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Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions

INSIDE: Continuing Education Examination

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Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions

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Summary

Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulations, laboratory testing is categorized as waived (from routine regulatory oversight) or nonwaived based on the complexity of the tests; tests of moderate and high complexity are nonwaived tests. Laboratories that perform molecular genetic testing are subject to the general CLIA quality systems requirements for nonwaived testing and the CLIA personnel requirements for tests of high complexity. Although many laboratories that perform molecular genetic testing comply with applicable regulatory requirements and adhere to professional practice guidelines, specific guidelines for quality assurance are needed to ensure the quality of test performance. To enhance the oversight of genetic testing under the CLIA framework, CDC and the Centers for Medicare & Medicaid Services (CMS) have taken practical steps to address the quality management concerns in molecular genetic testing, including working with the Clinical Laboratory Improvement Advisory Committee (CLIAC). This report provides CLIAC recommendations for good laboratory practices for ensuring the quality of molecular genetic testing for heritable diseases and conditions. The recommended practices address the total testing process (including the preanalytic, analytic, and postanalytic phases), laboratory responsibilities regarding authorized persons, confidentiality of patient information, personnel competency, considerations before introducing molecular genetic testing or offering new molecular genetic tests, and the quality management system approach to molecular genetic testing. These recommendations are intended for laboratories that perform molecular genetic testing for heritable diseases and conditions and for medical and public health professionals who evaluate laboratory practices and policies to improve the quality of molecular genetic laboratory services. This report also is intended to be a resource for users of laboratory services to aid in their use of molecular genetic tests and test results in health assessment and care. Improvements in the quality and use of genetic laboratory services should improve the quality of health care and health outcomes for patients and families of patients.

Introduction

Genetic testing encompasses a broad range of laboratory tests performed to analyze DNA, RNA, chromosomes, proteins, and certain metabolites using biochemical, cytogenetic, or molecular methods or a combination of these methods. In 1992, the regulations for the Clinical Laboratory Improvement Amendments of 1988 (CLIA) were published and began to be implemented. Since that time, advances in scientific research and technology have led to a substantial increase both in the health conditions for which genetic defects or variations can

be detected with molecular methods and in the spectrum of the molecular testing methods (1). As the number of molecular genetic tests performed for patient testing has steadily increased, so has the number of laboratories that perform molecular genetic testing for heritable diseases and conditions (2,3). With increasing use in clinical and public health practices, molecular genetic testing affects persons and their families in every life stage by contributing to disease diagnosis, prediction of future disease risk, optimization of treatment, prevention of adverse drug response, and health assessment and management. For example, preconception testing for cystic fibrosis and other heritable diseases has become standard practice for the care of women who are either pregnant or considering pregnancy and are at risk for giving birth to an infant with one of these conditions (4). DNA-based diagnostic testing often is crucial for confirming presumptive results from newborn screening tests, which are performed for approximately 95% of the 4 million infants born in the United States each year (5,6). In addition, pharmacogenetic and pharmacogenomic tests, which identify individual varia-

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tions in single-nucleotide polymorphisms, haplotype markers, or alterations in gene expression, are considered essential for personalized medicine, which involves customizing medical care on the basis of genetic information (7).

The expanding field of molecular genetic testing has prompted measures both in the United States and worldwide to assess factors that affect the quality of performance and delivery of testing services, the adequacy of oversight and quality assurance mechanisms, and the areas of laboratory practice in need of improvement. Problems that could affect patient testing outcomes that have been reported include inadequate establishment or verification of test performance specifications, inadequate personnel training or qualifications, inappropriate test selection and specimen submission, inadequate quality assurance practices, problems in proficiency testing, misunderstanding or misinterpretation of test results, and other concerns associated with one or more phases of the testing process (8–11).

Under CLIA, laboratory testing is categorized as waived testing or nonwaived (which includes tests of moderate and high complexity) based on the level of testing complexity. Laboratories that perform molecular genetic testing are subject to general CLIA requirements for nonwaived testing and CLIA personnel requirements for high-complexity testing; no molecular genetic test has been categorized as waived or moderate complexity. Many laboratories also adhere to professional practice guidelines and voluntary or accreditation standards, such as those developed by the American College of Medical Genetics (ACMG), the Clinical and Laboratory Standards Institute (CLSI), and the College of American Pathologists (CAP), which provide specific guidance for molecular genetic testing (12–14). In addition, certain state programs, such as the New York State Clinical Laboratory Evaluation Program (CLEP), have specific requirements that apply to genetic testing laboratories in their purview (15). However, no specific requirements exist at the federal level for laboratory performance of molecular genetic testing for heritable diseases and conditions.

Since 1997, CDC and the Centers for Medicare & Medicaid Services (CMS) have worked with other federal agencies, professional organizations, standard-setting organizations, CLIAC, and other advisory committees to promote the quality of genetic testing and improve the appropriate use of genetic tests in health care. To enhance the oversight of genetic testing under CLIA, CMS developed a multifaceted action plan aimed at providing guidelines, including the good laboratory practice recommendations in this report, rather than prescriptive regulations (16). Many of the activities in the action

plan have been implemented or are in progress, including 1) providing CMS and state CLIA surveyors with guidelines and technical training on assessing genetic testing laboratories for compliance with applicable CLIA requirements, 2) developing educational materials on CLIA compliance for genetic testing laboratories, 3) collecting data on laboratory performance in genetic testing, 4) working with CLIAC and standard-setting organizations on oversight concerns, and 5) collaborating with CDC and the Food and Drug Administration (FDA) on ongoing oversight activities (16). This plan also was supported by the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) in its 2008 report providing recommendations regarding future oversight of genetic testing (1).

The purposes of this report are to 1) highlight areas of molecular genetic testing that have been recognized by CLIAC as needing specific guidelines for compliance with existing CLIA requirements or needing quality assurance measures in addition to CLIA requirements and 2) provide CLIAC recommendations for good laboratory practices to ensure the quality of molecular genetic testing for heritable diseases and conditions. These recommendations are intended primarily for genetic testing that is conducted to diagnose, prevent, or treat disease or for health assessment purposes. The recommendations are distinct from the good laboratory practice regulations for nonclinical laboratory studies under FDA oversight (21 CFR Part 58) (17). The recommended laboratory practices provide guidelines for ensuring the quality of the testing process (including the preanalytic, analytic, and postanalytic phases of molecular genetic testing), laboratory responsibilities regarding authorized persons, confidentiality of patient information, and personnel competency. The recommendations also address factors to consider before introducing molecular genetic testing or offering new molecular genetic tests and the quality management system approach in molecular genetic testing. Implementation of the recommendations in laboratories that perform molecular genetic testing for heritable diseases and conditions and an understanding of these recommendations by users of laboratory services are expected to prevent or reduce errors and problems related to test selection and requests, specimen submission, test performance, and reporting and interpretation of results, leading to improved use of molecular genetic laboratory services, better health outcome for patients, and in many instances, better health outcomes for families of patients. In future reports, recommendations will be provided for good laboratory practices focusing on other areas of genetic testing, such as biochemical genetic testing, molecular cytogenetic testing, and somatic genetic testing.

Background

With the completion of the human genome project, discoveries linking genetic mutations or variations to specific diseases and biologic processes are frequently reported (18). The rapid progress in biomedical research, accompanied by advances in laboratory technology, have led to increased opportunities for development and implementation of new molecular genetic tests. For example, the number of heritable diseases and conditions for which clinical genetic tests are available more than tripled in 8 years, from 423 diseases in November 2000 to approximately 1,300 diseases and conditions in October 2008 (2,19). Molecular genetic testing is performed not only to detect or confirm rare genetic diseases or heritable conditions (20) but also to detect mutations or genetic variations associated with more common and complex conditions such as cancer (21,22), coagulation disorders (23), cardiovascular diseases (24), and diabetes (25). As the rapid pace of genetic research results in a better understanding of the role of genetic variations in diseases and health conditions, the development and clinical use of molecular genetic tests continues to expand (26–28).

Despite considerable information gaps regarding the number of U.S. laboratories that perform molecular genetic tests for heritable diseases and conditions and the number of specific genetic tests being performed (1), molecular genetic testing is one of the areas of laboratory testing that is increasing most rapidly. Molecular genetic tests are performed by a broad range of laboratories, including laboratories that have CLIA certificates for chemistry, pathology, clinical cytogenetics, or other specialties or subspecialties (11). Although nationwide data are not available, data from state programs indicate considerable increases in the numbers of laboratories that perform molecular genetic tests. For example, the number of approved laboratories in the state of New York that perform molecular genetic testing for heritable diseases and conditions increased 36% in 6 years, from 25 laboratories in February 2002 to 34 laboratories in October 2008 (29).

Although comprehensive data on the annual number of molecular genetic tests performed nationwide are not available, industry reports indicate a steady increase in the number of common molecular genetic tests for heritable diseases and conditions, such as mutation testing for cystic fibrosis and factor V Leiden thrombophilia (3). The number of cystic fibrosis mutation tests has increased significantly since 2001, pursuant to the recommendations of the American College of Obstetricians and Gynecologists and ACMG for preconception and prenatal carrier screening (30,31). The DNA-based cystic fibrosis mutation tests are now considered to be some of the most commonly performed genetic tests in the United

States and have become an essential component of several state newborn screening programs for confirming presumptive screening results of infants (32). The overall increase in molecular genetic testing from 2006 to 2007 worldwide has been reported to be 15% in some market analyses, outpacing other areas of molecular diagnostic testing (33).

CLIA Oversight for Molecular Genetic Testing

In 1988, Congress enacted Public Law 100-578, a revision of Section 353 of the Public Health Service Act (42 U.S.C. 263a) that amended the Clinical Laboratory Improvement Act of 1967 and required the Department of Health and Human Services (HHS) to establish regulations to ensure the quality and reliability of laboratory testing on human specimens for disease diagnosis, prevention, or treatment or for health assessment purposes. In 1992, HHS published CLIA regulations that describe requirements for all laboratories that perform patient testing (34). Facilities that perform testing for forensic purposes only and research laboratories that test human specimens but do not report patient-specific results are exempt from CLIA regulations (34). CMS (formerly the Health Care Financing Administration) administers the CLIA laboratory certification program in conjunction with FDA and CDC. FDA is responsible for test categorization, and CDC is responsible for CLIA studies, convening CLIAC, and providing scientific and technical support to CMS. CLIAC was chartered by HHS to provide recommendations and advice regarding CLIA regulations, the impact of CLIA regulations on medical and laboratory practices, and modifications needed to CLIA standards to accommodate technological advances.

In 2003, CMS and CDC published CLIA regulatory revisions to reorganize and revise CLIA requirements for quality systems for nonwaived testing and the laboratory director qualifications for high-complexity testing (35). The revised regulations included facility administration and quality system requirements for every phase of the testing process (35). Requirements for the clinical cytogenetics specialty also were reorganized and revised. Other genetic tests, such as molecular genetic tests, are not recognized as a specialty or subspecialty under CLIA. However, because these tests are considered high complexity, laboratories that perform molecular genetic testing for heritable diseases and conditions must meet applicable general CLIA requirements for nonwaived testing and the personnel requirements for high-complexity testing (36).

To enhance oversight of genetic testing under CLIA, CMS developed a plan to promote a comprehensive approach for effective application of current regulations and to provide

training and guidelines to surveyors and laboratories that perform genetic testing (16). CDC and CMS also have been assessing the need to revise and update CLIA requirements for proficiency testing programs and laboratories, taking into consideration the need for improved performance evaluation for laboratories that perform genetic testing (37).

Concerns Related to Molecular Genetic Testing

Studies and reports since 1997 have revealed a broad range of concerns related to molecular genetic testing for heritable diseases and conditions, including safe and effective translation of research findings into patient testing, the quality of test performance and results interpretation, appropriate use of testing information and services in health management and patient care, the adequacy of quality assurance measures, and concerns involving the ethical, legal, economic, and social aspects of molecular genetic testing (1,9,22,38,39). Some of these concerns are indicative of the areas of laboratory practice that are in need of improvement, such as performance establishment and verification, proficiency testing, personnel qualifications and training, and results reporting (1,9,11,22,39).

Errors Associated with and Needed Improvements in the Three Phases of Molecular Genetic Testing

Studies have indicated that although error rates associated with different areas of laboratory testing vary (40), the overall distribution of errors reported in the preanalytic, analytic, and postanalytic phases of the testing process are similar for many testing areas, including molecular genetic testing (9,11,39,40). The preanalytic phase encompasses test selection and ordering and specimen collection, processing, handling, and delivery to the testing site. The analytic phase includes selection of test methods, performance of test procedures, monitoring and verification of the accuracy and reliability of test results, and documentation of test findings. The postanalytic phase includes reporting test results and archiving records, reports, and tested specimens (41).

Studies have indicated that errors are more likely to occur during the preanalytic and postanalytic phases of the testing process than during the analytic phase, with most errors reported for the preanalytic phase (40,42–44). In the preanalytic phase, inappropriate selection of laboratory tests has been a significant source of errors (42,43). Misuse of laboratory services, such as unnecessary or inappropriate test requests, might lead to increased risk for medical errors, adverse patient outcome, and increased health-care costs (43). Although no

study has determined the overall number of molecular genetic tests performed that could be considered unwarranted or unnecessary, a study of the use and interpretation of adenomatous polyposis coli gene (*APC*) testing for familial adenomatous polyposis and other heritable conditions associated with colonic polyposis indicated that 17% of the cases evaluated did not have valid indications for testing (22).

Although data are limited, studies also indicate that improvements are needed in the analytic phase of molecular genetic testing. A study of the frequency and severity of errors associated with DNA-based genetic testing revealed that errors related to specimen handling in the laboratory and other analytic steps ranged from 0.06% to 0.12% of approximately 92,000 tests evaluated (39). A subsequent meta-analysis indicated that these self-reported error rates were comparable to those detected in nongenetic laboratory testing (40). An analysis of performance data from the CAP molecular genetic survey program during 1995–2000 estimated the overall error rate for cystic fibrosis mutation analysis to be 1.5%, of which approximately 50% of the errors occurred during the analytic or postanalytic phases of testing (45). Unrecognized sequence variations or polymorphisms also could affect the ability of molecular genetic tests to detect or distinguish the genotypes being analyzed, leading to false-positive or false-negative test results. Such problems have been reported for some commonly performed genetic tests such as cystic fibrosis mutation analysis and testing for *HFE*-associated hereditary hemochromatosis (46,47).

The postanalytic phase of molecular genetic testing involves analysis of test results, preparation of test reports, and results reporting. The study on the use of the *APC* gene testing and interpretation of test results indicated that lack of awareness among health-care providers of *APC* test limitations was a primary reason for misinterpretation of test results (22). In a study assessing the comprehensiveness and usefulness of reports for cystic fibrosis and factor V Leiden thrombophilia testing, physicians in many medical specialties considered reports that included information beyond that specified by the general CLIA test report requirements to be more informative and useful than test reports that only met CLIA requirements; additional information included patient race/ethnicity, clinical history, reasons for test referral, test methodology, recommendations for follow-up testing, implications for family members, and suggestions for genetic counseling (48). Consistent with these findings, international guidelines for quality assurance in molecular genetic testing recommend that molecular genetic test reports be accurate, concise, and comprehensive and communicate all essential information to enable effective decision-making by patients and health care professionals (49).

Proficiency Testing

Proficiency testing is a well-established practice for monitoring and improving the quality of laboratory testing (50,51) and is a key component of the external quality assessment process. Studies have indicated that using proficiency testing samples that resemble actual patient specimens could improve monitoring of laboratory performance (50,52–54). Participation in proficiency testing has helped laboratories reduce analytic deficiencies, improve testing procedures, and take steps to prevent future errors (55–59).

CLIA regulations have not yet included proficiency testing requirements for molecular genetic tests. Laboratories that perform molecular genetic testing must meet the general CLIA requirement to verify, at least twice annually, the accuracy of the genetic tests they perform (§493.1236[c]) (36). Laboratories may participate in available proficiency testing programs for the genetic tests they perform to meet this CLIA alternative performance assessment requirement. Proficiency testing participation correlates significantly with the quality assurance measures in place among laboratories that perform molecular genetic testing (9,10). Because proficiency testing is a rigorous external assessment for laboratory performance, in 2008, SACGHS recommended that proficiency testing participation be required for all molecular genetic tests for which proficiency testing programs are available (1). Formal molecular genetic proficiency testing programs are available only for a limited number of tests for heritable diseases and conditions; in addition, the samples provided often are purified DNA, which do not typically require performance of all steps of the testing process, such as nucleic acid extraction and preparation (60). For many genetic conditions that are either rare or for which testing is performed by one or a few laboratories, substantial challenges in developing formal proficiency testing programs have been recognized (1).

Development of effective alternative performance assessment approaches to proficiency testing is essential for ensuring the quality of molecular genetic testing (1). Professional guidelines have been developed for laboratories to evaluate and monitor test performance when proficiency testing programs are not available (61). However, reports of the CAP molecular pathology on-site inspections indicate that deficiencies related to participation in interlaboratory comparison or alternative performance assessment are among the most frequently identified deficiencies, accounting for 3.9% of all deficiencies cited (62).

Clinical Validity and Potential Risks Associated with Certain Molecular Genetic Tests

The ability of a test to diagnose or predict risk for a particular health condition is the test's clinical validity, which often is measured by clinical (or diagnostic) sensitivity, clinical (or diagnostic) specificity, and predictive values of the test for a given health condition. Clinical validity can be influenced by factors such as the prevalence of the disease or health condition, penetrance (proportion of persons with a mutation causing a particular disorder who exhibit clinical symptoms of the disorder), and modifiers (genetic or environmental factors that might affect the variability of signs or symptoms that occur with a phenotype of a genetic alteration). For genetic tests, clinical validity refers to the ability of a test to detect or predict the presence or absence of a particular disease or phenotype and often corresponds to associations between genotypes and phenotypes (1,28,63–69). The usefulness of a test in clinical practice, referred to as clinical utility, involves identifying the outcomes associated with specific test results (28). Clinical validity and clinical utility should be assessed individually for each genetic test because the implications might vary depending on the health condition and population being tested (38).

As advances in genomic research and technology result in rapid development of new genetic tests, concerns have been raised that certain tests, particularly predictive genetic tests, could become available without adequate assessment of their validity, benefits, and utility. Consequently, health professionals and consumers might not be able to make a fully informed decision about whether or how to use these tests. In 1997, a task force formed by a National Institutes of Health (NIH)–Department of Energy workgroup recommended that laboratories that perform patient testing establish clinical validity for the genetic tests they develop before offering them for patient testing and carefully review and document evidence of test validity if the test has been developed elsewhere (70). This recommendation was later included in a report of the Secretary's Advisory Committee on Genetic Testing (SACGT), which was established in 1998 to advise HHS on medical, scientific, ethical, legal, and social concerns raised by the development and use of genetic tests (38).

Public concerns about inadequate knowledge or documentation of the clinical validity of certain genetic tests were also recognized by SACGHS, the advisory committee that was established by HHS in 2002 to supersede SACGT (1).

SACGHS recommended the development and support of sustainable public-private collaborations to fill the gaps in knowledge of the analytic validity, clinical validity, clinical utility, economic value, and population health impact of molecular genetic tests (1). Collaborative efforts that have been recognized include the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) program, a CDC initiative to establish and evaluate a systematic, evidence-based process for assessing genetic tests and other applications of genomic technology in transition from research to clinical practice and public health (71), and the Collaboration, Education, and Test Translation (CETT) Program, which is overseen by the NIH Office of Rare Diseases to promote the effective transition of potential genetic tests for rare diseases from research settings into clinical settings (72).

The increase in direct-to-consumer (DTC) genetic testing (i.e., genetic tests offered directly to consumers with no health-care provider involvement) has raised concerns about the potential risks or misuses of certain genetic tests (73). As of October 2008, consumers could directly order laboratory tests in 27 states; in another 10 states, consumer-ordered tests are allowed under defined circumstances (74). As DTC genetic tests become increasingly available, various genetic profile tests have been marketed directly to the public that claim to answer questions regarding cardiovascular risks, drug metabolism, dietary arrangements, and lifestyles (73). In addition, DTC advertisements have caused a substantial increase in the demand for molecular genetic tests, such as those for hereditary breast and ovarian cancers (75,76). Although allowing easy access to the testing services, DTC genetic testing has raised concerns about the potential for inadequate pretest decision-making, misunderstanding of test results, access to tests of questionable clinical value, lack of necessary follow-up, and unexpected additional responsibilities for primary care physicians (77–80). Both the government and professional organizations have developed educational materials that provide guidance to consumers, laboratories, genetics professionals, and professional organizations regarding DTC genetic tests (80–82).

Personnel Qualifications and Training

Studies indicate that qualifications of laboratory personnel, including training and experience, are critical for ensuring quality performance of genetic testing, because human error has the greatest potential influence on the quality of laboratory test results (9,83,84). A study of laboratories in the United States that perform molecular genetic testing suggested that laboratory adherence to voluntary quality standards and guidelines for genetic testing was significantly associated with laboratories directed or supervised by persons with board certification in medical genetics (9). Results of an international survey revealed

a similar correlation between the quality assurance practices of a molecular genetic testing laboratory and the formal training of the laboratory director (10). Overall, the concerns recognized in publications and documented cases support the need to have trained, qualified personnel at all levels to ensure the quality of all phases of the genetic testing process.

Methods

Information Collection and Assessment

To monitor and assess the scope and growth of molecular genetic testing in the United States, data were collected and analyzed from scientific articles, government reports, the CMS CLIA database, information from state programs, studies by professional groups, publicly available directories and databases of laboratories and laboratory testing, industry reports, and CDC studies (1–3,5,6,9,29,38,83,85–88). To evaluate factors in molecular genetic testing that might affect testing quality and to identify areas that would benefit from quality assurance guidelines, various documents were considered, including professional practice guidelines, CAP laboratory accreditation checklists, CLSI guidelines, state requirements, and international guidelines and standards (12–15,49,61,89–95).

Development of CLIAC Recommendations for Good Laboratory Practices in Molecular Genetic Testing

Since 1997, CLIAC has provided HHS with recommendations on approaches needed to ensure the quality of genetic testing (37). At the February 2007 CLIAC meeting, CLIAC asked CDC and CMS to clarify critical concerns in genetic testing oversight and to provide a status report at the subsequent CLIAC meeting. At the September 2007 CLIAC meeting, CDC presented an overview of the regulatory oversight and voluntary measures for quality assurance of genetic testing and described a plan to develop and publish educational material on good laboratory practices. CDC solicited CLIAC recommendations to address concerns that presented particular challenges related to genetic testing oversight, including establishment and verification of performance specifications, control procedures for molecular amplification assays, proficiency testing, genetic test reports, personnel competency assessment, and the definition of genetic tests. CLIAC recommended convening a workgroup of experts in genetic testing to consider these concerns and provide input for CLIAC deliberation.

The CLIAC Genetic Testing Good Laboratory Practices Workgroup was formed. The workgroup conducted a series of meetings on the scope of laboratory practice recommendations needed for genetic testing and suggested that recommendations first be developed for molecular genetic testing for heritable diseases and conditions. The workgroup evaluated good laboratory practices for all phases of the genetic testing process after reviewing professional guidelines, regulatory and voluntary standards, accreditation checklists, international standards and guidelines, and other documents that provided general or specific quality standards applicable to molecular genetic testing for heritable diseases and conditions (1,12–15,36,41,49,61,80,82,91–109). The workgroup also reviewed information on the HHS-approved and other certification boards for laboratory personnel and the number of persons certified in each of the specialties for which certification is available (110–118). Workgroup suggestions were reported to CLIAC at the September 2008 committee meeting. The CLIAC recommendations were formed on the basis of the workgroup report and additional CLIAC recommendations. The committee recommended that CDC include the CLIAC-recommended good laboratory practices for molecular genetic testing in the planned publication. Summaries of CLIAC meetings and CLIAC recommendations are available (37).

Recommended Good Laboratory Practices

The following recommended good laboratory practices are for areas of molecular genetic testing for heritable diseases and conditions in need of guidelines for complying with existing CLIA requirements or in need of additional quality assurance measures. These recommendations are not intended to encompass the entire realm of laboratory practice; they are meant to provide guidelines for specific quality concerns in the performance and delivery of laboratory services for molecular genetic testing for heritable diseases and conditions.

These recommendations address laboratory practices for the total testing process, including the preanalytic, analytic, and postanalytic phases of molecular genetic testing. The recommendations for the preanalytic phase include guidelines for laboratory responsibilities for providing information to users of laboratory services, informed consent, test requests, specimen submission and handling, test referrals, and preanalytic systems assessment. The recommendations for the analytic phase include guidelines for establishment and verification of performance specifications, quality control procedures, proficiency testing, and alternative performance assessment. The recommendations for the postanalytic phase include guidelines

for test reports, retention of records and reports, and specimen retention. The recommendations also address responsibilities of laboratories regarding authorized persons, confidentiality of patient information and test results, personnel competency, factors to consider before introducing molecular genetic testing or offering new molecular genetic tests, and the potential benefits of the quality management system approach in molecular genetic testing. Recommendations are provided in relation to applicable provisions in the CLIA regulations and, when necessary, are followed by a description of how the recommended practices can be used to improve quality assurance and quality assessment for molecular genetic testing. A list of terms and abbreviations used in this report also is provided (Appendix A).

The Preanalytic Testing Phase

Test Information to Provide to Users of Laboratory Services

Laboratories are responsible for providing information regarding the molecular genetic tests they perform to users of their services; users include authorized persons under applicable state law, health-care professionals, patients, referring laboratories, and payers of laboratory services. Laboratories should review the genetic tests they perform and the procedures they use to provide and update the recommended test information that follows. At a minimum, laboratories should ensure that the test information is available from accessible sources such as websites, service directories, information pamphlets or brochures, newsletters, instructions for specimen submission, and test request forms. Laboratories that already provide the information from these sources should continue to do so. However, laboratories also might decide to provide the information more directly to their users (e.g., by telephone, e-mail, or in an in-person meeting) and should determine the situations in which such direct communication is necessary. The complexity of language used should be appropriate for the particular laboratory user groups (e.g., for patients, plain language understandable by the general public).

Test selection, test performance, and specimen submission. Laboratories should provide information regarding the molecular genetic tests they perform to users of their services to facilitate appropriate test selection and requests, specimen handling and submission, and patient care. Each laboratory that performs molecular genetic testing for heritable diseases and conditions should provide the following information to its users:

- Information necessary for selecting appropriate tests, including a list of the molecular genetic tests the laboratory

performs. For each molecular genetic test, the following information should be provided:

- Intended use of the test, including the nucleic acid target of the test (e.g., genes, sequences, mutations, or polymorphisms), the purpose of testing (e.g., diagnostic, preconception, or predictive), and the recommended patient populations
- Indications for testing
- Test method to be used, presented in user-friendly language in relation to the performance specifications and the limitations of the test (with Current Procedural Terminology [CPT] codes included when appropriate)
- Specifications of applicable performance characteristics, including information on analytic validity and clinical validity
- Limitations of the test
- Whether testing is performed with an FDA-approved or FDA-cleared test system, with a laboratory-developed test or test system that is not approved or cleared by FDA, or with an investigational test under FDA oversight
- Information on appropriate collection, handling, transport, and submission of specimens
- Patient information necessary for the laboratory to perform the test and report test results, including relevant clinical or laboratory information, and, if applicable, racial/ethnic information, family history, pedigree, and consent information in compliance with federal, state, and local requirements
- A statement indicating that test results are likely to have implications for the family members of the patient
- Availability of laboratory consultations regarding test selection and ordering, specimen submission, results interpretation, and implications of test results

Cost. When possible and practical, laboratories should provide users with information on the charges for molecular genetic tests being performed. Estimating the expenses that a patient might incur from a particular genetic test might be difficult for certain laboratories and providers because fee schedules of individual laboratories can vary depending on the health-care payment policy selections of each patient. However, advising the patient and family members of the financial implications of the tests, whenever possible, facilitates informed decision-making.

Discussion. Under CLIA, laboratories are required to develop and follow written policies and procedures for specimen submission and handling, specimen referral, and test requests (42 CFR §§493.1241 and 1242). Laboratories

must ensure positive identification and optimum integrity of specimens from the time of collection or receipt through the completion of testing and reporting of test results (42 CFR §493.1232). In addition, laboratories that perform nonwaived testing must ensure that a qualified clinical consultant is available to assist laboratory clients with ordering tests appropriate for meeting clinical expectations (42 CFR §493.1457[b]). The recommended laboratory practices in this report describe laboratory responsibilities for ensuring appropriate test requests and specimen submission for the molecular genetic tests they perform, in addition to laboratory responsibilities for meeting CLIA requirements. The recommendations emphasize the role of laboratories in providing specific information needed by users before decisions are made regarding test selection and ordering, based on consideration of several factors.

First, molecular genetic tests for heritable diseases and conditions are being rapidly developed and increasingly used in health-care settings. Users of laboratory services need the ability to easily access information regarding the intended use, performance specifications, and limitations of the molecular genetic tests a laboratory offers to determine appropriate testing for specific patient conditions.

Second, many molecular genetic tests are performed using laboratory-developed tests or test systems. The performance specifications and limitations of the testing might vary among laboratories, even for the same disease or condition, depending on the specific procedures used. Users of laboratory services who are not provided information related to the appropriateness of the tests being considered might select tests that are not indicated or cannot meet clinical expectations.

Third, for many heritable diseases and conditions, test performance and interpretation of test results require information regarding patient race/ethnicity, family history, and other pertinent clinical and laboratory information. Informing users before tests are ordered of the specific patient information needed by the laboratory should facilitate test requests and allow prompt initiation of appropriate testing procedures and accurate interpretation of test results.

Finally, providing information to users on performance specifications and limitations of tests before test selection and ordering prepares users of laboratory services for understanding test results and implications. CLIA test report requirements (42 CFR §493.1291[e]) indicate that laboratories are required to provide users of their services, on request, with information on laboratory test methods and the performance specifications the laboratory has established or verified for the tests. However, for molecular genetic tests for heritable diseases and conditions, laboratories should provide test performance information to users before test selection and ordering, rather than waiting

for a request after the test has been performed. The information provided in the preanalytic phase must be consistent with information included on test reports.

Providing molecular genetic testing information to users before tests are selected and ordered should improve test requests and specimen submission and might reduce unnecessary or unwarranted testing. The recommended practices also might increase informed decision-making, improve interpretation of results, and improve patient outcome.

Informed Consent

A person who provides informed consent voluntarily confirms a willingness to undergo a particular test, after having been informed of all aspects of the test that are relevant to the patient's decision (49). Informed consent for genetic testing or specific types of genetic tests is required by law in certain states; as of June 2008, 12 states required that informed consent be obtained before a genetic test is requested or performed (119). In addition, certain states (e.g., Massachusetts, Michigan, Nebraska, New York, and South Dakota) have included required informed consent components in their statutes [97,120–123] (Appendix B). These state statutes can be used as examples for laboratories in other states that are developing specific informed consent forms. Professional organizations recommend that informed consent be obtained for testing for many inherited genetic conditions (12,13). CLIA regulations have no requirements for laboratory documentation of informed consent for requested tests; however, medical decisions for patient diagnosis or treatment should be based on informed decision-making (124). Regardless of whether informed consent is required, laboratories that perform molecular genetic tests for heritable diseases and conditions should be responsible for providing users with the information necessary to make informed decisions.

Informed consent is in the purview of the practice of medicine; the persons authorized to order the tests are responsible for obtaining the appropriate level of informed consent (67). Unless mandated by state or local requirements, obtaining informed consent before performing a test generally is not considered a laboratory responsibility. For molecular genetic testing for heritable diseases and conditions, not all tests require written patient consent before testing (125). However, when informed consent for patient testing is recommended or required by law or other applicable requirements as a method for documenting the process and outcome of informed decision-making, laboratories should ensure that certain practices are followed:

- Be available to assist users of laboratory services with determining the appropriate level of informed consent by providing useful and necessary information.

- Include appropriate methods for documenting informed consent on test request forms, and determine whether the consent information is provided with the test request before initiating testing. Laboratories may determine situations in which a patient specimen can be stabilized until informed consent is obtained, following the practices for specimen retention recommended in these guidelines.

Laboratories should refer to professional guidelines for additional information regarding informed consent for molecular genetic tests and should consider available models when developing the content, format, and procedures for documentation of patient consent.

Test Requests

CLIA requirements (42 CFR §493.1241[c]) specify that laboratories that perform nonwaived testing must ensure that the test request solicits the following information: 1) the name and address or other suitable identifiers of the authorized person requesting the test and (if applicable) the person responsible for using the test results, or the name and address of the laboratory submitting the specimen, including (if applicable) a contact person to enable reporting of imminently life-threatening laboratory results or critical values; 2) patient name or a unique patient identifier; 3) sex and either age or date of birth of the patient; 4) the tests to be performed; 5) the source of the specimen (if applicable); 6) the date and (if applicable) time of specimen collection; and 7) any additional information relevant and necessary for a specific test to ensure accurate and timely testing and reporting of results, including interpretation (if applicable). For molecular genetic testing for heritable diseases and conditions, laboratories must comply with these CLIA requirements and should solicit the following additional information on test requests:

- Patient name and any other unique identifiers needed for testing
- Patient date of birth
- Indication for testing and relevant clinical or laboratory information
- Patient racial/ethnic information (if applicable)
- Information on patient family history, pedigree, or both that is pertinent to the disease or condition being evaluated or the testing to be performed (if applicable)
- Appropriate international classification of diseases (ICD) codes or other information indicating diseases or conditions for which the patient is being tested (e.g., codes associated with an advance beneficiary notice)
- If applicable, indication that the appropriate level of informed consent has been obtained in compliance with federal, state, and local requirements

Patient name and any other unique identifiers needed for testing. CLIA test request requirements indicate that laboratories must solicit patient names or unique patient identifiers on test requests (42 CFR §493.1241[c][2]). Laboratories that perform molecular genetic testing for heritable diseases and conditions should ensure that at least two unique identifiers are solicited on these test requests, which should include patient names, when possible, and any other unique identifiers needed to ensure patient identification. In certain situations (e.g., compatibility testing for which donor names are not always provided to the laboratory), an alternative unique identifier is appropriate.

Date of birth. CLIA requirements specify that test requests must solicit the sex and either age or date of birth of the patient (42 CFR §493.1241[c][3]). For molecular genetic testing for heritable diseases and conditions, patient date of birth is more informative than age and should be obtained when possible.

Indications for testing, relevant clinical and laboratory information, patient race/ethnicity, family history, and pedigree. Obtaining information on indications for testing, relevant clinical or laboratory information, patient racial/ethnic background, family history, and pedigree is critical for selecting appropriate test methods, determining the mutations or variants to be tested, interpreting test results, and timely reporting of test results. Genetic conditions often have different disease prevalences with various mutation frequencies and distributions among racial/ethnic groups. Unique, or private, mutations or genotypes might be present only in specific families or can be associated with founder effects (i.e., gene mutations observed in high frequency in a specific population because of the presence of the mutation in a single ancestor or small number of ancestors in the founding population). Family history and other relevant clinical or laboratory information are often important for determining whether the test requested might meet the clinical expectations, including the likelihood of identifying a disease-causing mutation. Specific race/ethnicity, family history, and other pertinent information to be solicited on a test request should be determined according to the specific disease or condition for which the patient is being tested. Laboratories should consider available guidelines for requesting and obtaining this additional information and determine circumstances in which more specific patient information is needed for particular genetic tests (126,127). Although this information is not specified in CLIA, the regulations provide laboratories the flexibility to determine and solicit relevant and necessary information for a specific test (42 CFR §493.1241[c][8]). The recommended test request components also are consistent with many voluntary professional and accreditation guidelines (12–14).

Documentation of informed consent. Methods for indicating and documenting informed consent on a test request might include a statement, text box, or check-off box on the test request form to be signed or checked by the test requestor; a separate form to be signed as part of the test request; or another method that complies with applicable requirements and adheres to professional guidelines. In addition, when state or local laws or regulations specify that patient consent must be obtained regarding the use of tested specimens for quality assurance or other purposes, the test request must include a way for the test requestor to indicate the decision of the patient. Laboratories also might determine that other situations merit documentation of consent before testing.

Specimen Submission, Handling, and Referral

CLIA requires laboratories to establish and follow written policies and procedures for patient preparation, specimen collection, specimen labeling (including patient name or unique patient identifier and, when appropriate, specimen source), specimen storage and preservation, conditions for specimen transportation, specimen processing, specimen acceptability and rejection, and referral of specimens to another laboratory (42 CFR §493.1242). If a laboratory accepts a referral specimen, appropriate written instructions providing information on specimen handling and submission must be available to the laboratory clients. The following recommendations are intended to help laboratories that perform molecular genetic testing meet general CLIA requirements and to provide additional guidelines on quality assurance measures for specimen submission, handling, and referral for molecular genetic testing. Before test selection and ordering, laboratories that perform molecular genetic testing should provide their users with instructions on specimen collection, handling, transport, and submission. Information on appropriate collection, handling, and submission of specimens for molecular genetic tests should include the following:

- Appropriate type and amount of specimens to be collected
- Collection container or device to be used (e.g., tubes with specific anticoagulants, specific cups or tubes containing sterile tissue culture media, or buccal swabs)
- Special timing of specimen collection (if required)
- Specimen preparation and handling before submission to the laboratory (e.g., dissection of chorionic villus sampling and safe disposal of materials used in specimen collection)
- Specimen stability information, including the time frame beyond which the stability and integrity of a specimen

or the analytes to be detected in a specimen might be compromised

- Specimen transport conditions (e.g., ambient temperature, refrigeration, and immediate delivery)
- Reasons for rejection of specimens

Criteria for specimen acceptance or rejection. Laboratories should have written criteria for acceptance or rejection of specimens for the molecular genetic tests they perform and should promptly notify the authorized person when a specimen meets the rejection criteria and is determined to be unsuitable for testing. The criteria should include information on determining the existence of and addressing the following situations:

- Improper handling or transport of specimens
- Specimen exposure to temperature extremes that affect sample stability or integrity
- Insufficient specimen volume or amount
- Use of inappropriate anticoagulants or media, specimen degradation, or inappropriate specimen types
- Commingled specimens or possible contamination of specimens that might affect results of molecular amplification procedures
- Specimens that are mislabeled or lack unique identifiers
- Lack of unique identifiers on the test request form
- Lack of other information needed to determine whether the specimen or test requested is appropriate for answering the clinical question

Retention and exchange of information throughout the testing process. Information on test requests and test reports is a particularly important component of the complex communication between genetic testing laboratories and their users. Laboratories should have policies and procedures in place to ensure that information needed for selection of appropriate test methods, test performance, and results interpretation is retained throughout the entire molecular genetic testing process. This recommendation is based on CLIA recognition of instances in which information on test requests or test reports was removed by electronic or other information systems during specimen submission, results reporting, or test referral. CLIA requires laboratories to ensure the accuracy of test request or authorization information when transcribing or entering the information into a record system or a laboratory information system (42 CFR §493.1241[e]). For molecular genetic tests, information on test requests and test reports should be retained accurately and completely throughout the testing process.

Specimen referral. CLIA requires laboratories to refer specimens for any type of patient testing to CLIA-certified laboratories or laboratories that meet equivalent requirements as determined by CMS (42 CFR §493.1242[c]). Examples of laboratories that meet equivalent requirements include

Department of Veterans Affairs laboratories, Department of Defense laboratories, and laboratories in CLIA-exempt states.

Preanalytic Systems Quality Assessment

Laboratories must have written policies and procedures for assessing and correcting problems identified in test requests, specimen submission, and other preanalytic steps of molecular genetic testing (42 CFR §493.1249). The preanalytic systems assessment for molecular genetic testing should include the following practices:

- Establish and follow procedures for ensuring the testing requested meets the clinical expectation to the extent possible with available information. Laboratories should seek clarification for test requests that are unclear or lack critical information, are submitted with inappropriate specimens, or are inconsistent with the expected use of test results. For example, if a test request has no information on patient race/ethnicity or family history information, but this information is needed to determine the proper test method or mutations to be detected, the laboratory should contact the test requestor and obtain the information. In addition, if the ICD code provided does not match the test requested, the laboratory should consider the code and the additional information provided, including the indications for the test request, and contact the test requestor for clarification if needed.
- Follow written policies and procedures to ensure that information necessary for selection of appropriate test methods, performance, and results interpretation is retained throughout specimen submission, reporting of test results, and specimen referral. Information received by the laboratory should be monitored to ensure completeness and accuracy; efforts should be made to correct the problems and prevent recurrence. If a laboratory realizes that needed information has been automatically removed electronically from test requests during specimen submission or referral, the laboratory should contact the test requestor or referring laboratory to obtain the information and establish effective procedures to ensure the needed information is retained during the entire testing process.

The Analytic Testing Phase

Establishment and Verification of Performance Specifications

CLIA requires laboratories to establish or verify the analytic performance of all nonwaived tests and test systems before introducing them for patient testing and to determine

the calibration and control procedures of tests based on the performance specifications verified or established. Before reporting patient test results, each laboratory that introduces an unmodified, FDA-cleared or FDA-approved test system must 1) demonstrate that the manufacturer-established performance specifications for accuracy, precision, and reportable range of test results can be reproduced and 2) verify that the manufacturer-provided reference intervals (or normal values) are appropriate for the laboratory patient population (42 CFR §493.1253). Laboratories are subject to more stringent requirements when introducing 1) FDA-cleared or FDA-approved test systems that have been modified by the laboratory, 2) laboratory-developed tests or test systems that are not subject to FDA clearance or approval (e.g., standardized methods and textbook procedures), or 3) test systems with no manufacturer-provided performance specifications. In these instances, before reporting patient test results, laboratories must conduct more extensive procedures to establish applicable performance specifications for accuracy, precision, analytic sensitivity, analytic specificity; reportable range of test results; reference intervals, or normal values; and other performance characteristics required for test performance.

Although laboratories that perform molecular genetic testing for heritable diseases and conditions must comply with these general CLIA requirements, additional guidelines are needed to assist with establishment and verification of performance specifications for these tests. The recommended laboratory practices that follow are primarily intended to provide specific guidelines for establishing performance specifications for laboratory-developed molecular genetic tests to ensure valid and reliable test performance and interpretation of results. The recommendations also might be used by laboratories to verify performance specifications of unmodified FDA-cleared or FDA-approved molecular genetic test systems to be introduced for patient testing.

Factors that should be considered when developing performance specifications for molecular genetic tests include the intended use of the test; target genes, sequences, and mutations; intended patient populations; test methods; and samples to be used (99). The following five steps should be considered general principles for establishing performance specifications of each new molecular genetic test:

- Conduct a review of available scientific studies and pertinent references.
- Define appropriate patient populations for which the test should be performed.
- Select the appropriate test methodology for the disease or condition being evaluated.

- Establish analytic performance specifications and determine quality control procedures using the appropriate number, type, and variety of samples.
- Ensure that test results and their implications can be interpreted for an individual patient or family and that the limitations of the test are defined and reported.

Samples for establishment of performance specifications.

Establishment of performance specifications should be based on an adequate number, type, and variety of samples to ensure that test results can be interpreted for specific patient conditions and that the limitations of the testing and test results are known. When selecting samples, the following factors should be considered:

- The prevalence of the disease and the mutations or variants being evaluated. Laboratories should not set lower standards for rare diseases or rare mutations; samples should be adequate and appropriate for establishing test performance specifications and defining limitations.
- Inclusion of samples that represent each type of patient specimen expected for the assay (e.g., blood, buccal swabs, dried blood spots, fresh or frozen tissue, paraffin-embedded tissue, or prenatal specimens).
- Inclusion of samples that represent each of the possible reportable results (or genotypes). For a multiplex genetic test or a test using targeted detection methods to evaluate multiple nucleic acid targets, all the mutations or variants to be detected should be included in the performance establishment. In certain situations, naturally occurring samples that contain target genotypes are difficult to obtain for rare mutations and variants, or a disease is not associated with common mutations; in these instances, the alternative control samples and alternative control procedures that will be used should be included in the establishment of performance specifications.
- Performance specifications to be established.
- Control materials, calibration materials, and other reference materials needed for the test procedures.

Analytic performance specifications. Laboratories should determine performance specifications for all of the following analytic performance characteristics for molecular genetic tests that are not cleared or approved by FDA before introducing the tests for patient testing:

- Accuracy
- Precision
- Analytic sensitivity
- Analytic specificity
- Reportable range of test results for the test system
- Reference range or normal values
- Other performance characteristics required or necessary for test performance

Accuracy. Accuracy is commonly defined as “closeness of the agreement between the result of a measurement and a true value of the measurand” (128). For qualitative molecular genetic tests, laboratories are responsible for verifying or establishing the accuracy of the method used to identify the presence or absence of the analytes being evaluated (e.g., mutations, variants, or other targeted nucleic acids). Accuracy might be assessed by testing reference materials, comparing test results against results of a reference method, comparing split-sample results with results obtained from a method shown to provide clinically valid results, or correlating research results with the clinical presentation when establishing a test system for a new analyte, such as a newly identified disease gene (96).

Precision. Precision is defined as “closeness of agreement between independent test results obtained under stipulated conditions” (129). Precision is commonly determined by assessing repeatability (i.e., closeness of agreement between independent test results for the same measurand under the same conditions) and reproducibility (i.e., closeness of agreement between independent test results for the same measurand under changed conditions). Precision can be verified or established by assessing day-to-day, run-to-run, and within-run variation (as well as operator variance) by repeat testing of known patient samples, quality control materials, or calibration materials over time (96).

Analytic sensitivity. Practice guidelines vary in their definitions of analytic sensitivity; certain guidelines consider analytic sensitivity to be the ability of an assay to detect a given analyte, or the lower limit of detection (LOD) (93), whereas guidelines for molecular genetic testing for heritable diseases consider analytic sensitivity to be “the proportion of biological samples that have a positive test result or known mutation and that are correctly classified as positive” (12). However, determining the LOD of a molecular genetic test or test system is often needed as part of the performance establishment and verification (93). To avoid potential confusion among users and the general public in understanding the test performance and test results, laboratories should review and follow applicable professional guidelines before testing is introduced and ensure the guidelines are followed consistently throughout performance establishment and verification and during subsequent patient testing. Analytic sensitivity should be determined for each molecular genetic test before the test is used for patient testing.

Analytic specificity. Analytic specificity is generally defined as the ability of a test method to determine only the target analytes to be detected or measured and not the interfering substances that might affect laboratory testing. Interfering substances include factors associated with specimens (e.g., specimen hemolysis, anticoagulant, lipemia, and turbidity) and

factors associated with patients (e.g., clinical conditions, disease states, and medications) (96). Laboratories must document information regarding interfering substances and should use product information, literature, or the laboratory’s own testing (96). Accepted practice guidelines for molecular genetic testing, such as those developed by ACMG, CAP, and CLSI, define analytic specificity as the ability of a test to distinguish the target sequences, alleles, or mutations from other sequences or alleles in the specimen or genome being analyzed (12–14). The guidelines also address documentation and determination of common interfering substances specific for molecular detection (e.g., homologous sequences, contaminants, and other exogenous or endogenous substances) (12–14). Laboratories should adhere to these specific guidelines in establishing or verifying analytic specificity for each of their molecular genetic tests.

Reportable range of test results. As defined by CLIA, the reportable range of test results is “the span of test result values over which the laboratory can establish or verify the accuracy of the instrument or test system measurement response” (36). The reportable range of patient test results can be established or verified by assaying low and high calibration materials or control materials or by evaluating known samples of abnormally high and low values (96). For example, laboratories should assay quality control or reference materials, or known normal samples, and samples containing mutations to be detected for targeted mutation analyses. For analysis of trinucleotide repeats, laboratories should include samples representing the full range of expected allele lengths (130).

Reference range, or reference interval (i.e., normal values). As defined by CLIA, a reference range, or reference interval, is “the range of test values expected for a designated population of persons (e.g., 95% of persons that are presumed to be healthy [or normal])” (36). The CMS *Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services* provides general guidelines regarding the use of manufacturer-provided or published reference ranges appropriate for the patient population and evaluation of an appropriate number of samples to verify manufacturer claims or published reference ranges (96). For all laboratory-developed tests, the laboratory is responsible for establishing the reference range appropriate for the laboratory patient population (including demographic variables such as age and sex) and specimen types (96). For molecular genetic tests for heritable diseases and conditions, normal values might refer to normal alleles in targeted mutation analyses or the reference sequences for sequencing assays. Laboratories should be aware that advances in knowledge and testing technology might affect the recognition and documentation of normal sequences and should keep an updated database for the molecular genetic tests they perform.

Quality control procedures. CLIA requires laboratories to determine the calibration and control procedures for non-waived tests or test systems on the basis of the verification or establishment of performance specifications for the tests (42 CFR §493.1253[b][3]). Laboratories that perform molecular genetic tests must meet these requirements and, for every molecular genetic test to be introduced for patient testing, should consider the recommended quality control practices.

Documentation of information on clinical validity. Laboratories should ensure that the molecular genetic tests they perform are clinically usable and can be interpreted for specific patient situations. Laboratory responsibilities for clinical validity include the following:

- Documenting information regarding clinical validity (including clinical sensitivity, clinical specificity, positive predictive value, and negative predictive value) of all genetic tests the laboratory performs from available information sources (e.g., published studies and professional practice guidelines)
- Providing clinical validity information to users of laboratory services before tests are selected and specimens submitted
- If clinical validity information is not available from published sources, establishing clinical sensitivity, clinical specificity, and predictive values on the basis of internal study results
- Documenting whether the clinical claims in the references or information sources used can be reproduced in the laboratory and providing this information to users, including indicating test limitations in all test reports
- Informing users of changes in clinical validity values as a result of knowledge advancement
- Specifying that the responsibilities of the laboratory director and technical supervisor include ensuring appropriate documentation and reporting of clinical validity information for molecular genetic tests performed by the laboratory

Although CLIA regulations do not include validation of clinical performance specifications of new tests or test systems, laboratories are required to ensure that the tests being performed meet clinical expectations. For tests of high complexity, such as molecular genetic tests, laboratory directors and technical supervisors are responsible for ensuring that the testing method is appropriate for the clinical use of the test results and can provide the quality of results needed for patient care (36). Laboratory directors and clinical consultants must ensure laboratory consultations are available for laboratory clients regarding the appropriateness of the tests ordered and interpretation of test results (36). Documentation of available

clinical validity information helps laboratories that perform molecular genetic testing to fulfill their responsibilities for consulting with health-care professionals and other users of laboratory services, especially regarding tests that evaluate germline mutations or variants that might be performed only once during a patient's lifetime.

Establishing clinical validity is a continuous process and might require extended studies and involvement of many disciplines (38). The recommendations in this report emphasize the responsibility of laboratories that perform molecular genetic testing to document available information from medical and scientific research studies on the intended patient populations to be able to perform testing and provide results interpretation appropriate for specific clinical contexts. Laboratory directors are responsible for using professional judgment to evaluate the results of such studies as applied to newly discovered gene targets, especially those of a predictive or incompletely penetrant nature, in considering potential new tests. The recommendations in this report are consistent with the voluntary professional and accreditation guidelines of ACMG, CLSI, and CAP for molecular genetic testing (12–14,93,94).

Control Procedures

General quality control practices. The analytic phase of molecular genetic testing often includes the following steps: specimen processing; nucleic acid extraction, preparation, and assessment; enzymatic reaction or amplification; analyte detection; and recording of test results. Laboratories that perform molecular genetic testing must meet the general CLIA requirements for nonwaived testing (42 CFR §493.1256) (36), including the following applicable quality control requirements:

- Laboratories must have control procedures in place to monitor the accuracy and precision of the entire analytic process for each test system.
- The number and type of control materials and the frequency of control procedures must be established using applicable performance specifications verified or established by the laboratory.
- Control procedures must be in place for laboratories to detect immediate errors caused by test system failure, adverse environmental conditions, and operator performance to monitor the accuracy and precision of test performance over time.
- At least once each day that patient specimens are tested, the laboratory must include the following:
 - At least two control materials of different concentrations for each quantitative procedure
 - A negative control material and a positive control material for each qualitative procedure

- A negative control material and a control material with graded or titered reactivity, respectively, for each test procedure producing graded or titered results
- Two control materials, including one that is capable of detecting errors in the extraction process, for each test system that has an extraction phase
- Two control materials for each molecular amplification procedure and, if reaction inhibition is a substantial source of false-negative results, a control material capable of detecting the inhibition
- If control materials are not available, the laboratory must have an alternative method for detecting immediate errors and monitoring test system performance over time; the performance of the alternative control procedures must be documented.

Specific quality control practices. Specific quality control practices are necessary for ensuring the quality of molecular genetic test performance. The following recommendations include specific guidelines for meeting the general CLIA quality control requirements and additional measures that are more stringent or explicit than the CLIA requirements for monitoring and ensuring the quality of the molecular genetic testing process:

- When possible, include quality control samples that are similar to patient specimens to monitor the quality of all analytic steps of the testing process.
- Include an extraction control for any test that has a nucleic acid extraction step to monitor and determine the quality and integrity of the specimens, evaluate whether the yield of nucleic acid extraction is appropriate for the test, and detect the presence of inhibitors.
- Validate and monitor sampling instruments to ensure no carryover (i.e., contamination) occurs between sample testing on automated instruments. For example, if DNA extraction is performed by an automated system, the positioning and regular testing of appropriate controls should be included in the quality control procedures. Experiments in which samples containing target nucleic acids are interspaced with samples with no template nucleic acids (i.e., checkerboard experiments) might be considered as a method for monitoring and detecting carryover.
- Perform control procedures each time patient specimens are tested.
- Ensure that the type and variety of the control materials included in tests are as comprehensive as possible, representing the genotypes expected for the patient population according to the prevalence of the disease and frequency of the mutations or variants. For example, either a heterozy-

gous sample or a normal sample and a homozygous mutant sample might be considered sufficient for a test being used to detect a single mutation. For a sequencing assay performed for a known mutation, such as testing a patient's family member for a mutation that the laboratory previously detected in the patient, the laboratory should include the patient's sample as a positive control for the testing.

Alternative control procedures. Ideally, laboratories should use control materials to monitor the entire testing process, but such materials are not always practical or available. Appropriate alternative control procedures depend on the specific test and the control materials needed. Following are examples of accepted alternative control procedures when control materials are not available:

- If the positive control material for a specific mutation is not available for a targeted mutation analysis, alternative control procedures could include direct sequencing or testing of the patient sample by a reference laboratory to confirm the finding before reporting the test result.
- Inclusion of a normal control is important for sequencing procedures. A normal control could be a tested, well-characterized patient sample that contains the reference sequence or a sample that contains subcloned reference sequence. If a positive control is not available, alternative control procedures could include bidirectional sequencing, which should use a separately extracted nucleic acid sample (if possible).
- If having positive controls for each variant or mutation is impractical in testing that detects multiple mutations or variants, rotating all positive controls within a time frame that is reasonable and effective for monitoring test performance over time and detecting immediate errors is important.
- If a commercial test system provides some but not all of the controls needed for testing, the laboratory must perform and follow the manufacturer recommendations for control testing and should determine the additional control procedures (including the number and types of control materials and the frequency of testing them) necessary for monitoring and ensuring the quality of test performance (36,96).
- Laboratories must have an alternative mechanism capable of monitoring DNA extraction and the preceding analytic steps if 1) purified DNA samples are used as control materials for circumstances in which incorporation of an extraction control is impractical or 2) when testing is performed for a rare disease or rare variants for which no control material is available for the extraction phase. For example, testing patient specimens for an internal control

sequence (e.g., a housekeeping gene or a spiked-in control sequence) might allow for monitoring of the sample quality and integrity, the presence of inhibitors, and proper amplification (12,93). A positive control, or a control sample capable of monitoring the ability of a test system to detect the nucleic acid targets, should be tested periodically and carried through the extraction step to monitor and verify the performance of the test system.

The CMS *Survey Procedures and Interpretive Guidelines for Laboratories and Laboratory Services* provides general guidelines for alternative control procedures and encourages laboratories to use multiple mechanisms for ensuring testing quality (96). Following are examples of procedures that, when applicable, should be followed by laboratories that perform molecular genetic testing:

- Split specimens for testing by another method or in another laboratory.
- Include previously tested patient specimens (both positive and negative) as surrogate controls.
- Test each patient specimen in duplicate.
- Test multiple types of specimens from the same patient (e.g., saliva, urine, or serum).
- Perform serial dilutions of positive specimens to confirm positive reactions.
- Conduct an additional supervisory review of results before release.

Unidirectional workflow for molecular amplification procedures. CLIA requires laboratories to have procedures in place to monitor and minimize contamination during the testing process and to ensure a unidirectional workflow for amplification procedures that are not contained in closed systems (42 CFR §493.1101) (36). In this context, a closed system is a test system designed to be fully integrated and automated to purify, concentrate, amplify, detect, and identify targeted nucleic acid sequences. Such a modular system generates test results directly from unprocessed samples without manipulation or handling by the user; the system does not pose a risk for cross-contamination because amplicon-containing tubes and compartments remain completely closed during and after the testing process. For example, according to CLIA regulations, an FDA-cleared or FDA-approved test system that contains amplification and detection steps in sealed tubes that are never opened or reopened during or after the testing process and that is used as provided by the manufacturer (i.e., without any modifications) is considered a closed system.

The requirement for a unidirectional workflow, which includes having separate areas for specimen preparation, amplification, product detection, and reagent preparation, applies to any testing that involves molecular amplification procedures. The following recommendations provide more spe-

cific guidelines for laboratories that perform molecular genetic testing for heritable diseases and conditions using amplification procedures that are not in a closed system:

- Include at least one no-template control (NTC) sample each time patient specimens are assayed. Molecular amplification procedures are especially sensitive to carryover and cross-contamination. Although laboratories must ensure a unidirectional workflow and might use reagents and other methods to prevent or minimize carryover, inclusion of NTC samples in these procedures is essential for monitoring the test procedures and indicating whether measures taken to minimize cross-contamination are effective. At a minimum, the NTC sample should be included in the amplification step and carried through the subsequent steps detecting test results. When possible, an NTC sample also should be included in the extraction step, in addition to the NTC sample for the amplification. If multiple units (e.g., multiple 96-well plates) are used 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.
- Determine the order of samples, including the number and positions of the NTC and other control samples, to adequately monitor carryover contamination. For testing performed in multiple units, the number and positions of NTC samples also may be used for unambiguous identification of each unit.
- Ensure that specific procedures are in place to monitor the unidirectional workflow and to prevent cross-contamination for tests using successive amplification procedures (e.g., amplification of nucleic acid targets from a previous polymerase chain reaction [PCR] or nested PCR) if reaction tubes are opened after amplification for subsequent manipulation with the amplicons. Additives that destroy amplicons from previous PCR reactions also may be used.

Laboratories should recognize that methods such as PCR amplification, whole genome amplification, or subcloning to prepare quality control materials might be a substantial source of laboratory contamination. These laboratories should have the following specific procedures to monitor, detect, and prevent cross-contamination:

- Separation of the workflow of generating and preparing synthetic or amplified products for use as control materials from the patient testing process. To prevent laboratory contamination, control materials should be processed and stored separately from the areas for preparation and storage of patient specimens and testing reagents.
- Regular testing of appropriate control samples at a frequency adequate to monitor cross-contamination.

These practices also should be considered by laboratories that purchase amplified materials for use as control materials, calibration materials, or competitors.

Proficiency Testing and Alternative Performance Assessment

Proficiency testing is an important tool for assessing laboratory competence, evaluating the laboratory testing process, and providing education for the laboratory personnel. For certain analytes and testing specialties for which CLIA regulations specifically require proficiency testing, proficiency testing is provided by private-sector and state-operated programs that are approved by HHS because they meet CLIA standards (42 CFR Part 493). These approved programs also may provide proficiency testing for genetic tests and other tests that are not on the list of regulated analytes and specialties (131). Although the CLIA regulations do not have proficiency testing requirements specific for molecular genetic tests, laboratories that perform genetic tests must comply with the general requirements for alternative performance assessment for any test or analyte not specified as a regulated analyte to, at least twice annually, verify the accuracy of any genetic test or procedure they perform (42 CFR §493.1236[c]). Laboratories can meet this requirement by participating in available proficiency testing programs for the genetic tests they perform (132).

The following recommended practices provide more specific and stringent measures than the current CLIA requirements for performance assessment of molecular genetic testing. The recommendations should be considered by laboratories that perform molecular genetic testing to monitor and evaluate the ongoing quality of the testing they perform:

- Participate in available proficiency testing, at least twice per year, for each molecular genetic test the laboratory performs. Proficiency testing is available for a limited number of molecular genetic tests (e.g., fragile X syndrome, factor V Leiden thrombophilia, and cystic fibrosis) (Appendix C). Laboratories that perform molecular genetic testing should regularly review information on the development of additional proficiency testing programs and ensure participation as new programs become available.
- Test analyte-specific or disease-specific proficiency testing challenges with the laboratory's regular patient testing workload by personnel who routinely perform the tests in the laboratory (as required by CLIA for regulated analytes).
- Evaluate proficiency testing results reported by the proficiency testing program and take steps to investigate and correct disparate results. The corrective actions to be taken after disparate proficiency testing results should include re-evaluation of previous patient test results and, if neces-

sary, of retained patient specimens that were previously tested.

Proficiency testing samples. When possible, proficiency testing samples should resemble patient specimens; at a minimum, samples resembling patient specimens should be used for proficiency testing for the most common genetic tests. When proficiency testing samples are provided in the form of purified DNA, participating laboratories do not perform all the analytic steps that occur during the patient testing process (e.g., nucleic acid extraction and preparation). Such practical limitations should be recognized when assessing proficiency testing performance. Laboratories are encouraged to enroll in proficiency testing programs that examine the entire testing process, including the preanalytic, analytic, and postanalytic phases.

Alternative performance assessment. For molecular genetic tests for which no proficiency testing program is available, alternative performance assessments must be performed at least twice per year to meet the applicable requirements of CLIA and requirements of certain states and accrediting organizations. The following recommendations should be considered when conducting alternative performance assessments:

- Although no data are available to determine whether alternative performance assessments are as effective as proficiency testing, professional guidelines (e.g., from CLSI and CAP) provide information on acceptable alternative performance assessment approaches (14,61). Laboratories that perform molecular genetic tests for which no proficiency testing program is available should adhere to these guidelines.
- Laboratories should ensure that alternative assessments reflect the test methods involved in performing the testing and that the number of samples in each assessment is adequate to verify the accuracy and reliability of test results.
- Ideally, alternative assessments should be performed through interlaboratory exchange (Appendix C) or using externally derived materials, because external quality assessments might detect errors or problems that would not be detected by an internal assessment.
- When interlaboratory exchange or obtaining external materials is not practical (e.g., testing for rare diseases, testing performed by only one laboratory, patented testing, or unstable analytes such as RNA or enzymes), laboratories may consider options such as repeat testing of blinded samples, blind testing of materials with known values, exchange with either a research facility or a laboratory in another country, splitting samples with another instrument or method, or interlaboratory data comparison (96).

Various resources for proficiency testing and external quality assessment (60,133,134) and for facilitating interlaboratory sample exchanges (135,136) are available to help laboratories consider approaches to meeting the proficiency testing and alternative performance assessment needs of their molecular genetic testing (Appendix C).

The Postanalytic Testing Phase

Molecular Genetic Test Reports

Content. Molecular genetic test reports must comply with the CLIA general test report requirements (42 CFR §493.1291) and should include the additional information that follows to ensure accurate understanding and interpretation of test results. CLIA requires that test reports for nonwaived testing include the following information:

- Patient name and identification number or a unique patient identifier and identification number
- Name and address of laboratory where the test was performed
- Test report date
- Test performed
- Specimen source (when appropriate)
- Test results and (if applicable) units of measurement or interpretation
- Information regarding the condition and disposition of specimens that did not meet laboratory criteria for acceptability

For in-house developed tests using analyte-specific reagents, test reports must include the following statement: “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” (21 CFR §809.30[e]).

Test reports of molecular genetic testing for heritable conditions should include the following additional information to ensure accurate results interpretation, patient management, and, the ordering of any needed additional tests by persons receiving or using the test results:

- *Patient name and any other necessary unique identifiers.*
The patient name should be included on the test report when possible, in addition to other necessary unique identifiers.
- *Patient date of birth*
- *Indication for testing*
- *Date and (if applicable) time of specimen collection and arrival in laboratory*
- *Name of referring physician or authorized person who ordered the test*

- *Test method, including the nucleic acid targets of the test.* Laboratories should indicate on the test report the test method used to perform the test, including the nucleic acid targets of the test and the analytic method (e.g., targeted mutation detection or DNA sequence analysis).
- *Test performance specifications and limitations.* CLIA requires laboratories to provide clients, on request, with a list of tests they perform and the required performance specifications (42 CFR §493.1291[e]). For molecular genetic tests, information on performance specifications and limitations (e.g., statement on the intended use and the technical limitations of the test methodology) should be essential components of the test report rather than information that is available only when requested.
- *Test results in current recommended standard nomenclature.* Molecular genetics nomenclature is evolving, and laboratories or users of laboratory services might not be familiar with the new nomenclature. Therefore, test results should be provided in current recommended standard nomenclature, which should include clarifications and commonly used terms (if the terms differ from the current recommended terms) and should indicate the genotypes detected. For certain genetic variants or diseases associated with more than one common version of nomenclature (e.g., cytochrome P450 [*CYP*] genes or hemoglobinopathies), laboratories might need to report all versions to ensure that test results are understandable and to avoid unnecessary repetition of the testing solely because the nomenclature varies or has changed over time. If no mutation is detected, the test report should indicate “no mutation detected” rather than “normal.”
- *Interpretation of test results.* Laboratories are required by CLIA to include interpretation of test results on test reports (if applicable). However, results interpretation should be included in all test reports of molecular genetic testing for heritable diseases and conditions. Laboratories should provide information on interpretation of test results in a clinically relevant manner that is relative to the purpose for the testing and should explain how technical limitations might affect the clinical use of the test results. When appropriate and necessary, test results can be explained in reference to family members (e.g., mutations previously detected in a family member that was used for selection of the test method) to ensure appropriate interpretation of results and understanding of their implications by the persons receiving or using the test results.
- *References to literature (if applicable)*
- *Recommendation for genetics consultation (when appropriate).* A genetics consultation might encompass genetic services (including genetic counseling) provided by trained,

qualified genetics professionals (e.g., genetic counselors, clinical geneticists, or other qualified professionals) for health-care providers, patients, or family members at risk for the condition.

- *Implications of test results for relatives or family members who might benefit from the information (if applicable)*
- *Statement indicating that the test results and interpretation are based on current knowledge and technology*

Updates and revisions. CLIA requires laboratories to provide pertinent updates on testing information to clients when changes occur that affect the test results or interpretation of test results (42 CFR §493.1291[e]). Because the field of molecular genetic testing is evolving rapidly, laboratories should consider the following:

- Keep an up-to-date database for the molecular genetic tests performed in the laboratory, and provide updates to users when knowledge advancement affects performance specifications, interpretation of test results, or both.
- Provide a revised test report if the interpretation of the original analytic result changes because of advances in knowledge or testing technology. Indications for providing revised test reports include the following:
 - A better interpretation is available on a previously detected variant.
 - Interpretation of previous test results has changed (e.g., a previously determined mutation is later recognized as a benign variant or polymorphism or vice versa).

Molecular genetic tests for germline mutations or variants or for other heritable conditions often are one-time tests, with results that can have life-time implications for the patients and family members. Decisions regarding health-care management should be made with consideration of changes or improvements in the interpretation of genetic test results as testing technology and knowledge advance. However, practical limitations, such as the logistical difficulty of recontacting previous users of laboratory services, also should be considered. Laboratories that perform molecular genetic testing for heritable diseases and conditions should have procedures in place that adhere to accepted professional practice guidelines regarding the duty to recontact previous users and should make a good-faith effort to provide updates and revisions to previous test reports, when appropriate (137). When establishing these procedures, laboratories also might consider the retention time frame of their molecular genetic test reports.

Signatures. Review of molecular genetic test reports by trained qualified personnel, before reports are released, is critical. The review should be appropriately documented with written or electronic signatures or by other methods. Laboratories should determine which persons should review and sign the

test reports in accordance with personnel competency and responsibilities.

Format, style, media, and language. Laboratories should assess the needs of laboratory users when determining the format, style, media, and language of molecular genetic test reports. The language used, which includes terminology and nomenclature, should be understandable by nongeneticist health professionals and other specific users of the test results. This practice should be part of the laboratory quality management policies. Test reports should include all necessary information, be easy to understand, and be structured in a way that encourages users read the entire report, rather than just a positive or negative indication. Following the format recommended in accepted practice guidelines should help ensure that the reports are structured effectively (12–14, 49, 93, 94, 100).

Retention of Reports, Records, and Tested Specimens

Reports. CLIA requires laboratories to retain or have the ability to retrieve a copy of an original test report (including final, preliminary, and corrected reports) for at least 2 years after the date of reporting and to retain pathology test reports for at least 10 years after the date of reporting (42 CFR §493.1105). A longer retention time frame than required by CLIA is warranted for reports of molecular genetic tests for heritable diseases and conditions. These test reports should be retained for at least 25 years after the date the results are reported.

Retaining molecular genetic test reports for a longer time frame is recommended because the results can have long-term, often lifetime, implications for patients and their families, and future generations might need the information to make health-related decisions. In addition, advances in testing technology and increased knowledge of disease processes could change the interpretation of the original test results, enable improved interpretation of test results, or permit future retesting with greater sensitivity and accuracy. Laboratories need the ability to retrieve previous test reports, which are valuable resources for conducting quality assessment activities, helping patients and family members make health decisions, and managing the health care of the patient and family members. As laboratories that perform molecular genetic testing for heritable diseases and conditions review and update policies and procedures for report retention, they should consider the financial ramifications of the policies, as well as technology and space concerns. Laboratories may consider retaining test reports electronically, on microfilms, or by other methods but must ensure that all of the information on the original reports is retained and that copies (whether electronic or hard copies) of the original reports can be retrieved.

The laboratory policies and procedures for test report retention must comply with applicable state laws and other requirements (e.g., of accrediting organizations if the laboratory is accredited) and should follow practice guidelines developed by recognized professional or standard-setting organizations. If state regulations require retention of genetic test reports for >25 years after the date of results reporting, laboratories must comply. Laboratories also might decide that retaining reports for >25 years is necessary for molecular genetic test reports for heritable diseases and conditions to accommodate patient testing needs and ongoing quality assessment activities.

Records. CLIA requires laboratories to retain records of patient testing, including test requests and authorizations, test procedures, analytic systems records, records of test system performance specifications, proficiency testing records, and quality system assessment records, for a minimum of 2 years (42 CFR §493.1105); these requirements apply to molecular genetic testing. Retention policies and procedures must also comply with applicable state laws and other requirements (e.g., of accrediting organizations if the laboratory is accredited). Laboratories should ensure that electronic records are accessible.

Tested specimens. CLIA 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 test results (42 CFR §493.1232). Depending on sample stability, technology, space, and cost, tested specimens for molecular genetic tests for heritable conditions should be retained as long as possible after the completion of testing and reporting of results. At a minimum, tested patient specimens that are stable should be retained until the next proficiency testing or the next alternative performance assessment to allow for identification of problems in patient testing and for corrective action to be taken. Tested specimens also might be needed for testing of current or future family members and for more definitive diagnosis as technology and knowledge evolve. A laboratory specimen retention policy should consider the following factors:

- Type of specimens retained (e.g., whole blood or DNA samples)
- Analytes tested (e.g., DNA, RNA, or both)
- Test results or the genotypes detected. (If only abnormal specimens are retained, identifying false-negative results at a later date will be difficult. This practice also might introduce bias if a preponderance of samples with abnormal test results is used to verify or establish performance specifications for future testing.)
- Test volume

- New technologies that might not produce residual specimens

The laboratory director is responsible for ensuring that the laboratory policies and procedures for specimen retention comply with applicable federal, state, and local requirements (including laboratory accreditation requirements, if applicable) and are consistent with the laboratory quality assurance and quality assessment activities. In circumstances in which required patient consent is not provided with the test request, the laboratory should 1) notify the test requestor and 2) determine the time frame after which the test request might be rejected and the specimen discarded because of specimen degradation or deterioration. Laboratory specimen retention procedures should be consistent with patient decisions.

Laboratory Responsibilities Regarding Authorized Persons

CLIA regulations define an authorized person as a person authorized by state laws or regulations to order tests, receive test results, or both. Laboratories must have a written or an electronic test request from an authorized person (42 CFR §493.1241[a]). Laboratories may only release test results to authorized persons, the person responsible for using the test results (if applicable), and the laboratory that initially requested the test (42 CFR §493.1291[f]). Laboratories that perform molecular genetic testing must ensure compliance with these requirements in their policies and procedures for receiving test requests and reporting test results and should ensure that qualified laboratory personnel with appropriate experience and expertise are available to assist authorized persons with test requests and interpretation of test results.

Laboratories must comply with applicable federal, state, and local requirements regarding whether genetic tests may be offered directly to consumers and should use accepted professional guidelines for additional information. The following recommendations will help laboratories meet CLIA requirements (42 CFR §§493.1241[a] and 1291[f]), particularly those related to genetic testing offered directly to consumers:

- The laboratory that initially accepts a test request (regardless of whether the laboratory performs the testing on-site or refers the patient specimens to another laboratory) is responsible for verifying that the test requestor is authorized by state laws and regulations to do so. Laboratories that receive patient specimens from multiple states or have specimen collection sites in multiple states should keep an updated copy of the requirements of each state regarding authorized persons and review test requests accordingly.
- Although referral laboratories might be unable to verify that the person submitting the original test request quali-

fies as an authorized person, the test results may only be released to persons authorized by state laws and regulations to receive the results, the persons responsible for using the test results, and the referring laboratory.

Ensuring Confidentiality of Patient Information

CLIA requires laboratories to ensure confidentiality of patient information throughout all phases of the testing process that are under laboratory control (42 CFR §493.1231). Laboratories should follow more specific requirements and comply with additional guidelines (e.g., the Health Insurance Portability and Accountability Act of 1996 [HIPAA] Privacy Rule, state requirements, accreditation standards, and professional guidelines) to establish procedures and protocols to protect the confidentiality of patient information, including information related to genetic testing. Laboratories that perform molecular genetic testing should establish and follow procedures and protocols that include defined responsibilities of all employees to ensure appropriate access, documentation, storage, release, and transfer of confidential information and prohibit unauthorized or unnecessary access or disclosure.

Information Regarding Family Members

In certain circumstances, information about family members is needed for test performance or should be included in test reports to ensure appropriate interpretation of test results. Therefore, laboratories must have procedures and systems in place to ensure confidentiality of all patient information, including that of family members, in all testing procedures and reports, in compliance with CLIA requirements and other applicable federal, state, and local regulations.

Requests for Test Results to Assist with Providing Health Care for a Family Member

When a health-care provider requests the genetic test information of a patient to assist with providing care for a family member of the patient, the following practices are recommended:

- Requests should be handled following established laboratory procedures regarding release and transfer of confidential patient information.
- Laboratories may release patient test information only to the authorized person ordering the test, the persons responsible for using the test results (e.g., health-care providers of the patient designated by the authorized person to receive test results), and the laboratory that initially requested the test. If a health-care provider who provides care for a family member of the patient is authorized to

request patient test information, the laboratory should request the patient's authorization before releasing the patient's genetic test results.

- When patient consent is required for testing, the consent form should include the laboratory confidentiality policies and procedures and describe situations in which test results might be requested by health-care providers caring for family members of the patient.
- Laboratory directors should be responsible for determining and approving circumstances in which access to confidential patient information is appropriate, as well as when, how, and to whom information is to be released, in compliance with federal, state, and local requirements.

The HIPAA Privacy Rule and CLIA regulations are federal regulations intended to provide minimum standards for ensuring confidentiality of patient information; states or localities might have higher standards. Although the HIPAA Privacy Rule allows health-care providers that are covered entities (i.e., health-care providers that conduct certain transactions in electronic form, health-care clearinghouses, and health plans) to use or disclose protected health information for treatment purposes without patient authorization and to share protected health information to consult with other providers to treat a different patient or to refer a patient, the regulation indicates that states or institutions may implement stricter standards to protect the privacy of patients and the confidentiality of patient information (138). Laboratories that perform molecular genetic testing must comply with applicable requirements and follow professional practice guidelines in establishing policies and procedures to ensure confidentiality of patient information, including molecular genetic testing information and test results.

Personnel Qualifications, Responsibilities, and Competency Assessments

Laboratory Director Qualifications and Responsibilities

Qualifications. CLIA requires directors of laboratories that perform high-complexity testing to meet at least one of the following sets of qualifications (42 CFR §493.1443):

- Be a doctor of medicine or a doctor of osteopathy and have board certification in anatomic or clinical pathology or both
- Be a doctor of medicine, doctor of osteopathy, or doctor of podiatric medicine and have at least 1 year of laboratory training during residency or at least 2 years of experience directing or supervising high-complexity testing

- Have an earned doctoral degree in a chemical, physical, biological, or clinical laboratory science from an accredited institution and current certification by a board approved by HHS

Directors of laboratories that perform molecular genetic testing for heritable diseases and conditions must meet these qualification requirements. Because CLIA requirements are minimum qualifications, laboratories that perform molecular genetic testing for heritable diseases and conditions should evaluate the tests they perform to determine whether additional knowledge, training, or expertise is necessary for fulfilling the responsibilities of laboratory director.

Responsibilities. CLIA requires directors of laboratories that perform high-complexity testing to be responsible for the overall operation and administration of the laboratory, which includes responsibility for the following (42 CFR §493.1445):

- Ensuring the quality of all aspects of test performance and results reporting for each test performed in the laboratory
- Ensuring that the physical and environmental conditions of the laboratory are appropriate and safe
- Ensuring enrollment in HHS-approved proficiency testing programs
- Employing a sufficient number of laboratory personnel with appropriate education, experience, training, and competency required for patient testing
- Establishing policies and procedures for personnel competency assessment and monitoring
- Specifying the responsibilities and duties of each consultant, supervisor, and testing employee
- Ensuring compliance with applicable requirements and regulations

Directors of laboratories that perform molecular genetic testing for heritable diseases and conditions must fulfill these CLIA responsibility requirements. In addition, these laboratory directors should be responsible for the following:

- Ensuring documentation of the clinical validity of any molecular genetic tests the laboratory performs, following the recommended practices
- Ensuring the specimen retention policy is consistent with the laboratory quality assessment activities

Technical Supervisor Qualifications and Responsibilities

Qualifications. CLIA regulations do not specify qualification requirements for technical supervisors of molecular genetic testing. Technical supervisors of laboratories that perform molecular genetic testing for heritable diseases and conditions should have either one of the following sets of qualifications:

- Qualifications equivalent to the CLIA qualification requirements for clinical cytogenetics technical supervisors (42 CFR §493.1449[p]), which include either one of the following sets of qualifications:
 - Be a doctor of medicine, doctor of osteopathy, or doctor of podiatric medicine licensed to practice medicine, osteopathy, or podiatry in the state in which the laboratory is located and have 4 years of training or experience (or both) in genetics, 2 of which are in the area of molecular genetic testing for heritable diseases and conditions
 - Have an earned doctoral degree in a chemical, physical, biological, or clinical laboratory science from an accredited institution and have 4 years of training or experience (or both) in genetics, 2 of which are in the area of molecular genetic testing for heritable diseases and conditions
- Current certification in molecular genetic testing by a board approved by HHS (e.g., the American Board of Medical Genetics [ABMG]) or in molecular genetic pathology by ABMG and the American Board of Pathology

The recommended technical supervisor qualifications are based on the complexity of molecular genetic testing for heritable diseases and conditions and the training, experience, and expertise needed to provide technical supervision for laboratories that perform these tests. Certain laboratories that perform molecular genetic testing for heritable diseases and conditions might have technical supervisors who meet the applicable CLIA qualification requirements for the high-complexity testing their laboratories perform but do not meet the recommended qualifications in this section. These recommended qualifications are not regulatory requirements and are not intended to restrict access to certain molecular genetic tests; rather, they should be considered part of recommended laboratory practices for ensuring the quality of molecular genetic testing for heritable diseases and conditions. However, because CLIA qualification requirements are intended to be minimum standards, laboratories should assess the tests they perform to determine whether additional qualifications are needed for their technical supervisors to ensure quality throughout the testing process. These recommended qualifications should apply to all high-complexity molecular genetic tests for heritable diseases and conditions.

Responsibilities. CLIA requires technical supervisors of laboratories that perform high-complexity testing to be responsible for the technical and scientific oversight of the laboratories (42 CFR §493.1451). Technical supervisor responsibilities include the following:

- Selecting testing methods appropriate for the clinical use of the test results

- Verifying or establishing performance specifications for each test or test system
- Enrolling the laboratory in HHS-approved proficiency testing programs
- Establishing and maintaining an appropriate quality control program and ensuring the quality of test performance throughout the testing process
- Resolving technical problems
- Ensuring all necessary remedial or corrective actions are taken before patient test results are reported
- Implementing laboratory personnel competency assessment policies, including evaluating and ensuring the competency of all testing personnel, identifying training needs, ensuring testing personnel receive regular in-service training and education appropriate for the type and complexity of the laboratory services performed, and documenting performance of testing personnel regularly as required

Technical supervisors of laboratories that perform molecular genetic testing for heritable diseases and conditions must fulfill these CLIA responsibility requirements for high-complexity testing. In addition, when deemed necessary by the laboratory director, the responsibilities of the technical supervisor also might include one or more of the following tasks:

- Assessing the suitability of test requests for the expected clinical use of the test results
- Ensuring appropriate documentation of clinical validity information before offering new testing for patients
- Reviewing test results and their interpretation before reporting test results, and if appropriate, signing test reports or providing other documentation of the review on the test reports
- Providing explanations or clarifications to questions regarding test reports, including test results and interpretation
- Providing on-site technical supervision for molecular genetic testing

Clinical Consultant Qualifications and Responsibilities

Qualifications. CLIA requires clinical consultants for high-complexity testing to have either one of the following sets of qualifications (42 CFR §493.1455):

- Be qualified as a laboratory director for high-complexity testing as specified in the regulations
- Be a doctor of medicine, doctor of osteopathy, or doctor of podiatric medicine licensed to practice medicine, osteopathy, or podiatry in the state in which the laboratory is located

These CLIA requirements provide minimum qualifications required for persons who provide clinical consultations for high-complexity testing. For molecular genetic testing for heritable diseases and conditions, clinical consultants should have relevant training, experience, or both in the testing for which they consult. Preferably, clinical consultants for molecular genetic testing for heritable diseases and conditions should have either one of the following sets of qualifications, which are more specific than those required by CLIA:

- Be a doctor of medicine, doctor of osteopathy, or doctor of podiatric medicine and have 2 years of training or experience in genetic testing relevant to the clinical consultation to be provided
- Have an earned doctoral degree in a relevant discipline, be currently certified by a board approved by HHS, and have 2 years of training or experience in genetic testing relevant to the clinical consultation to be provided

Although genetic counselors who have a master's degree do not meet CLIA requirements for clinical consultants, they perform important functions such as communicating with health-care providers, patients, and family members at risk for certain conditions or diseases regarding test selection, interpretation, of test results, and implications of test results for specific patients and families.

Responsibilities. CLIA requires clinical consultants for high-complexity tests to be responsible for providing consultation to laboratory clients regarding the appropriateness of the testing ordered and the interpretation of test results (42 CFR §493.1457). Persons providing clinical consultation for molecular genetic testing must meet the following CLIA responsibility requirements:

- Be available to provide consultation to laboratory clients, which includes assisting clients with ordering appropriate tests to meet clinical expectations and discussing the quality of test results and interpretation result
- Ensure that test reports include pertinent information required for interpretation of specific patient conditions

General Supervisor Qualifications and Responsibilities

Qualifications. CLIA requires general supervisors of laboratories that perform high-complexity tests to have at least one of the following sets of qualifications (42 CFR §§493.1461 and 1462):

- Be qualified as a laboratory director or technical supervisor
- Be a doctor of medicine, doctor of osteopathy, or doctor of podiatric medicine licensed to practice medicine, osteopathy, or podiatry in the state in which the laboratory is located

- Have a doctoral, master's, or bachelor's degree in a chemical, physical, biological or clinical laboratory science and 1 year of training or experience in high-complexity testing
- Have an associate's degree or equivalent in a chemical, physical, biological, or clinical laboratory science and 2 years of training or experience in high-complexity testing
- Meet the CLIA requirements to be grandfathered in on the basis of training, experience, and employment before 1992

General supervisors of laboratories that perform molecular genetic testing for heritable conditions must fulfill these CLIA qualification requirements for high-complexity testing. Because the CLIA qualification requirements apply to high-complexity testing in general, laboratories that perform molecular genetic testing should ensure that general supervisors have specific training or experience in the high-complexity molecular genetic testing the laboratory performs.

Responsibilities. CLIA requires general supervisors for high-complexity tests to be responsible for day-to-day supervision or oversight of laboratory operations and of the personnel who are performing testing and reporting test results (42 CFR §493.1463). General supervisors of laboratories that perform molecular genetic testing for heritable diseases and conditions must meet the following CLIA responsibility requirements:

- Be accessible to testing personnel at all times testing is performed
- Provide day-to-day supervision and direct supervision of all testing personnel, including those who have been grandfathered in
- Monitor testing procedures to ensure the quality of analytic performance
- Fulfill the following duties when delegated by the laboratory director or technical supervisor:
 - Ensure that remedial actions are taken when test systems deviate from the established performance specifications.
 - Ensure that patient test results are not reported until all corrective actions have been taken and the test system is properly functioning.
 - Provide orientation for all testing personnel.
 - Annually evaluate and document the performance of all testing personnel.

Testing Personnel Qualifications and Responsibilities

Qualifications. CLIA requires testing personnel who perform high-complexity testing to have at least one of the following sets of qualifications (42 CFR §§493.1489 and 1491):

- Be a doctor of medicine, doctor of osteopathy, or doctor of podiatric medicine
- Have an earned doctoral, master's, or bachelor's degree in a chemical, physical, biological or clinical laboratory science or medical technology from an accredited institution
- Have an earned associate's degree in a laboratory science or medical laboratory technology from an accredited institution
- Meet the CLIA requirements to be grandfathered in on the basis of training, experience, and employment before 1992

These qualification requirements apply to testing personnel who perform molecular genetic testing for heritable diseases and conditions. Laboratories should ensure that testing personnel have received adequate training, including on-the-job training, and demonstrate competency in high-complexity molecular genetic testing before performing patient testing.

Responsibilities. CLIA requires persons who perform high-complexity testing to follow laboratory procedures and protocols for test performance, quality control, results reporting, documentation, and problem identification and correction (42 CFR §493.1495). Personnel who perform molecular genetic testing for heritable diseases and conditions must meet these requirements.

Personnel Competency Assessment

CLIA requires laboratories to establish and follow written policies and procedures to assess employee competency, and if applicable, consultant competency (42 CFR §493.1235). CLIA requirements for laboratory director responsibilities (42 CFR §493.1445[e][13]) specify that laboratory directors must ensure that policies and procedures are established for monitoring and ensuring the competency of testing personnel and for identifying needs for remedial training or continuing education to improve skills. Technical supervisors are responsible for implementing the personnel competency assessment policies and procedures, including evaluating and ensuring competency of testing personnel (42 CFR §493.1451[b][8]). Laboratories that perform molecular genetic testing for heritable diseases and conditions must meet these general personnel competency assessment requirements. Laboratories also should follow the applicable CMS guidelines to establish and implement policies and procedures specific for assessing and ensuring the competency of all types of laboratory personnel, including technical supervisors, clinical consultants, general supervisors, and testing personnel, in performing duties and responsibilities (96). For example, the performance of testing personnel must be evaluated and documented at least semiannually during the first year a person tests patient specimens. Thereafter, evaluations must be performed at least annually;

however, if test methodology or instrumentation changes, performance must be re-evaluated to include the use of the new test methodology or instrumentation before testing personnel can report patient test results. Personnel competency assessments should identify training needs and ensure that persons responsible for performance of molecular genetic testing receive regular in-service training and education appropriate for the services performed.

Considerations Before Introducing Molecular Genetic Testing or Offering New Molecular Genetic Tests

Recommendations described in this report should be considered, in addition to appropriate professional guidelines and recommendations, when planning and preparing for the introduction of molecular genetic testing or offering new molecular genetic tests. The following scenarios should be considered during the planning stage:

- Introducing a new molecular genetic test that has not been offered in any laboratory
- Introducing a genetic test that previously has been referred to another laboratory but will be performed in-house
- Introducing an additional genetic test that can complement a molecular genetic test that has been performed for patient testing

These scenarios present different planning concerns, including needs and requirements for training and competency of laboratory personnel, laboratory facilities and equipment, selection of test methods, development of procedure manuals, establishment or verification of performance specifications, and personnel responsibilities. In addition, the following factors should be assessed:

- Needs and demands of the new test, which can be assessed by consulting with ordering physicians and other potential users of laboratory services and by conducting other market analyses
- Intellectual property or licensing concerns that might result in restricted use, increased costs, or both of certain genetic tests

Quality Management System Approach for Molecular Genetic Testing

The quality management system (QMS) approach provides a framework for managing and monitoring activities to address quality standards and achieve organizational goals, with a focus on user needs (41,109). QMS has been the basis for many international quality standards, such as the International

Organization for Standardization (ISO) standards ISO 15189, ISO 17025, and ISO 9001 (91,139,140). These international QMS standards overlap with certain CLIA requirements but are distinct from CLIA regulations.

Because QMS is not yet a widely adopted approach in the United States, laboratories that perform molecular genetic testing might not be familiar with QMS implementation in current practice. The QMS approach has been described in several CLSI guidelines (41,109). New York state CLEP and CAP have included QMS concepts in the general laboratory standards (15,102), and CAP and the American Association for Laboratory Accreditation have begun to provide laboratory accreditation to ISO 15189 (141,142). Laboratories that perform molecular genetic testing should monitor QMS development, because implementing the QMS approach could help laboratories accept international test referrals and improve quality management of testing.

Conclusion

The recommendations in this report are intended to serve as guidelines for considering and implementing good laboratory practices to 1) improve quality and health-care outcomes related to molecular genetic testing for heritable diseases and conditions and 2) enhance oversight and quality assurance practices for molecular genetic testing under the CLIA regulatory framework. The report can be adapted for use in different settings where molecular genetic testing is conducted or evaluated. Continual monitoring of the practice and test performance of molecular genetic tests is needed to evaluate the effectiveness of these recommendations and to develop additional guidelines for good laboratory practices for genetic testing, which will ultimately improve public health.

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Appendix A

Terms and Abbreviations Used In This Report

ABMG	American Board of Medical Genetics
ABN	Advance beneficiary notice
Accuracy	Closeness of the agreement between the result of a measurement and a true value of the measurand
ACMG	American College of Medical Genetics
Allele	One version of a gene at a given location (locus) along a chromosome
AMP	Association for Molecular Pathology
Amplicon	Piece of nucleic acid formed as the product of molecular amplification
Amplification	In vitro enzymatic replication of a target nucleic acid (e.g., polymerase chain reaction [PCR])
ASR	Analyte-specific reagent
Bidirectional sequencing	A method used to determine the positions of a selected nucleotide base in a target region on both strands of a denatured duplex nucleic acid polymer
CAP	College of American Pathologists
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments of 1988
CLIAAC	Clinical Laboratory Improvement Advisory Committee
CLSI	Clinical and Laboratory Standards Institute (formerly NCCLS)
CMS	Centers for Medicare & Medicaid Services
Competency assessment	Evaluation of a person's ability to perform all aspects of testing, from specimen collection to result reporting
Control material	A device, material, solution, or lyophilized preparation intended for use in the quality-control process
CPT	Current Procedural Terminology
CVS	Chorionic villus sampling
DNA	Deoxyribonucleic acid, the molecule that encodes genetic information
DTC	Direct to consumer
Family history	The genetic relationships and medical history of a family; also referred to as a pedigree when represented in diagram form using standardized symbols and terminology
FDA	Food and Drug Administration
Founder effect	The presence of gene mutation in high frequency in a specific population that arises because the gene mutation was present in a single ancestor or small number of ancestors in the founding population
Genetics	The study of inheritance patterns of specific traits
Genome	The complete genetic content of an organism
Genotype	The genetic constitution of an organism or cell; also refers to the specific set of alleles inherited at a locus
Germline mutation	The presence of an altered gene within the egg or sperm (germ cell), such that the altered gene can be passed to subsequent generations
Heterozygote	A person with two different alleles at a particular locus, one on each chromosome of a pair, typically with one normal and one abnormal allele
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act of 1996
Homozygote	Person with two identical alleles at a particular locus, one on each chromosome of a pair
ICD	International Classification of Disease

Informed consent process	For molecular genetic testing, the process by which a person voluntarily confirms the willingness to participate in a particular test, after having been informed of all aspects of the test that are relevant to the decision to participate
LOD	Lower limit of detection
Modifiers	Genetic or environmental factors that might affect the expressivity (the variability of signs or symptoms that occur with a phenotype) of a genetic alteration
Mutation	An alteration in a gene, which might cause a disease, be a benign alteration, or result in a normal variant
Newborn screening	Testing conducted within days of birth to identify infants at increased risk for specific genetic disorders, allowing education and counseling for parents and treatment for patients to be initiated as soon as possible
NTC	No-template control
Pedigree	A diagram using standard symbols and terminology to indicate the genetic relationships and medical history of a family
Penetrance	The proportion of persons with a mutation causing a particular disorder who exhibit clinical symptoms of the disorder
Personalized medicine	Approach to medicine involving use of genomic and molecular data to better target health care, facilitate discovery and clinical testing of new products, and determine patient risk for a particular disease or condition
Phenotype	The observable physical and biochemical traits resulting from of the expression of a gene; the clinical presentation of a person with a particular genotype
Polymerase chain reaction (PCR)	A DNA amplification procedure that produces millions of copies of a short segment of DNA through repeated cycles of 1) denaturation, 2) annealing, and 3) elongation; a very common procedure in molecular genetic testing used to generate a sufficient quantity of DNA to perform a test (e.g., sequence analysis or mutation scanning) or as a test itself (e.g., allele-specific amplification or trinucleotide repeat quantification)
Positive predictive value	The likelihood that a person with a positive test result actually has a particular gene, is affected by the gene, or will develop the disease
Precision	Closeness of agreement between independent test results obtained under stipulated conditions
Private mutation	A rare, disease-causing mutation occurring in a few families
Proficiency testing	An external quality assessment program in which samples are periodically sent to testing sites for analysis
Quality assessment	A group of activities to monitor and evaluate the entire testing process; used to help ensure that test results are reliable, improve the testing process, and promote good quality testing practices
Quality control	Measures taken to detect, reduce, and correct deficiencies in a laboratory's internal analytical process prior to the release of patient results and to improve the quality of the results reported by the laboratory
Reagent	A substance that produces a chemical or biological reaction with a patient specimen, allowing detection or measurement of the analyte for which the test is designed
Reference interval	Interval between and including the lower reference limit through the upper reference limit of the reference population (e.g., 95% of persons presumed to be healthy [or normal])
Reportable range	The range of test values over which the relationship between the instrument, kit, or measurement response of the system is shown to be valid
RNA	Ribonucleic acid
SACGHS	Secretary's Advisory Committee on Genetics, Health, and Society
Sequencing	A procedure used to determine the order of nucleotides (base sequence) in a DNA or RNA molecule or the order of amino acids in a protein

Targeted mutation analysis

Testing for one or more specific mutations

Total testing process

Series of activities or workflow for performing testing; includes three major phases: pre-analytic, analytic, and postanalytic

Unidirectional workflow

The manner in which testing personnel and patient specimens move through the molecular amplification testing process to prevent cross-contamination

Variant

Any heritable change in DNA sequence

Appendix B

Examples of State-Required Components of Informed Consent for Genetic Testing – Selected States*

Massachusetts†

- A statement of the purpose of the test
- A statement that before signing the consent form, the consenting person discussed with the medical practitioner ordering the test the reliability of positive or negative test results and the level of certainty that a positive test result for that disease or condition serves as a predictor of such disease
- A statement that the consenting person was informed about the availability and importance of genetic counseling and provided with written information identifying a genetic counselor or medical geneticist from whom the consenting person might obtain such counseling
- A general description of each specific disease or condition tested for
- The persons to whom the test results may be disclosed

Michigan§

- The nature and purpose of the presymptomatic or predictive genetic test
- The effectiveness and limitations of the presymptomatic or predictive genetic test
- The implications of taking the presymptomatic or predictive genetic test, including, but not limited to, the medical risks and benefits
- The future uses of the sample taken from the test participant to conduct the presymptomatic or predictive genetic test and the information obtained from the presymptomatic or predictive genetic test

- The meaning of the presymptomatic or predictive genetic test results and the procedure for providing notice of the results to the test participant
- Who will have access to the sample taken from the test participant to conduct the presymptomatic or predictive genetic test and the information obtained from the presymptomatic or predictive genetic test, and the test participant's right to confidential treatment of the sample and the information

Nebraska¶

- The nature and purpose of the presymptomatic or predictive genetic test
- The effectiveness and limitations of the presymptomatic or predictive genetic test
- The implications of taking the presymptomatic or predictive genetic test, including the medical risks and benefits
- The future uses of the sample taken to conduct the presymptomatic or predictive genetic test and the genetic information obtained from the presymptomatic or predictive genetic test
- The meaning of the presymptomatic or predictive genetic test results and the procedure for providing notice of the results to the patient
- Who will have access to the sample taken to conduct the presymptomatic or predictive genetic test and the genetic information obtained from the presymptomatic or predictive genetic test and the patient's right to confidential treatment of the sample and the genetic information

New York**

- A general description of the test
- A statement of the purpose of the test
- A statement indicating that the person might consider obtaining professional genetic counseling before signing the informed consent

* The National Conference of State Legislatures provides a summary table of each state's genetic testing privacy statutes (available at <http://www.ncsl.org/programs/health/genetics/prt.htm>). As of June 2008, 12 states required informed consent for a third party to perform or request a genetic test; the five states included in this appendix (Massachusetts, Michigan, Nebraska, New York, and South Dakota) have specific informed consent components in the statutes.

† State of Massachusetts. Chapter 111: §70G. Genetic information and reports protected as private information; prior written consent for genetic testing. Available at <http://www.mass.gov/legis/laws/mgl/111-70g.htm>.

§ State of Michigan. Public Health Code. Act 368 of 1978. §333.17520. Genetic test; informed consent. Available at [http://www.legislature.mi.gov/\(S\(n1vwrs55k0f0v2zec544quuk\)\)/mileg.aspx?page=getobject&objectName=mcl-333-17020](http://www.legislature.mi.gov/(S(n1vwrs55k0f0v2zec544quuk))/mileg.aspx?page=getobject&objectName=mcl-333-17020).

¶ State of Nebraska. Nebraska revised statutes. §71-551. Physician; genetic tests; written informed consent; requirements; Department of Health and Human Services; duty. Available at <http://uniweb.legislature.ne.gov/laws/statutes.php?statute=s7105051000>.

** New York State. Civil Rights Law. §79-I: confidentiality of records of genetic tests; 2002. Available at http://www.wadsworth.org/labcert/regaffairs/clinical/79-1_1_2002.pdf.

- A statement that a positive test result is an indication that the person might be predisposed to or have the specific disease or condition being tested for and might consider additional independent testing, consult a personal physician, or pursue genetic counseling
- A general description of each specific disease or condition being tested for
- The level of certainty that a positive test result for the disease or condition serves as a predictor of such disease. (If no level of certainty has been established, this may be disregarded.)
- The name of the person or categories of persons or organizations to whom the test results may be disclosed
- A statement that no tests other than those authorized will be performed on the biological sample and that the sample will be destroyed at the end of the testing process or not more than 60 days after the sample was taken, unless a longer period of retention is expressly authorized in the consent
- The signature of the person being tested or, if that person lacks the capacity to consent, the signature of the person authorized to consent for the person being tested

South Dakota^{††}

- The nature and purpose of the test
- The effectiveness and limitations of the test
- The implications of taking the test, including, the medical risks and benefits
- The future uses of the sample taken from the person tested to conduct the test and the information obtained from the test
- The meaning of the test results and the procedure for providing notice of the results to the person tested
- A list of who will have access to the sample taken from the person tested and the information obtained from the test and the person's right to confidential treatment of the sample and the information

^{††}State of South Dakota. South Dakota codified laws. Chapter 34-14-22; SL 2001, chapter 184, §2. Available at <http://legis.state.sd.us/statutes/Display-Statute.aspx?Statute=34-14-22&Type=Statute>.

Appendix C

Selected Proficiency Testing Programs and Interlaboratory Sample Exchange Programs for Molecular Genetic Testing for Heritable Diseases and Conditions

College of American Pathologists (CAP)*

Proficiency Testing

Sample type: purified DNA

- *BRCA1* and *BRCA2* genes (familial breast and ovarian cancer)
- Canavan disease
- Nonsyndromic hearing loss and deafness (*GJB2*-[connexin 26-]related DFNA 3)
- Cystic fibrosis
- Duchenne muscular dystrophy, Becker muscular dystrophy
- Factor V Leiden thrombophilia
- Familial dysautonomia
- Fragile X syndrome
- Friedreich ataxia
- Hereditary hemochromatosis
- Sickle cell disease
- Huntington disease
- *MTHFR* (5,10-methylenetetrahydrofolate reductase gene)
- Multiple endocrine neoplasia type 2 (*RET* gene)
- Myotonic dystrophy
- Prader-Willi syndrome, Angelman syndrome
- Prothrombin thrombophilia
- *RHD* genotyping
- Spinal muscular atrophy
- Spinocerebellar ataxia
- Tay-Sachs disease

Pharmacogenetic Proficiency Testing

Sample type: purified DNA

- *CYP2C9* (cytochrome P450, family 2, subfamily C, polypeptide 9 gene)
- *CYP2C19* (cytochrome P450, family 2, subfamily C, polypeptide 19 gene)

- *CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6 gene)
- *UGT1A1* (UDP glucuronosyltransferase 1 family, polypeptide A1 gene) (Gilbert syndrome)
- *VKORC1* (vitamin K epoxide reductase complex, subunit 1 gene)

CDC Newborn Screening Quality Assurance Program†

Proficiency Testing

Sample type: dried blood spots

Proficiency testing is available for DNA-based detection of cystic fibrosis mutations

EuroGentest§

External Quality Assessment

Sample types: blood spots, purified DNA, lyophilized human blood plasma, and serum

External quality assessments are similar to proficiency testing in the United States. Assessments are provided by one or more individual programs in Europe and facilitated by EuroGentest.

- *ACE* (angiotensin-converting enzyme gene)
- Adenomatous polyposis of the colon (*APC* gene)
- Congenital adrenal hyperplasia
- Alpha-1 antitrypsin inhibitor
- *ApoB*-100 (apolipoprotein B-100) genotyping
- *ApoE* (apolipoprotein E); *ApoE2*, *ApoE3*, *ApoE4*
- *BRCA1* and *BRCA2* genes (familial breast and ovarian cancer)
- *CETP* (cholesteryl ester transfer protein) genotyping
- Charcot-Marie-Tooth disease
- Cystic fibrosis

* College of American Pathologists. 2008 surveys & anatomic pathology education programs. Available at http://www.cap.org/apps/docs/proficiency_testing/surveys_catalog/2008_full_catalog.pdf.

† CDC. Newborn Screening Quality Assurance Program; 2007. Available at <http://www.cdc.gov/labstandards/nsqap.htm>.

§ EuroGentest. Harmonizing genetic testing across Europe; 2008. Available at <http://www.eurogentest.org/news/db/news/416/index.xhtml>.

- Duchenne muscular dystrophy, Becker muscular dystrophy
- Factor V Leiden thrombophilia
- Factor XIII deficiency
- Fragile X syndrome
- Friedreich ataxia
- GP IIB/IIIA (glycoprotein IIB genotyping)
- Hemophilia A (factor VIII)
- Hemophilia B (factor IX)
- Hereditary hemochromatosis (*HFE*)
- Hereditary nonpolyposis colon cancer (HNPCC)
- Huntington disease (*HD* gene)
- Lactose intolerance
- Maturity onset diabetes of the young (MODY)
- Mitochondrial disorders
- *MTHFR* (5,10-methylenetetrahydrofolate reductase gene)
- Multiple endocrine neoplasia type 2 (*MEN 2*)
- Myotonic dystrophy
- Phenylketonuria
- Plasminogen activator inhibitor gene (*PAI-1*)
- Prader-Willi syndrome, Angelman syndrome
- Prothrombin thrombophilia
- Retinoblastoma
- Spinal muscular atrophy
- Spinocerebellar ataxia
- Thalassemia, alpha and beta
- *TPMT* (thiopurine S-methyltransferase gene)
- *UGT1A1* (UDP glucuronosyltransferase 1 family, polypeptide A1 gene)
- Variegate porphyria
- von Hippel-Lindau syndrome
- von Willebrand disease
- Wilson disease
- Y chromosome microdeletions (*AZF* and *DAZ* genes)

Pharmacogenetic External Quality Assessment

- *BCHE* (butyrylcholinesterase gene)
- *CYP2D6* (cytochrome P450, family 2, subfamily D, polypeptide 6 gene)

- *GHR* (growth hormone receptor)
- *UGT1A6* (UDP glucuronosyltransferase 1 family, polypeptide A6 gene)

Methodological External Quality Assessment

- DNA sequencing
- Mutation scanning
- Qualitative polymerase chain reaction

CAP Registry Service for Genetic Testing[†]

Interlaboratory Exchange

The CAP registry service is an Internet-based service that facilitates contact among genetic testing laboratories that perform less frequently performed genetic tests. Laboratories enroll online; when CAP identifies three laboratories that are testing for the same genetic disorder, CAP facilitates communication for making exchange arrangements. The CAP/ACMG Biochemical and Molecular Genetics Committee reviews the results and procedures and makes comments in the Molecular Genetics Survey's Participant Summary Report regarding the overall performance.

Association for Molecular Pathology (AMP)**

Interlaboratory Exchange

AMP facilitates sample exchanges between laboratories through the AMP listserv (CHAMP). Laboratories seeking others to evaluate performance on specific analytes contact one another via the listserv. Laboratories are responsible for establishing testing parameters and facilitating exchange of specimens and test results.

[†] College of American Pathologists. Registry service for genetic testing. Available at <http://www.cap.org>.

** Association for Molecular Pathology. CHAMP listserv. Available at <http://www.amp.org/membership/champ.htm>.

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Designated Federal Official: Thomas L. Hearn, PhD, National Center for Preparedness, Detection, and Control of Infectious Diseases, CDC, Atlanta, Georgia.

Ex-Officio Members: Steven L. Gutman, MD, Food and Drug Administration, Rockville, Maryland; Judith Yost, MA, Division Laboratory Services, Centers for Medicare & Medicaid Services, Baltimore, Maryland; Devery Howerton, PhD, National Center for Preparedness, Detection, and Control of Infectious Diseases, CDC, Atlanta, Georgia.

Liaison Representative: Luann Ochs, MS, Becton-Dickinson Diagnostics—TriPath, Durham, North Carolina.



Morbidity and Mortality Weekly Report
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Recommendations and Reports
June 12, 2009 / Vol. 58 / RR-6

Continuing Education Activity Sponsored by CDC

Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions

EXPIRATION – June 12, 2011

You must complete and return the response form electronically or by mail by **June 12, 2011**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 2.5 hours Continuing Medical Education (CME) credit; 0.2 Continuing Education Units (CEUs); 2.5 contact hours Continuing Nursing Education (CNE) credit; or 2.5 contact

hours Certified Health Education Specialist (CHES) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

INSTRUCTIONS

By Internet

1. Read this *MMWR* (Vol. 58, RR-6), which contains the correct answers to the questions beginning on the next page.
2. Go to the *MMWR* Continuing Education Internet site at <http://www.cdc.gov/mmwr/cme/conted.html>.
3. Select which exam you want to take and select whether you want to register for CME, CEU, CNE, or CHES credit.
4. Fill out and submit the registration form.
5. Select exam questions. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
6. Submit your answers no later than **June 12, 2011**.
7. Immediately print your Certificate of Completion for your records.

By Mail or Fax

1. Read this *MMWR* (Vol. 58, RR-6), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address.
3. Indicate whether you are registering for CME, CEU, CNE, or CHES credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
5. Sign and date the response form or a photocopy of the form and send no later than **June 12, 2011**, to
Fax: 404-498-2388
Mail: MMWR CE Credit
CCHIS, Centers for Disease Control and Prevention
1600 Clifton Rd, N.E., MS E-90
Atlanta, GA 30333
6. Your Certificate of Completion will be mailed to you within 30 days.

ACCREDITATION

Continuing Medical Education (CME). CDC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 2.5 AMA PRA category 1 credits. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Certified Health Education Specialist (CHES). CDC is a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is a designated event for the CHES to receive 2.5 category I contact hours in health education, CDC provider number GA0082.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

Goal and Objectives

The goal of this report is to improve the quality and usefulness of laboratory services for genetic testing to achieve better health outcomes for the public. Upon completion of this educational activity, the reader should be able to 1) describe the recommended good laboratory practices for each of the three phases of the molecular genetic testing process; 2) describe qualifications, responsibilities, and competency of laboratory personnel; 3) describe planning for introducing molecular genetic testing; and 4) describe how to ensure the confidentiality of patient information in molecular genetic testing for heritable diseases and conditions.

To receive continuing education credit, please answer all of the following questions.

1. **Under the Clinical Laboratory Improvement Amendments (CLIA) regulations, laboratories performing molecular genetic testing that they have developed are subject to...** (*Indicate all that apply.*)
 - A. the general quality systems requirements for nonwaived testing.
 - B. personnel requirements for high-complexity testing.
 - C. specialty requirements for molecular genetic testing.
2. **For each molecular genetic test a laboratory performs, the laboratory should provide the following information to the users of its services before test selection and ordering:** (*Indicate all that apply.*)
 - A. The intended use of the test.
 - B. Information on analytic validity and clinical validity of the test.
 - C. Indications for testing.
 - D. Information on appropriate collection, handling, and submission of specimens.
 - E. The specific types of patient information needed to perform the testing and interpret test results.
 - F. Laboratory contact information for consultation and discussion regarding a test being considered.
3. **For testing of mutations associated with human genetic diseases such as cystic fibrosis and Tay-Sachs disease, laboratories need to solicit the patient's race/ethnicity and family history information with the test request to determine all of the following except...**
 - A. the type and amount of specimen needed.
 - B. whether the specimen should be referred to another laboratory.
 - C. the test methods to be used.
 - D. the specific mutations to be tested.
 - E. interpretation of test results.
4. **CLIA regulations require laboratories to refer a specimen for patient testing only to a CLIA-certified laboratory or a laboratory meeting equivalent requirements as determined by Centers for Medicare & Medicaid Services (CMS). Which of the following does not meet this CLIA requirement?**
 - A. Laboratories of the Department of Veterans Affairs.
 - B. Laboratory facilities of the Department of Defense.
 - C. Laboratories approved by the New York State Clinical Laboratory Evaluation Program.
 - D. Laboratories approved by the Washington State Laboratory Quality Assurance Program.
 - E. Research laboratories that do not have a CLIA certificate.
5. **For molecular amplification procedures, which of the following is considered an effective mechanism for monitoring and detecting cross-contamination of patient specimens?**
 - A. Inclusion of a positive control that represent the genotype to be detected with each run of patient specimens.
 - B. Inclusion of a normal sample as the negative control with each run of patient specimens.
 - C. Inclusion of a no-template control sample that contains all components of the amplification reaction except nucleic acid templates with each run of patient specimens.
 - D. Inclusion of a spiked-in internal control in each amplification sample.
6. **Test reports of molecular genetic testing for heritable diseases or conditions should be retained for the longest possible time frame for all the following reasons except...**
 - A. Test results have long-term implications for the patients.
 - B. Test results have implications for patients' families and future generations.
 - C. Advances in knowledge and understanding of disease processes might lead to improved interpretation of test results.
 - D. Laboratories need to access previous test reports to conduct quality assessment activities.
 - E. Laboratories must protect the confidentiality of patient information.
7. **A molecular genetic test report should ...**
 - A. be understood by geneticists only.
 - B. be understandable by nongeneticist health professionals and other authorized users of the test results.
 - C. always be written in English.
 - D. indicate "test result is negative" if no mutation is detected so that the test result can be easily understood.
8. **The director of a laboratory performing molecular genetic testing should...** (*Indicate all that apply.*)
 - A. ensure effective policies and procedures are in place for monitoring and maintaining the competency of the laboratory personnel.
 - B. be able to perform a molecular genetic test better than anyone else in the laboratory.
 - C. ensure available information needed to interpret test results for a patient is documented for each molecular genetic test the laboratory performs.
9. **When considering whether a new molecular genetic test should be introduced to the patient testing offered by a laboratory, the laboratory should consider...** (*Indicate all that apply.*)
 - A. evidence in published literature on the intended use of the new test.
 - B. test methodology needed to perform the new test.
 - C. whether laboratory personnel are capable of performing the test and communicating test results to the laboratory's clients.
 - D. the needs and demands of the new test based on a market analysis.
10. **Information on the clinical validity of a test to diagnose or predict risk for a health condition is often affected by...** (*Indicate all that apply.*)
 - A. clinical sensitivity.
 - B. prevalence of the disease or health condition.
 - C. clinical specificity.
 - D. penetrance.
 - E. current knowledge and testing technology.
11. **How often should control procedures be performed for molecular genetic testing for heritable diseases or conditions?**
 - A. Each time patient testing is performed.
 - B. Once each day patient specimens are assayed.
 - C. Once each week patient testing is performed.
 - D. Once each month patient testing is performed.

12. When a laboratory uses a purified DNA sample extracted from a cell line containing a rare mutation as a positive control in patient testing, which of the following is considered appropriate for monitoring the DNA extraction step of the testing process? (Indicate all that apply.)
- A. Testing patient samples for a housekeeping gene to determine specimen quality and integrity each time patient testing is performed.
 - B. Testing patient samples for a spiked-in control sequence to assess the presence of inhibitors each time patient testing is performed.
 - C. Testing patient samples for a housekeeping gene to determine specimen quality and integrity once each day patient testing is performed.
 - D. Testing patient samples for a spiked-in control sequence to assess the presence of inhibitors once each day patient testing is performed.
13. Which best describes your professional activities?
- A. Physician.
 - B. Nurse.
 - C. Health educator.
 - D. Office staff.
 - E. Laboratory professional.
 - F. Public health professional.
 - G. Payer of laboratory services.
 - H. Other.
14. I plan to use these recommendations as the basis for... (Indicate all that apply.)
- A. health education materials.
 - B. insurance reimbursement policies.
 - C. local practice guidelines.
 - D. public policy.
 - E. other.
15. Overall, the length of the journal report was...
- A. much too long.
 - B. a little too long.
 - C. just right.
 - D. a little too short.
 - E. much too short.

16. After reading this report, I am confident I can describe the recommended good laboratory practices for each of the three phases of the molecular genetic testing process.
- A. Strongly agree
 - B. Agree
 - C. Undecided.
 - D. Disagree
 - E. Strongly disagree
17. After reading this report, I am confident I can describe the qualifications, responsibilities, and competency of laboratory personnel.
- A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.
18. After reading this report, I am confident I can describe planning for introducing molecular genetic testing.
- A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.
19. After reading this report, I am confident I can describe how to ensure the confidentiality of patient information in molecular genetic testing for heritable diseases and conditions.
- A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.
20. The learning outcomes (objectives) were relevant to the goals of this report.
- A. Strongly agree.
 - B. Agree.
 - C. Undecided.
 - D. Disagree.
 - E. Strongly disagree.

(Continued on pg CE-4)

MMWR Response Form for Continuing Education Credit
June 12, 2009/Vol. 58/No. RR-6
Good Laboratory Practices for Molecular Genetic Testing
for Heritable Diseases and Conditions

To receive continuing education credit, you must

1. provide your contact information (please print or type);
2. indicate your choice of CME, CME for nonphysicians, CEU, CNE, or CHES credit;
3. answer all of the test questions;
4. sign and date this form or a photocopy;
5. submit your answer form by June 12, 2011.

Failure to complete these items can result in a delay or rejection of your application for continuing education credit.

Detach or photocopy.

Check One

CME Credit

CME for Nonphysicians Credit

CEU Credit

CNE Credit

CHES Credit

Last Name (print or type) First Name

Street Address or P.O. Box

Apartment or Suite

City State ZIP Code

Phone Number Fax Number

E-Mail Address

Fill in the appropriate blocks to indicate your answers. Remember, you must answer all of the questions to receive continuing education credit!

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Signature _____ Date / Completed Exam _____

21. The instructional strategies used in this report (text and appendices) helped me learn the material.

- A. Strongly agree. D. Disagree.
 B. Agree. E. Strongly disagree.
 C. Undecided.

22. The content was appropriate given the stated objectives of the report.

- A. Strongly agree. D. Disagree.
 B. Agree. E. Strongly disagree.
 C. Undecided.

23. The content experts demonstrated expertise in the subject matter.

- A. Strongly agree. D. Disagree.
 B. Agree. E. Strongly disagree.
 C. Undecided.

24. Overall, the quality of the journal report was excellent.

- A. Strongly agree. D. Disagree.
 B. Agree. E. Strongly disagree.
 C. Undecided.

25. These recommendations will improve the quality of my practice.

- A. Strongly agree. D. Disagree.
 B. Agree. E. Strongly disagree.
 C. Undecided.

26. The availability of continuing education credit influenced my decision to read this report.

- A. Strongly agree. D. Disagree.
 B. Agree. E. Strongly disagree.
 C. Undecided.

27. The MMWR format was conducive to learning this content.

- A. Strongly agree. D. Disagree.
 B. Agree. E. Strongly disagree.
 C. Undecided.

28. Do you feel this course was commercially biased? (Indicate yes or no; if yes, please explain in the space provided.)

- A. Yes.
 B. No.

29. How did you learn about the continuing education activity?

- A. Internet.
 B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
 C. Coworker/supervisor.
 D. Conference presentation.
 E. *MMWR* subscription.
 F. Other.

Correct answers for questions 1–12:
 1. A,B; 2. All; 3. A; 4. E; 5. C; 6. E; 7. B; 8. A,C; 9. All; 10. All; 11. A;
 12. A,B.