring participants to perform the entire testing process. Such practical limitations should be recognized in assessing test performance.</p>

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	<p>samples it receives from the proficiency testing program in the same manner as it tests patient specimens.</p> <p>(1) <u>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.</u> 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.</p> <p>(2) The laboratory must test samples the same number of times that it routinely tests patient samples.</p>	<p>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 molecular genetic test is included on the current list of regulated analytes).</p> <p>5. Laboratories should evaluate their PT results and perform an investigation and corrective action for disparate results (See clarification point #3).</p> <p>6. 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 (See clarification point #4).</p> <p>7. Methodology-based PT may be useful for quality assurance for molecular genetic testing. Appropriate methodology-based PT programs should be explored to supplement disease-specific PT programs.</p> <p>a. Methodology-based PT should take into consideration sample type and variables of the testing process.</p> <p>b. Data should be collected and evaluated on the use of methodology-based PT for quality assurance in molecular genetic testing.</p> <p>c. Examples of methodology-based PT programs include cytogenetics, FISH assays, and sequencing.</p> <p>8. Alternative performance assessment should be performed at least twice per year, for molecular genetic tests for which no PT program is available, in meeting the applicable requirements of CLIA, state programs, and accrediting agencies (See clarification point #5).</p> <p>a. While data is currently unavailable on whether alternative performance assessments are as robust or effective as PT, professional guidelines, such as those developed by the Clinical and Laboratory Standards Institute (CLSI) and the College of American Pathologists (CAP), provide guidance on what would be considered acceptable alternative performance assessment approaches.</p> <p>b. Alternative assessment should ideally be performed by inter-laboratory exchange or using externally derived materials (See clarification point #6).</p> <p>c. In circumstances when inter-laboratory exchange or</p>	<p>3. The corrective action that should be taken after disparate PT results should include re-evaluation of previous patient test results and, if necessary, retained previously tested patient specimens.</p> <p>4. The PT/EQA and inter-laboratory exchange resources include the efforts supported by CAP, the Association for Molecular Pathology (AMP) (as summarized in a report of the Secretary's Advisory Committee on Genetics, Health, and Society), EuroGenTest, and other sources. The MMWR will include this list of resources.</p> <p>5. For rare diseases and genetic tests that are performed by a single laboratory or only a few laboratories, PT programs may be unavailable or not feasible.</p> <p>6. External quality assessment may be able to detect errors or problems that internal assessment may not.</p>

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		externally derived materials are not practical or feasible, such as testing for rare diseases, testing performed by only one laboratory, unstable analytes (e.g., RNA, 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.	
<b>Test report</b>	<p>§493.1291(c) The test report must indicate the following:</p> <p>(1) For positive patient identification, either <u>the patient's name</u> and identification number, or a unique patient identifier and identification number.</p> <p>(2) <u>The name and address of the laboratory location where the test was performed.</u></p> <p>(3) <u>The test report date.</u></p> <p>(4) <u>The test performed.</u></p> <p>(5) Specimen source, when appropriate.</p> <p>(6) <u>The test result and, if applicable, the units of measurement or interpretation, or both.</u></p> <p>(7) Any information regarding the condition and disposition of specimens that do not meet the laboratory's criteria for acceptability.</p> <p>(d) Pertinent ``reference intervals" or ``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.</p> <p>(e) <u>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 Sec. 493.1253.</u> In addition, information that may affect the interpretation of test results, for</p>	<p><u>1. Content of genetic test reports:</u> The following additional elements (in addition to CLIA requirements at §493.1291(c)) should be included on genetic test reports:</p> <ol style="list-style-type: none"> <li>a. Patient's name;</li> <li>b. Patient's date of birth;</li> <li>c. Indication for testing;</li> <li>d. The date and, if appropriate, time of specimen collection and arrival in the laboratory;</li> <li>e. Name of the referring physician or authorized individual who ordered the test;</li> <li>f. Test method, including the nucleic acid target(s) the test intended to detect;</li> <li>g. Performance specifications and limitations of the test (see clarification points #1 and #2);</li> <li>h. Test results in current recommended standard nomenclature, which should: <ol style="list-style-type: none"> <li>1) Include clarifications and commonly used terms if different from the current/recommended (see clarification #3),</li> <li>2) Indicate genotype found or detected, and</li> <li>3) If no mutation is detected, indicate as such, rather than reporting a "normal" status.</li> </ol> </li> <li>i. Result interpretation (see clarification #4);</li> <li>j. References to the literature if applicable;</li> <li>k. Recommendation for consultation with a genetics professional, when appropriate and indicated (see clarification #5);</li> <li>l. When appropriate, implications of test results for relatives or family members who may benefit from the information;</li> <li>m. For any in-house developed test using any analyte-specific reagent (ASR), the statement required by 21 CFR 809.30(e): "This test was developed and its performance characteristics determined by (Laboratory Name). It has not been cleared or approved by the U.S. Food and Drug Administration" (see clarification #6);</li> </ol>	<ol style="list-style-type: none"> <li>1. CLIA requires laboratories to, <u>upon request</u>, provide a list of tests they performed to the clients, as well as the required performance specifications. For genetic tests, this information should not be "available on request" only, but should be part of the report.</li> <li>2. The test report should include limitations of the test, such as a statement on the intended use and the technical limitation on the test methodology (e.g., targeted mutation detection or DNA sequence analysis).</li> <li><u>3. Clarifications on nomenclature issues:</u> <ol style="list-style-type: none"> <li>a. The nomenclature in molecular genetics is evolving. New standardized nomenclature may not initially be familiar to laboratories or users of laboratory services.</li> <li>b. Certain genetic variants or diseases, such as CYP genes and the hemoglobinopathies, may be associated with multiple versions of nomenclature. Laboratories may need to report all versions to ensure test results are understandable throughout the medical community.</li> <li>c. Nomenclature should be easy to use and can be communicated and</li> </ol> </li> </ol>

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	<p>example test interferences, must be provided upon request. <u>Pertinent updates on testing information must be provided to clients whenever changes occur that affect the test results or interpretation of test results.</u></p> <p>§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.</p> <p><u>Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services</u> provide guidance for meeting the test report requirements, including:</p> <ul style="list-style-type: none"> <li>• Interpretive Guidelines for §493.1291(c) - For genetic tests, laboratories should include the test method(s) employed and any mutations on test reports.</li> <li>• 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.</li> </ul>	<p>n. A statement indicating that the result and interpretation given is based on current knowledge and technology.</p> <p><u>2. Suggested clarification to §493.1291(d)</u></p> <ol style="list-style-type: none"> <li>The "normal values" may be clarified or interpreted for molecular genetic tests as normal alleles.</li> <li>For sequencing assays, normal values should be the reference sequence(s).</li> <li>What is considered normal is subject to the test technology and knowledge advancement.</li> </ol> <p><u>3. Suggested clarification to §493.1291(e).</u> The WG recognized the applicability of the CLIA requirements, which specifies "Pertinent updates on testing information must be provided to clients whenever changes occur that affect the test results or interpretation of test results", to the rapidly evolving field of molecular genetic testing. The WG suggested this CLIA requirement be clarified for molecular genetic testing as the following:</p> <ol style="list-style-type: none"> <li>Laboratories should keep an up-to-date database for the molecular genetic tests they perform, and provide updates to users when knowledge advancement affects the performance specifications and/or interpretation of test results.</li> <li>Considering molecular genetic tests for heritable conditions (or germline mutations or variants) are often one-time tests and test results may have life-time implications for patients and family members, if the interpretation of the original analytic result changes due to advances in knowledge or technology, the laboratory is obligated to issue a revised report. Indications for providing updates or revised reports should include: <ol style="list-style-type: none"> <li>1) When a better interpretation is available on a variant found, or</li> <li>2) When knowledge advancement changes the interpretation of previous results (e.g., a previously determined mutation is now recognized as a polymorphism, or vice versa) (see clarification point #7).</li> </ol> </li> </ol> <p><u>4. Signature on test report</u></p> <ol style="list-style-type: none"> <li>Ideally, molecular genetic test reports should be reviewed and signed out by trained qualified personnel before release. The individuals who should sign the</li> </ol>	<p>understood.</p> <p>d. Heritable mutation or genetic variant testing are considered one-time tests and do not necessarily need to be repeated just because the nomenclature has changed over time.</p> <p><u>4. Interpretation of test results:</u></p> <ol style="list-style-type: none"> <li>Should be provided for all genetic test reports.</li> <li>Should be linked to the reason that the test was ordered, and communicated in a clinically relevant manner.</li> <li>Should explain how technical limitations impact the clinical use of the test results for the person receiving the report.</li> <li>When appropriate and necessary, may indicate the test results in reference to information on family members, for example information regarding mutation(s) previously detected in a relative that was used for selection of the test method, to assure appropriate interpretation of the test results and understanding of their implications.</li> </ol> <p><u>5. Genetic consultation</u></p> <ol style="list-style-type: none"> <li>The WG considered 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.</li> <li>Providing information regarding the need for genetic consultation can also be an educational</li> </ol>

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		<p>test reports should be linked to personnel competency and responsibilities.</p> <p>b. Some WG members pointed out it may not be practical for all genetics test reports to include signatures.</p> <p><u>5. Report format, style, and language.</u></p> <p>a. Laboratories should assess the needs of the users in determining the media, format, style, and language of test reports. This practice should be part of the laboratory's QMS policies (see clarification point #8).</p> <p>b. Reports should be informative with all necessary information included, should be easy to understand, and should be effective in ensuring that users read the entire report, rather than just positive and negative indications.</p>	<p>initiative, to improve understanding of genetic tests in the medical community.</p> <p>6. 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.</p> <p>7. The WG was in agreement in supporting Key point #3-a, noting that this suggestion is consistent with the Interpretive Guidelines for the CLIA requirement at §493.1291(e). Some WG members disagreed with #3-b, considering the potential burden on laboratories and the difficulty to re-contact clients.</p> <p><u>8. Report format and style</u></p> <p>a. Information elements on test reports may be divided into essential or minimum information and additional information elements as appropriate, as recommended by the OECD guidelines for molecular genetic testing.</p> <p>b. 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.</p>
<b>Retention of records and reports</b>	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,	<p>1. For QC, PT, and other laboratory records, the CLIA-required 2-year minimum retention timeframe is adequate for molecular genetic testing.</p> <p>2. Genetic test reports should be retained for the longest possible timeframe, ideally for at least one generation</p>	<p>1. Information on genetic test report should be kept available as long as possible because future generations may need the information.</p> <p>2. The financial impact of the suggested</p>

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	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.	<p>(usually referred to as 20 years) (see clarification point #1).</p> <ol style="list-style-type: none"> <li>3. Retention policies and procedures should comply with applicable state laws and other requirements, such as those by accrediting organizations.</li> <li>4. Laboratories should ensure that electronic records and reports are accessible while the technology of electronic storage evolves.</li> </ol>	longer (than required by CLIA) retention timeframe for genetic test reports should be considered, as well as technology and space issues.
<b>Retention of specimens</b>	§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.	<ol style="list-style-type: none"> <li>1. Specimens should be retained for the longest possible timeframe as permitted by technology, space, and cost.</li> <li>2. At a minimum, tested patient specimens should be retained until the next PT event or alternative performance assessment, to allow for identification of any problems in patient testing and for corrective actions to be taken.</li> <li>3. The laboratory's specimen retention policy should consider the following: <ol style="list-style-type: none"> <li>a. The type of specimens to be retained (e.g., Blood or DNA);</li> <li>b. The analyte(s) tested (DNA or RNA);</li> <li>c. Test results of the specimens (genotype) may be considered, with the understanding that if only abnormal samples are retained, it would be difficult to identify false negatives later and there may be a bias using them in performance verification or establishment;</li> <li>d. Test volume (e.g., high-volume CF carrier testing and pharmacogenetic testing);</li> <li>e. New technologies that may not produce residual specimens.</li> </ol> </li> <li>4. The laboratory director should be responsible for ensuring the laboratory has and follows policies and procedures for specimen retention that are consistent with the laboratory's quality assessment activities, in compliance with applicable federal, state, and local laws and requirements, including requirements for laboratory accreditation.</li> <li>5. In circumstances where patient consent is required but is not included or does not come with the test request, the laboratory should determine the need to notify the test requestor regarding the informed consent requirement and the timeframe after which the test request may be rejected and specimen discarded due to specimen degradation or deterioration.</li> </ol>	<ol style="list-style-type: none"> <li>1. For genetic tests for heritable mutations, patient specimens should be retained as long as possible because they may be needed for testing of additional or future family members, and for more definitive diagnosis as technology and knowledge evolve.</li> </ol>

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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.	<ol style="list-style-type: none"> <li>1. 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.</li> <li>2. 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.</li> <li>3. Electronic records should be under proper access control to ensure patient confidentiality.</li> <li>4. The WG 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. The WG suggested 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 compliance with CLIA requirements and other applicable federal and state regulations.</li> <li>5. The WG made the following suggestions 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): <ol style="list-style-type: none"> <li>a. The requests should be handled in the same manner as requests for other protected patient information. Laboratory should release information only to ordering physicians or physicians cooperating in the care of the patient who was tested.</li> </ol> </li> </ol>	<p>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&amp;A below from the HHS Office of Civil Rights. Concerns about privacy and good medical care are occasionally in conflict in molecular genetics.</p> <p><b>HIPAA Frequent Questions:</b> - Does the HIPAA Privacy Rule permit doctors, nurses, and other health care providers to share patient health information for treatment purposes without the patient's authorization?</p> <p><b>HHS Answer:</b> Yes. The Privacy Rule allows those doctors, nurses, hospitals, laboratory technicians, and other health care providers that are covered entities to use or disclose protected health information, such as X-rays, laboratory and pathology reports, diagnoses, and other medical information for treatment purposes without the patient's authorization. This includes sharing the information to consult with other providers, including providers who are not covered entities, to treat a different patient, or to refer the patient. See 45 CFR 164.506.</p>

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		<p>b. Even though the HIPAA Privacy Rule permits the communication of patient information between healthcare providers for patient care purposes (see HHS Answer to HIPAA Frequent Questions in the clarification column), 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 to do it.</p> <p>c. When patient consent is required for the testing, the consent form should address situations in which test results may be requested by physicians caring for the patient's relatives, and should allow the patient to make decision on whether to authorize such release. Some WG members disagreed with this suggestion, noting that it may be difficult to implement in practice, and considered the issue already covered by Key point #5-b.</p> <p>d. 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.</p>	
<b>Laboratory Director Qualifications</b>	<p>§493.1443 Laboratory director qualifications (for high complexity testing; abbreviated)</p> <ul style="list-style-type: none"> <li>• Be an M.D. or D.O. certified in clinical and/or anatomic pathology;</li> <li>• 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;</li> <li>• 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</li> <li>• Be grandfathered.</li> </ul>	The current CLIA requirements for the qualifications of directors of laboratories performing high complexity testing are adequate for molecular genetic testing.	
<b>Laboratory Director Responsibilities</b>	<p>§493.1445 Laboratory director responsibilities. (Abbreviated) The laboratory director's responsibilities include -</p> <ul style="list-style-type: none"> <li>• Ensure each test performed in the laboratory provide quality laboratory services for all aspects of test performance;</li> </ul>	<p>1. ALL CLIA responsibility requirements for laboratory directors of high complexity testing apply to molecular genetic testing. In addition, laboratory directors should have the authority for ensuring laboratory testing quality and compliance with all applicable requirements for laboratory operation.</p> <p>2. For molecular genetic testing, laboratory directors should</p>	

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	<ul style="list-style-type: none"> <li>• Ensure physical and environmental conditions of the laboratory are appropriate and safe;</li> <li>• Ensure the test methodologies selected have the capability of providing the quality of results required for patient care;</li> <li>• Ensure adequate performance verification;</li> <li>• Ensure the quality of test performance;</li> <li>• Ensure enrollment in an HHS-approved proficiency testing program;</li> <li>• Ensure quality control and quality assessment programs are established and maintained;</li> <li>• Ensure establishment and maintenance of acceptable levels of analytical performance for each test system;</li> <li>• Ensure all necessary remedial actions are taken and documented and patient test results are reported only when the system is functioning properly;</li> <li>• Ensure test reports include pertinent information required for interpretation;</li> <li>• Ensure consultation is available to the laboratory's clients on the quality of test results and their interpretation;</li> <li>• Ensure on-site supervision of high complexity testing by a general supervisor;</li> <li>• 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,;</li> <li>• Ensure that policies and procedures are established for monitoring personnel competency and for identifying needs for remedial training or continuing education;</li> <li>• Ensure an approved procedure manual is available to all laboratory personnel;</li> <li>• Specify in writing the responsibilities and duties of each consultant, supervisor, and testing personnel.</li> </ul>	<p>have the following additional responsibilities:</p> <ol style="list-style-type: none"> <li>a. Ensuring the documentation of clinical validity of any molecular genetic test their laboratories offer.</li> <li>b. Ensuring specimen retention policy is consistent with the laboratory's quality assessment activities.</li> </ol>	
<b>Technical Supervisor Qualifications</b>	<p>§493.1449(p) Technical supervisor qualifications for clinical cytogenetics (abbreviated)</p> <ul style="list-style-type: none"> <li>• Be an M.D., D.O. or D.P.M.; and</li> </ul>	<ol style="list-style-type: none"> <li>1. The WG did not reach agreement on qualifications of technical supervisors for molecular genetic testing and was divided into the following opinions: <ol style="list-style-type: none"> <li>a. Preferably and ideally, technical supervisors for</li> </ol> </li> </ol>	<ol style="list-style-type: none"> <li>1. Individuals certified by ABMG after 1993 are required to participate in EMOC to maintain their certifications current or valid.</li> </ol>

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	<p>have four years of training or experience in genetics, two of which have been in clinical cytogenetics; or</p> <ul style="list-style-type: none"> <li>• 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.</li> </ul>	<p>molecular genetic testing should have the following qualifications:</p> <ol style="list-style-type: none"> <li>1) 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 molecular genetic testing for heritable conditions; or</li> <li>2) Have current certification in molecular genetic testing by HHS-approved boards, such as certifications by the American Board of Medical Genetics (ABMG) and the Molecular Genetic Pathology certification jointly administered by ABMG and the American Board of Pathology (See clarification point #1).</li> </ol> <p>b. A tiered system was suggested for technical supervisor qualifications for molecular genetic testing, based on the complexity of the tests and conditions being evaluated. However, the WG later concluded such a tiered system will not be possible in recognition that, despite repeated attempts by multiple groups since 1997, no practical approach has been accepted (See clarification point #2).</p> <p>c. Recognizing the ideal qualifications as suggested at Key point 1-a-1) could restrict access to simple molecular genetic tests and molecular genetic testing is not a specialty (or subspecialty) under CLIA, some WG members suggested the CLIA qualification requirements for technical supervisors of high complexity testing in current specialties and subspecialties are sufficient for molecular genetic testing.</p> <p>2. The considerations for technical supervisor qualifications in Key point #1 are for high complexity molecular genetic testing. If FDA-approved or cleared moderate complexity molecular genetic tests are available in the future, the WG would expect that the CLIA personnel requirements for moderate complexity testing would apply.</p> <p>3. Technical supervisor qualifications for tests that have molecular genetic components, such as array CGH and fluorescence <i>in situ</i> hybridization (FISH), should be addressed in another document suggested by the WG to provide good laboratory practice recommendations in these areas of testing.</p>	<p>2. The WG made a good-faith effort to explore the suggested tiered system approach, which was aimed at differentiating “low difficulty” molecular genetic tests for which the CLIA qualification requirements for technical supervisors of high complexity testing would be sufficient, from the “high difficulty” testing that would need higher qualifications such as specialized training, experience, and certification in molecular genetic testing. However, the WG could not identify a practical model for this approach.</p>
<b>Technical Supervisor Responsibilities</b>	<p>§493.1451 Technical supervisor responsibilities (High complexity testing) The technical supervisor is responsible for the technical and scientific oversight of the</p>	<p>1. The CLIA responsibility requirements for technical supervisors of high complexity testing are appropriate for molecular genetic testing.</p>	<p>The WG felt the technical supervisors might be the laboratory personnel with in-depth knowledge of the performance</p>

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	<p>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.</p> <p>(a) The technical supervisor must be accessible to the laboratory to provide on-site, telephone, or electronic consultation; and</p> <p>(b) The technical supervisor is responsible for--</p> <p>(1) Selection of the test methodology that is appropriate for the clinical use of the test results;</p> <p>(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;</p> <p>(3) Enrollment and participation in an HHS approved proficiency testing program commensurate with the services offered;</p> <p>(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;</p> <p>(5) Resolving technical problems and ensuring that remedial actions are taken whenever test systems deviate from the laboratory's established performance specifications;</p> <p>(6) Ensuring that patient test results are not reported until all corrective actions have been taken and the test system is functioning properly;</p> <p>(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;</p> <p>(8) Evaluating the competency of all testing</p>	<p>2. In addition, when determined by the laboratory director, technical supervisors for molecular genetic testing should have the following additional responsibilities:</p> <p>a. Assess the suitability of any particular test for a particular use.</p> <p>b. Ensure appropriate documentation of clinical validity information on the genetic tests their laboratories perform.</p> <p>c. Review test results and the interpretation.</p> <p>d. Review and/or sign test reports.</p> <p>e. Be available to answer questions about the test report.</p> <p>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, the WG felt certain on-site time in the laboratory should be stipulated for technical supervisors of molecular genetic testing, based on the complexity of the tests performed in the laboratory.</p>	<p>and clinical use of the molecular genetic tests their laboratories perform, so they should take an active role in ensuring the tests requested are appropriate for the clinical expectations and the test reports include appropriate interpretation.</p>

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	<p>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 are not limited to—</p> <ul style="list-style-type: none"> <li>(i) Direct observations of routine patient test performance, including patient preparation, if applicable, specimen handling, processing and testing.</li> <li>(ii) Monitoring the recording and reporting of test results.</li> <li>(iii) Review of intermediate test results or worksheets, quality control records, proficiency testing results, and preventive maintenance records</li> <li>(iv) Direct observation of performance of instrument maintenance and function checks;</li> <li>(v) Assessment of test performance through testing previously analyzed specimens, internal blind testing samples, external proficiency testing samples; and</li> <li>(vi) Assessment of problem solving skills.</li> </ul> <p>(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.</p>		
<b>Clinical Consultant Qualifications</b>	<p>§493.1455 Clinical consultant qualifications (abbreviated)</p> <ul style="list-style-type: none"> <li>• 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</li> <li>• Be a doctor of medicine, doctor of osteopathy, doctor of podiatric medicine licensed to practice</li> </ul>	<ol style="list-style-type: none"> <li>1. The CLIA requirements for clinical consultant qualifications for high complexity testing are minimum qualifications. For molecular genetic testing for heritable conditions, clinical consultants should have relevant training and/or experience in the testing for which they provide clinical consultation.</li> <li>2. Preferably, clinical consultants for molecular genetic testing should have the following qualifications: <ol style="list-style-type: none"> <li>a. Be an M.D., or D.O., and have two years experience in genetic testing; or</li> </ol> </li> </ol>	

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	medicine, osteopathy, or podiatry in the state in which the laboratory is located.	<p>b. Hold a Ph.D. in a relevant discipline, be board-certified, and have two years experience in genetic testing.</p> <p>3. While genetic counselors at the master-degree level are not qualified as clinical consultants under CLIA, they have an important role and perform important functions in the provision of laboratory services in molecular genetic testing.</p>	
<b>Clinical Consultant Responsibilities</b>	<p>§493.1457 Standard; Clinical consultant responsibilities</p> <p>The clinical consultant provides consultation regarding the appropriateness of the testing ordered and interpretation of test results. The clinical consultant must -</p> <p>(a) Be available to provide consultation to the laboratory's clients;</p> <p>(b) Be available to assist the laboratory's clients in ensuring that appropriate tests are ordered to meet the clinical expectations;</p> <p>(c) Ensure that reports of test results include pertinent information required for specific patient interpretation; and</p> <p>(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.</p>	The CLIA requirements for clinical consultant responsibilities are adequate for molecular genetic testing.	
<b>General supervisor qualifications and responsibilities</b>	<p>§493.1461 General supervisor qualifications (high complexity testing; abbreviated)</p> <ul style="list-style-type: none"> <li>• Be qualified as a laboratory director or technical supervisor;</li> <li>• Be an M.D., D.O., D.P.M.;</li> <li>• 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;</li> <li>• 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</li> <li>• Be grandfathered.</li> </ul> <p>§493.1463 General supervisor responsibilities (high complexity testing; abbreviated)</p> <p>Responsibilities of the general supervisor</p>	<p>1. The CLIA general supervisor qualification requirements for high complexity testing are adequate for molecular genetic testing, but the training or experience should be specifically in high complexity molecular genetic testing.</p> <p>2. The CLIA general supervisor responsibility requirements for high complexity testing are adequate for molecular genetic testing.</p>	

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	<p>include:</p> <ul style="list-style-type: none"> <li>• Be accessible to testing personnel at all times testing is performed;</li> <li>• Provide day-to-day supervision of high complexity testing</li> <li>• Be onsite to provide direct supervision when high complexity testing is performed by any grandfathered individual;</li> <li>• Monitor test analyses and specimen examinations to ensure that acceptable levels of analytic performance are maintained.</li> <li>• The laboratory director or technical supervisor may delegate to the general supervisor the responsibility for -- <ul style="list-style-type: none"> <li>○ Assuring that all remedial actions are taken whenever test systems deviate from the laboratory's established performance specifications;</li> <li>○ Ensuring that patient test results are not reported until all corrective actions have been taken and the test system is properly functioning;</li> <li>○ Providing orientation to all testing personnel;</li> <li>○ Annually evaluating and documenting the performance of all testing personnel.</li> </ul> </li> </ul>		
<p><b>Testing personnel qualifications and responsibilities</b></p>	<p>§493.1489 Testing personnel qualifications (abbreviated)</p> <ul style="list-style-type: none"> <li>• Be a MD, DO, or DPM;</li> <li>• 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;</li> <li>• Have earned an associate degree in a laboratory science, or medical laboratory technology from an accredited institution; or</li> <li>• Be grandfathered.</li> </ul> <p>§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,</p>	<ol style="list-style-type: none"> <li>1. The CLIA testing personnel qualification requirements for high complexity testing are adequate for molecular genetic tests, but the training or experience should be specifically in molecular genetic testing. Testing personnel who do not have adequate training/experience in molecular genetic testing should go into the trainee category.</li> <li>2. The CLIA testing personnel responsibility requirements for high complexity testing are adequate for molecular genetic testing.</li> </ol>	

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	<p>test analyses, reporting and maintaining records of patient test results;</p> <p>(2) Maintain records that demonstrate that proficiency testing samples are tested in the same manner as patient specimens;</p> <p>(3) Adhere to the laboratory's quality control policies, document all quality control activities, instrument and procedural calibrations and maintenance performed;</p> <p>(4) Follow the laboratory's established policies and procedures whenever test systems are not within the laboratory's established acceptable levels of performance;</p> <p>(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;</p> <p>(6) Document all corrective actions taken when test systems deviate from the laboratory's established performance specifications; and</p> <p>(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.</p>		
<b>Personnel Competency Assessment</b>	<p>§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.</p> <p>CLIA also specifies that competency assessments are the responsibilities of laboratory directors and technical supervisors:</p> <ul style="list-style-type: none"> <li>• §493.1445 (e)(13) requires laboratory directors to ensure that policies and procedures are established for</li> </ul>	<ol style="list-style-type: none"> <li>1. The CLIA personnel competency assessment requirements are adequate for molecular genetic testing.</li> <li>2. It should be the laboratory director's responsibility to determine <u>specific</u> policies and procedures for assessing and ensuring the competency of the following laboratory personnel: <ol style="list-style-type: none"> <li>a. Technical supervisor;</li> <li>b. Clinical consultant;</li> <li>c. General supervisor;</li> <li>d. Testing personnel.</li> </ol> </li> </ol>	

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	<p>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.</p> <ul style="list-style-type: none"> <li>• §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.</li> </ul>		
<p><b>Considerations before introducing genetic testing or offering new genetic tests</b></p>		<ol style="list-style-type: none"> <li>1. Considerations before introducing genetic testing or offering new genetic tests should include the following aspects: <ol style="list-style-type: none"> <li>a. Management responsibilities;</li> <li>b. Regulatory requirements;</li> <li>c. Benefit and cost considerations;</li> <li>d. Personnel considerations;</li> <li>e. Facility and laboratory safety considerations;</li> <li>f. Developing procedures and training personnel.</li> </ol> </li> <li>2. Many considerations elsewhere, such as analytical validity and clinical validity, apply to this section.</li> <li>3. The following additional thoughts were provided: <ol style="list-style-type: none"> <li>a. The following 3 scenarios should be considered: <ol style="list-style-type: none"> <li>1) Introducing a new genetic test that has not been offered anywhere;</li> <li>2) Introducing a test in house that has been referred out to another laboratory;</li> <li>3) Introducing a second test that can compliment the existing test.</li> </ol> </li> <li>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.</li> <li>c. Certain tests may be restricted due to intellectual property issues.</li> </ol> </li> <li>4. Consider appropriate professional guidelines, recommendations, and policy statements in introducing or offering new tests.</li> </ol>	

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Quality Management System (QMS) for molecular genetic testing	CLIA regulations overlap with the QMS model.	<ol style="list-style-type: none"> <li>1. The WG 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. Some WG members pointed out the benefits of QMS in molecular genetic testing, such as:               <ol style="list-style-type: none"> <li>a. Helping laboratories to meet CLIA requirements;</li> <li>b. Helping to improve quality and efficiency;</li> <li>c. Helping with international test referrals and global harmonization.</li> </ol> </li> <li>2. Based on the WG discussion, QMS policies and procedures may be helpful for the following specific areas:               <ol style="list-style-type: none"> <li>a. Determining effective ways to provide information to users of laboratory services based on assessment of user needs;</li> <li>b. Specimen submission;</li> <li>c. Test requisitions;</li> <li>d. Test reports, in determining the media, format, style, and language used in test reports based on assessment of user needs;</li> <li>e. Considerations before introducing genetic testing or offering new genetic tests.</li> </ol> </li> <li>3. Laboratories can refer to professional guidelines, accreditation standards, and other standards for guidance.</li> </ol>	<ol style="list-style-type: none"> <li>1. QMS provides a framework for managing and monitoring activities to address quality standards and achieve organizational goals.</li> <li>2. QMS reflects a commitment to quality from management and throughout the organization and a focus on user needs.</li> <li>3. ISO 15189 is written based on the QMS model; however, having QMS in place does not necessarily mean attaining accreditation to ISO 15189.</li> </ol>