



# Public Health at Risk: Failures in Oversight of Genetic Testing Laboratories



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## **ACKNOWLEDGEMENTS**

The Genetics and Public Policy Center acknowledges the special contributions to this report from staff members Rick Borchelt, David Kaufman, Juli Murphy, Joan Scott, Shawna Williams, and Sheryl Wood. The Center also thanks Mary Pendergast and Linda Bradley for their review of an earlier draft of this report. The Genetics and Public Policy Center assumes full responsibility for the report and its contents.

The Genetics and Public Policy Center is a source of accurate and trusted information about public policy related to human genetic technologies and is supported at the Berman Bioethics Institute of Johns Hopkins University by The Pew Charitable Trusts.

# Executive Summary

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The Human Genome Project unleashed a torrent of information about the human genome and the role of genetic variation in human health. As a result, genetic testing is now among the fastest-growing areas of laboratory medicine. Today, genetic tests for about 1000 diseases are clinically available, with hundreds more available in a research setting.

Making sure that laboratories can accurately and reliably perform genetic tests is a fundamental requirement for the success of genetic medicine, and the government has a key role to play in overseeing laboratory quality. Congress has provided federal agencies a broad mandate to ensure the accuracy and reliability of genetic testing, but inattention and delay have meant that this mandate has gone unheeded.

This report describes the role of the Clinical Laboratories Improvement Amendments of 1988 (CLIA) in ensuring laboratory quality, and documents the repeated failure of the Centers for Medicare and Medicaid Services (CMS) to implement this law with respect to genetic testing laboratories. It identifies the lack of transparency regarding laboratory quality as a key impediment to sound healthcare decision making by healthcare providers and patients.

The report also summarizes data from the Genetics and Public Policy Center's recent survey of genetic testing laboratory directors. Survey findings indicate a clear correlation between participation in proficiency testing, which is not currently required under CLIA for genetic testing, and test quality. The findings also show that nearly three-quarters of laboratory directors surveyed support more oversight of genetic testing under CLIA, and more than 90 percent found proficiency testing to be useful in improving genetic testing quality.

The report concludes that implementation of CLIA with respect to genetic testing laboratories through the creation of a genetic testing specialty is necessary to ensure the quality of genetic testing, to fulfill the promise of genetic medicine, and to protect the public's health.

# Introduction

The Clinical Laboratories Improvement Amendments of 1988 (CLIA) (1) is a little-heralded statute with an important mission. Congress enacted the law out of concern over the poor quality of services being offered by clinical laboratories. Congress wanted to make sure that the millions of tests performed on patients every year provided accurate and reliable results.

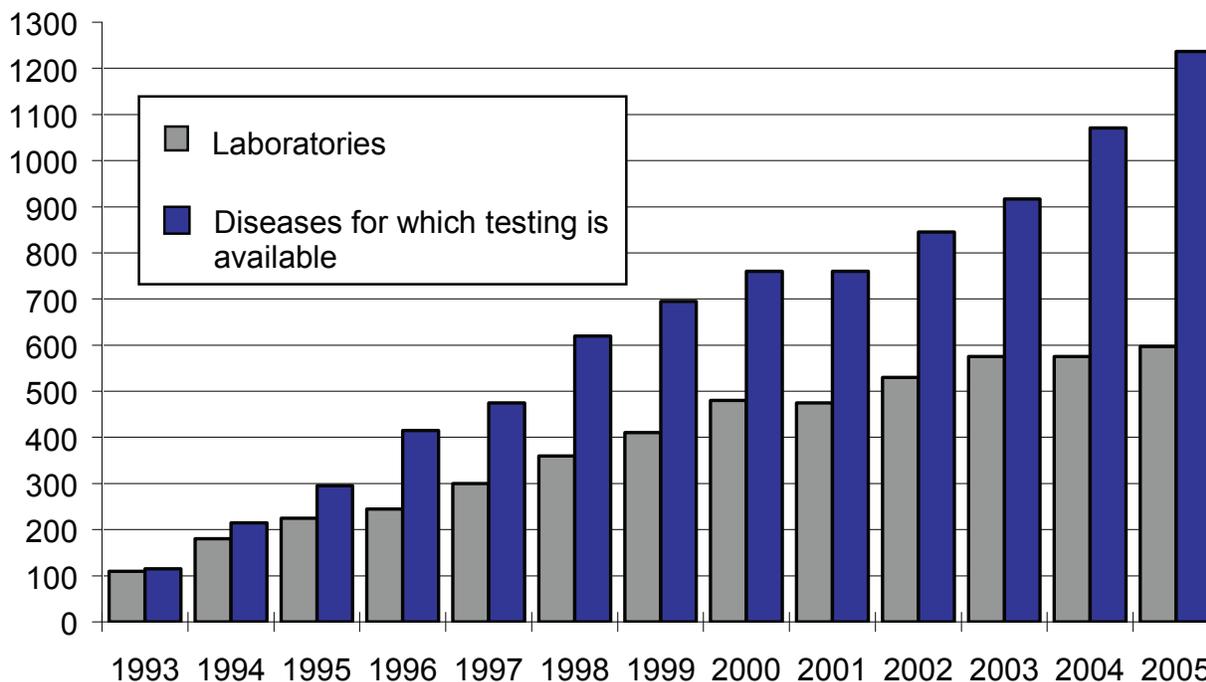
Authority for implementing CLIA was delegated to the Centers for Medicare and Medicaid Services (CMS). Thus, while much better-known for its role in administering the Medicare and Medicaid programs, CMS also is responsible for monitoring the quality of nearly 200,000 clinical laboratories in the United States (2), which together perform more than 10 billion tests each year (3).

At the time CLIA was enacted, few human genes had been identified and genetic testing

was a nascent field largely confined to esoteric research laboratories or prenatal testing for chromosomal disorders. Not surprisingly, in implementing CLIA CMS focused first on those testing areas that were mature and most in need of strengthened oversight. As a result, CLIA has improved the overall quality of clinical laboratory testing in the United States.

However, in the 18 years since CLIA was enacted and with the completion of the Human Genome Project, genetic testing has moved from the sidelines into mainstream medicine (4). Today there are about 1000 diseases for which genetic tests are available clinically, and several hundreds more are available in a research setting (5) (Figure 1). While initial research focused on rare diseases caused by a mutation in a single gene, more recent research has focused on the identification of genetic contributions to complex, multifactorial conditions such as cancer, diabetes, and heart disease (6, 7).

**Figure 1: Growth of Genetic Testing**



Data source: GeneTests database (2005) / [www.genetests.org](http://www.genetests.org)

Identifying the genetic underpinnings for variation in response to drugs has sparked interest in targeted drug design and in identifying those genetic variants that may predispose an individual to an adverse drug reaction, or, conversely, to a particularly good therapeutic response (8).

The common denominator in all of these current and future applications of genetic research to human health is the genetic test used to identify genetic variants. These involve testing DNA or RNA (molecular genetic tests), proteins or other metabolites (biochemical genetic tests), or chromosomes (cytogenetic tests). A genetic test can be performed on a wide variety of tissue samples and across the human lifespan. Accurate genetic test results are critical to diagnosis, prognosis, safe and effective treatment, and disease prevention. Genetic tests can lead to profound life-altering decisions, such as the decision to undergo surgery, undertake chemotherapy, discontinue a medication, or to become pregnant or continue a pregnancy. An accurate test result also can help patients make informed decisions about their health and healthcare.

During the 1990s, in anticipation of the “genetic revolution,” several government advisory bodies considered what regulatory changes would ensure the smooth transition of genetic testing from research to practice (9-11, 48). Key among the recommendations of these advisory committees was that CMS create regulations under CLIA that focused specifically on genetic tests through the creation of a new “specialty.” These expert bodies recognized that laboratory quality is a fundamental requirement of genetic testing quality and that current regulations were insufficient to ensure that quality.

Yet despite these recommendations, CMS has not acted. In 2000 the agency announced it would develop a genetic testing specialty (13). Dedicated personnel within the Centers for Disease Control (CDC), which advises CMS

on CLIA implementation, spent years working to develop the content for a genetic testing specialty and to solicit public input. Based on this work, in April 2006 the Department of Health and Human Services (HHS) placed the issuance of a genetic testing specialty on its regulatory agenda, with a target date of November 2006 (14).

However, in July 2006, CMS — with no notice to the public — abruptly reversed course, deciding not to issue a regulation for a genetic testing specialty. Despite the fact that genetic testing appears to be among the most rapidly expanding areas of laboratory medicine, CMS officials now assert that creating a specialty lacks sufficient “criticality” to warrant rulemaking and that existing regulations are adequate (15).

The government’s assessment is mistaken, and creation of a genetic testing specialty is critical to the public’s health. While admittedly only one component of a system needed for genetic testing quality, a CLIA specialty is central to the goal of ensuring the accuracy and reliability of genetic tests that are used to make important, indeed profound, life decisions. Conversely, an inaccurate test result can lead to ill-informed decisions with tragic consequences, and to wasted healthcare resources.

# CLIA: Intent and Implementation

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The federal government, through the Department of Health and Human Services (HHS), has been engaged in clinical laboratory oversight for nearly 50 years. Congress enacted the Clinical Laboratories Improvement Act of 1967 in response to reports of high error rates in laboratory testing (16). But the Act was limited in scope, and during the early 1980s Congress again became concerned about laboratory quality. In particular, Congressional hearings revealed that high numbers of false negative results were being reported by laboratories performing Pap smears to screen women for cervical cancer (17). Women with abnormal, possibly cancerous, cells were being incorrectly informed that their Pap smears were normal, leading to needless illness and death.

Congress enacted the Clinical Laboratory Improvement Amendments of 1988, referred to as CLIA, in order to address deficiencies in the original law, and to “strengthen federal oversight of clinical laboratories to assure that the tests results are accurate and reliable.”(17) Congress found that laboratory testing played a critical role in the delivery of health services and in maintaining good health, and that patients both “expect such testing to be done properly” and “assume, quite reasonably, that their interests and the public health are being protected by appropriate government agencies.”(17)

Among the problems uncovered by Congress were a “seriously flawed system” for ensuring laboratory compliance and an “ineffective proficiency-testing system for evaluating the performance of laboratories.” With respect to compliance, Congress found that the government’s reliance on private accrediting bodies had created weaknesses in the administration of quality standards, noting that while the government had delegated enforcement to these entities, “these bodies have made plain their preference and capacity is for education, not enforcement.”(17)

Congress noted that proficiency testing “should be the central element in determining a laboratory’s competence since it purports to measure actual test outcomes rather than merely gauging the potential for accurate outcomes.”(17) Proficiency testing requires a laboratory to demonstrate that it can obtain the correct answer when performing a test on a tissue sample; thus it serves as a “method of externally validating the level of a laboratory’s performance.”(17) But Congress identified serious defects including “lax federal oversight and direction, lack of proficiency testing for many analytes, inconsistent criteria for acceptable laboratory performance, and improprieties by laboratories in handling specimen samples.”(17) Congress intended CLIA to remedy these shortcomings through new, more rigorous laboratory standards (17).

Congressional intent was clear: HHS — of which CMS is an agency — was to require laboratories to participate in proficiency testing for each type of clinical test they performed, unless the secretary of HHS determined that “an appropriate proficiency test could not reasonably be developed and implemented.”(17) Congress did not intend for the secretary “to exempt analytes from proficiency testing merely because such testing is not currently available or because it is difficult to obtain consensus on the best method of proficiency testing.”(17) Additionally, Congress intended for laboratory performance on proficiency tests to be transparent. Under CLIA, the secretary “would be required to set up a system for compiling the results of proficiency testing and making them available on request to anyone interested [in] reviewing or comparing laboratory performance,” along with “some appropriate explanatory information that would assist the requester in understanding the meaning and validity of the information released.”(17)

Under CLIA, HHS is responsible for developing standards for quality assurance and quality control, record keeping, equipment and facilities, personnel and proficiency testing, as

well as other standards “necessary to protect the health and safety of patients.”(1) This authority was delegated to CMS.

Regulations implementing CLIA first went into effect in 1992 (18). The regulations categorize laboratory tests by complexity and specify different requirements depending on the complexity of a test. Tests either may be waived, moderate complexity, or high complexity. Tests are categorized based on specified criteria, which include the knowledge needed to perform the test, the training and experience required, the complexity of reagent and materials preparation, and degree of interpretation and judgment required (19). Waived tests are those that “are so simple and accurate as to render the likelihood of erroneous results negligible,” or which pose “no reasonable risk of harm to the patient if the test is performed incorrectly.”(20) Laboratories performing only waived tests are subject to only minimal regulation. They need to obtain a certificate of waiver from CMS, and must agree to permit inspection of their facilities.

Laboratories performing tests of moderate and/or high complexity must, in addition to general laboratory registration and inspection requirements, comply with applicable proficiency testing, patient test management, quality control, personnel, and quality assurance provisions. Also, they must be certified in each applicable testing specialty or subspecialty established in CLIA regulations.

Several specialty and subspecialty areas have been established pursuant to CLIA, each with its own requirements related to personnel, quality control, and proficiency testing, among others. Laboratories performing moderate or high-complexity tests must enroll in an approved proficiency-testing program for each specialty or subspecialty for which certification is sought (21). Requirements for proficiency-testing programs have been established for most specialties and subspecialties under CLIA. The regulations specify a minimum proficiency test

score that laboratories must receive for each specialty and subspecialty.

Proficiency testing is mandated for microbiology (including the subspecialties of bacteriology, mycobacteriology, mycology, parasitology, and virology), diagnostic immunology (including the subspecialties of syphilis serology and general immunology), chemistry (including the subspecialties of routine chemistry, endocrinology, and toxicology), hematology (including routine hematology and coagulation), cytology (gynecologic examinations), and immunohematology.

If a specialty or subspecialty has not been established in the regulations, then the laboratory must “establish and maintain the accuracy of its testing procedures” and verify the accuracy of its test results at least twice a year (22).

Consistent with Congressional intent that results of proficiency testing be made available to the public, the law directs HHS to “establish a system to make the results of the proficiency-testing programs . . . available, on a reasonable basis, upon request of any person. The Secretary shall include with results made available . . . such explanatory information as may be appropriate to assist in the interpretation of such results.”(1) However, no such system appears to have been established under CLIA regulations. With the exception of cytology, no information regarding laboratory performance on proficiency testing is available on CMS’s Web site, nor is information provided to the public or healthcare providers regarding how to request such information.

# CLIA and Genetic Tests

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Although Congress was quite clear in the purpose and requirements of CLIA, HHS's implementation of CLIA for genetic testing has been inadequate. Genetic tests are considered high-complexity tests, but no specialty or subspecialty for molecular or biochemical genetics has been established. Thus, there are no specific personnel, quality control, or proficiency-testing requirements for the vast majority of genetic tests. The regulations do include a subspecialty of clinical cytogenetics under the cytology specialty, and establish requirements related to cytogenetics-testing quality control. However, clinical cytogenetics is limited to chromosomal analysis and does not include molecular or biochemical genetic testing. A limited number of proficiency-testing programs exist for molecular and biochemical tests, but enrollment in these programs is not mandated under CLIA. Nor is information about an individual genetic testing laboratory's performance on proficiency testing accessible to the public.

In the absence of a genetic testing specialty for molecular and biochemical genetic testing, laboratories can choose to enroll in other specialties but are not required to. According to results from a recent survey conducted by the Genetics and Public Policy Center, 16 percent of genetic testing laboratories have no specialty certification at all, including a third of high-volume genetic testing laboratories. Among molecular and biochemical genetic testing laboratories with specialty certification, the most common are pathology, chemistry, and clinical cytogenetics (23). However, these specialties have little applicability to a laboratory's proficiency in performing genetic tests. No proficiency-testing programs are mandated for pathology or clinical cytogenetics under current regulations. Moreover, the proficiency-testing programs for chemistry address analytes such as glucose, cholesterol, potassium, and sodium – analytes that are not relevant to assessing proficiency in genetic testing.

Thus in significant ways genetic testing has been left out of CLIA implementation. This situation persists despite the fact that several federal advisory groups have recommended that CMS establish a genetic testing specialty under CLIA (9-11, 53). In 1997, the National Institutes of Health - Department of Energy Task Force on Genetic Testing determined that, in the absence of a genetic testing specialty, "there is no assurance that every laboratory performing genetic tests for clinical purposes meets high standards."<sup>(9)</sup> In addition to recommending that a specialty be established, the Task Force also recommended that proficiency testing be mandated for all laboratories doing genetic testing and that a list of laboratories performing genetic tests satisfactorily be made public. In 2000, the Secretary's Advisory Committee on Genetic Testing (SACGT), which succeeded the Task Force, similarly recommended that CLIA regulations be augmented with specific provisions for laboratories conducting genetic tests (10).

In 2000, HHS published a "Notice of Intent" in the Federal Register, announcing the government's intent to issue a proposed rule for a genetic testing specialty under CLIA (13). The Notice included the recommendations of the Clinical Laboratory Improvement Advisory Committee (CLIAC), an advisory group within the CDC. In the Notice HHS explained that, along with the "tremendous potential for improving health and preventing disease, genetic testing can also do great harm" if errors occur in test selection, performance, or interpretation. The Notice cited literature pointing to errors or substandard practice in each of these categories.

The Notice requested public comments on the CLIAC's recommendations. Fifty-seven comments were submitted to the government. The overwhelming majority of respondents supported the recommendation to create a genetic testing specialty for molecular and biochemical genetic tests as a means to promote their reliability, accuracy, and quality.

Moreover, there was little opposition to the recommendations for proficiency testing, personnel standards, or quality control – those elements considered to be the “core” of CLIA. However, some commenters were concerned that requiring laboratories to obtain patient consent and provide genetic counseling “overreached” CLIA’s mandate by requiring the laboratory to assume functions more appropriately handled by healthcare providers (24).

The CLIAC modified its recommendations in response to the comments received, and continued to recommend that HHS develop a proposed rule to create a genetic testing specialty under CLIA. For the next five years, CMS periodically reported to the CLIAC that development of a proposed rule for a genetic testing specialty was in progress (12).

In a September 2005 letter responding to an inquiry from the Genetics and Public Policy Center, CMS stated that “[u]nder a Notice of Proposed Rulemaking . . . we will propose to add a specialty category for genetic testing.”(25, 26) Similarly, in a January 2006 response to a Genetics and Public Policy Center inquiry (27), CMS averred that “we intend to publish a Notice for Proposed Rule Making for genetic testing as quickly as feasible.”(28) Consistent with this intent, in April 2006 HHS placed the issuance of a proposed rule on its semiannual regulatory agenda, with a target release date of November 2006 (14). CMS’s intent to move forward with the proposed rule was confirmed by the testimony of a CMS official before the SACGHS in June 2006. She stated that “we do have a notice of proposed rule making in CMS clearance at this time.”(29)

But one month later, at a hearing of the Senate Special Committee on Aging, CMS signaled it had abruptly shifted course and abandoned its six-year effort. The hearing was held to consider a report by the Government Accountability Office (GAO) indicating serious deficiencies on the part of companies providing direct-to-consumer “nutrigenetic” testing (30).

According to the GAO report, some of the laboratories performing the genetic testing were not CLIA certified and had returned incorrect test results to consumers. In his testimony, the director of CMS’s Survey and Certification Group made no mention of the proposed rule (2). Moreover, he testified that genetic testing already is adequately covered under existing regulations (2). Even more surprisingly, he testified that because genetic tests are high-complexity, laboratories must “participate in an approved proficiency-testing program” three times a year (2). This statement is at odds with current regulations. In fact, there currently are no regulations mandating that genetic testing laboratories enroll in available proficiency-testing programs. Data obtained by the Genetics and Public Policy Center show that many genetic testing laboratories do not enroll in available voluntary proficiency-testing programs or perform any type of proficiency testing for the genetic tests they offer (23).

The director further testified that “[t]ests for genetic markers are dispersed throughout various laboratory specialties and the requirements for those tests are encompassed by the current quality standards.”(2) However, as discussed below, a number of genetic testing laboratories are not certified in any specialty. Additionally, the relevance to genetic testing of certification in a specialty such as pathology or chemistry is unclear.

Finally, the director testified that a July 2003 quality control regulation promulgated by CMS incorporated some CLIAC recommendations for genetic testing, specifically, “confidentiality requirements, facility workflow requirements to minimize contamination, and quality control requirements for the genetic test method of polymerase chain reaction (PCR).”(2, 31) Notably missing from this list was any mention of proficiency testing. Additionally, PCR is only one of many methods used by genetic testing laboratories, and contamination is only one of the potential causes of laboratory error. Only 18 percent of laboratories surveyed by the Genetics

and Public Policy Center indicated they had encountered contamination during specimen testing in the past two years, compared with 27 percent that had experienced sample switches in the laboratory, 52 percent that had experienced equipment failure, and 44 percent that had encountered human error in data analysis (32). The contention that the 2003 regulation adequately addresses genetic testing quality is incorrect.

The proposal to create a genetic testing specialty was never mentioned in CMS's testimony. Its omission, together with the assertion that existing regulations are sufficient, revealed that CMS had reversed course. A July 2006 CMS letter to the Genetic Alliance, which represents 600 advocacy organizations, also indicated the agency's policy reversal. In response to a request that CMS issue a proposed rule for a genetic testing specialty (33), CMS replied that genetic testing laboratories already are adequately covered under CLIA, making no mention of the proposed rule (34).

Representatives of the Genetics and Public Policy Center met with CMS officials in August 2006 (15). During that meeting, officials confirmed that CMS no longer intended to issue a proposed rule, stating that the regulation lacked sufficient "criticality" to warrant moving forward and that CMS believed a regulation for a genetic testing specialty was unnecessary to ensure genetic testing quality. Additionally, CMS officials expressed concern about creating a specialty given the limited number of formal proficiency-testing programs currently available for genetic testing.

Thus, a decade-long saga has returned to where it began, having consumed substantial taxpayer dollars and produced no meaningful changes to ensure the quality of laboratories performing genetic testing.

## Oversight of Genetic Testing Laboratory Quality: A Timeline

**1988** – The Clinical Laboratory Improvement Amendments of 1988 (CLIA) is enacted (1) to “strengthen federal oversight of clinical laboratories to assure that the test results are accurate and reliable.”(17)

**1997** – The National Institutes of Health-Department of Energy (NIH-DOE) Task Force on Genetic Testing issues recommendations to improve the quality of genetic testing. Their report, “Promoting Safe and Effective Genetic Testing in the United States,” contains recommendations for enhanced regulation of genetic testing laboratories, including requiring clinical validity to be established for genetic tests, creating a genetic testing specialty under CLIA, establishing a national accreditation program for laboratories performing genetic tests, making public the names of laboratories performing satisfactorily, and requiring post-market surveillance to assess clinical validity and clinical utility (9).

**1998** – The Genetic Testing Working Group formed by the Clinical Laboratories Improvement Advisory Committee (CLIAC) in 1997 meets repeatedly to consider the applicability of CLIA to genetic testing and recommends that CLIA be amended to include a genetic testing specialty (53).

**2000** – The Secretary’s Advisory Committee on Genetic Testing (SACGT) states that “CLIA regulations should be augmented to provide more specific provisions ensuring the quality of laboratories conducting genetic tests.”(10)

**2000** – The Department of Health and Human Services (HHS) issues a Notice of Intent for public comment indicating that HHS is considering preparing a Notice of Proposed Rule Making (NPRM) to create a specialty area for molecular and biochemical genetic tests under CLIA (13).

**2001 January** – Secretary Shalala indicates the HHS intends to implement an enhanced system of oversight for genetic tests (54).

**2001 February** – Based on comments on the Notice of Intent, the CLIAC Genetic Testing Working Group presents revised recommendations to the full CLIAC. The CLIAC recommends that HHS proceed with the development of a proposed rule for a genetic testing specialty under CLIA (12).

**2003 January** – The Centers for Medicare and Medicaid Services (CMS) issues a final rule, Laboratory Requirements Relating to Quality Systems and Certain Personnel Qualifications (31). The rule introduces two requirements specific to genetic testing: a unidirectional workflow requirement for molecular amplification procedures that are not contained in closed systems, in order to reduce contamination, and a requirement that each molecular amplification procedure include two control materials, and if necessary, a control material capable of detecting false negative results.

**2005 September** – In response to an inquiry from the Genetics and Public Policy Center regarding the status of the proposed rule for a genetic testing specialty, CMS responds that “we will propose to add a specialty category for Genetic Testing,” and that the “publication date for the NPRM is expected to be sometime next year.” The letter adds that the “revised CLIA regulations contain sufficient generic and fail-safe language in the preanalytic, analytic, and postanalytic systems to accommodate the oversight of genetic testing until we establish specific requirements.”(26)

**2005 November** –The Genetics and Public Policy Center releases a White Paper, “Creating a Genetic Testing Specialty Under CLIA: What Are We Waiting For?” that reviews all of the comments submitted in response to the Notice of Intent and details widespread support for the creation of a genetic testing specialty (24).

**2005 November** – In a letter, the Genetics and Public Policy Center calls upon Mark McClellan, administrator of CMS, to end years of delay in issuing the proposed rule to create a genetic testing specialty under CLIA (27).

**2006 January** – In a written response, Thomas Hamilton, director, Center for Medicaid and State Operations/Survey Certification Group at CMS, states “[w]e [CMS] intend to publish a Notice of Proposed Rule Making for genetic testing as quickly as feasible” (28).

**2006 February** – The Genetic Alliance board of directors sends a letter to Administrator McClellan urging CMS to issue the proposed regulations for a genetic testing specialty under CLIA (33).

**2006 April** – The proposed rule “Quality Standards for Genetic Testing,” which would add a genetic testing specialty under CLIA, appears on CMS’s semiannual regulatory agenda for issuance in November 2006 (14).

**2006 June** – The Genetic Alliance, along with 75 signatories representing advocacy organizations, professional groups, and industry, sends a second letter to Administrator McClellan urging CMS to issue the proposed rule for a genetic testing specialty (50).

**2006 June** – Judith Yost, director of laboratory services at CMS, testifies at the Secretary’s Advisory Committee on Genetics, Health, and Society meeting that “we do have a notice of proposed rule making in CMS clearance at this time.”(29)

**2006 July** –In a letter to CMS, 14 women’s health organizations urge the agency to issue the proposed rule for a genetic testing specialty (51).

**2006 July** – CMS signals apparent change in its position on the creation of a genetic testing specialty in testimony by Thomas Hamilton before the Senate Special Committee on Aging. He testifies that “[t]ests for genetic markers are dispersed throughout various laboratory specialties and the requirements for those tests are encompassed by the current quality standards.”(2) He makes no mention of the agency’s plans to issue a proposed rule for a genetic testing specialty under CLIA. Similarly, in a letter to the Genetic Alliance, CMS indicates that current oversight of genetic testing under CLIA is adequate (34).

**2006 August** – In a meeting with representatives of the Genetics and Public Policy Center, CMS confirms it has decided not to issue a proposed rule for a genetic testing specialty under CLIA. CMS officials assert that the specialty lacks sufficient “criticality” to warrant rulemaking and that existing regulations are adequate (15).

# Genetic Testing Laboratory Errors

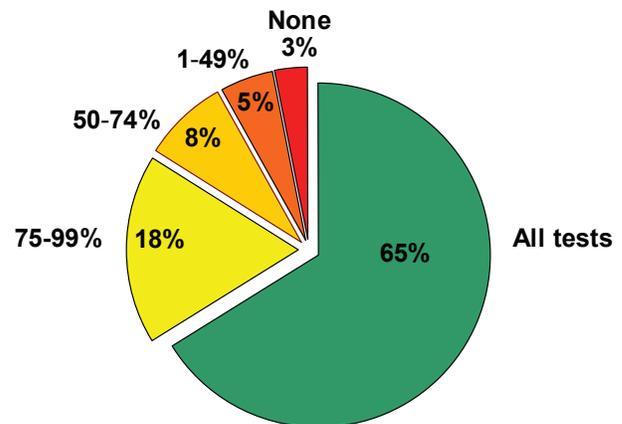
There is no formal system today for reporting and tracking laboratory errors. The lack of a formal reporting system makes it difficult to detect errors in laboratory testing, and to assess the frequency and consequences of such errors. To some extent, errors in laboratory testing, including genetic testing, are unavoidable, and the goal should be to implement systems designed to reduce errors to the extent feasible and to detect errors when they occur.

Ensuring that genetic testing is optimized to avoid error and that measures are available to detect substandard laboratory performance is of paramount importance. Equally important is providing healthcare providers and patients with sufficient information to assess the quality of genetic testing laboratories they rely on to provide critical healthcare information. Yet CMS has not provided a means for the public to access information about the quality of the laboratories it regulates, or even to determine whether a laboratory is CLIA certified.

Although a few studies previously had examined the types of laboratory errors that occur in both genetic (40) and non-genetic testing (41-44) laboratories, or have investigated adherence to professional standards (45), no prior studies had surveyed the practices of genetic testing laboratories or assessed whether the creation of a genetic testing specialty could improve testing quality.

To collect empirical data on laboratory practices and director attitudes regarding oversight, the Genetics and Public Policy Center surveyed 190 directors of molecular and biochemical genetic testing laboratories in the United States (23, 32). The survey sought information about whether laboratories were CLIA certified, were certified in a specialty area, enrolled in formal proficiency-testing programs, engaged in informal proficiency testing when formal programs were not available, had experienced deficiencies in formal proficiency testing, or had reported incorrect test results.

**Figure 2: What percent of tests offered by your laboratory do you conduct some sort of proficiency test on? (n=190)**

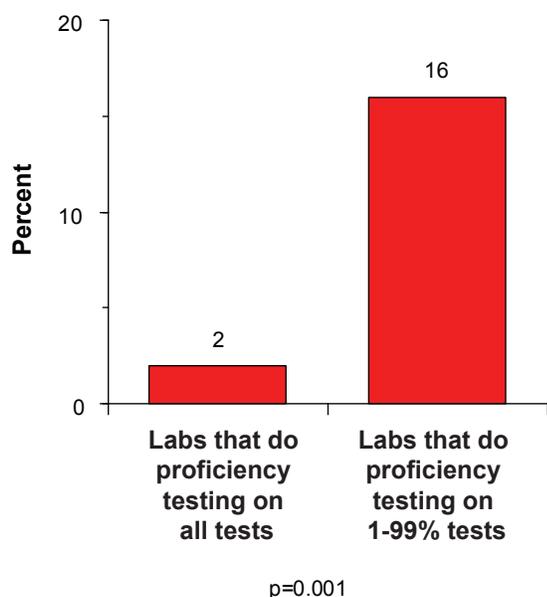


The survey also asked what types of errors were most frequently experienced by laboratories, and whether the laboratories complied with specific professional guidelines.

Results of the survey reveal wide variations in laboratory performance, as measured by the number of deficiencies in formal proficiency testing and the number of incorrect test results reported by the laboratory. Among the survey's findings (23):

- Many laboratories are not performing proficiency testing for all their tests. More than one-third of respondents offer some tests for which they perform no proficiency testing (Figure 2).
- Participation in proficiency testing has a clear association with laboratory quality as measured by the number of reported deficiencies in formal proficiency-testing programs. Laboratories that do not perform some type of proficiency testing on all of their tests were eight times more likely to report multiple deficiencies than laboratories that do (Figure 3).

**Figure 3: Percent of laboratories receiving multiple proficiency-testing deficiencies in the past two years. (n=155)**



- The number of deficiencies reported by a laboratory has a clear association with the number of reported errors. Laboratories that reported more proficiency-testing deficiencies also reported significantly higher numbers of incorrect test results. Laboratories that reported doing less proficiency testing also were more likely to report that their most common type of error is analytic.
- Even when formal proficiency-testing programs are available, some laboratories do not participate.
- When a formal proficiency-testing program is not available, laboratories do not always engage in informal proficiency testing. Twenty-three percent of respondents stated their laboratory does not always perform proficiency testing using some other mechanism when a formal proficiency-testing program is not available (Figure 4).

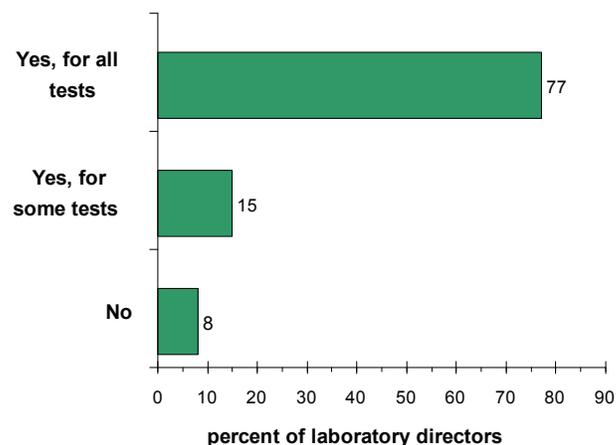
- Genetic testing laboratories are not always certified in other specialties. Sixteen percent of respondents reported no specialty area certification for their laboratory. Moreover, approximately one-third of both high-volume laboratories (those performing more than 15,000 genetic tests per year) and those with large testing menus reported having no specialty certification.

The survey also revealed wide variation in a number of key laboratory practices, as well as practices that were inconsistent with the American College of Medical Genetics Standards and Guidelines for Clinical Genetic Laboratories (46). For example, respondents were asked whether they always include maternal cell contamination studies in prenatal testing, perform prenatal testing in duplicate, and perform DNA sequencing in both directions.

Among the findings from the survey (32):

- About 40 percent of respondents do not always include maternal cell contamination studies when performing prenatal testing. Thirteen percent never or hardly ever follow this practice.

**Figure 4: When a formal external proficiency-testing program is unavailable, does your laboratory perform proficiency testing using some other mechanism? (n=189)**



- Eighteen percent of those surveyed never or hardly ever perform prenatal testing in duplicate.
- Twenty-three percent of respondents do not always sequence in both directions, and about six percent never or hardly ever do it.

Thus, in the absence of mandated standards for genetic testing laboratories, laboratories follow widely divergent practices. Although some of this variation may be appropriate given the different technologies and settings in which testing is performed, a genetic testing specialty would standardize quality control practices where appropriate and would provide the necessary enforcement mechanism to ensure that these measures were followed. These efforts would increase the quality of the tests and the medical decisions made by patients and their physicians.

**Genetic testing laboratory errors can have serious consequences. Some examples are presented below.**

- An Ohio woman who knew she was a carrier of an X-linked genetic disorder underwent prenatal testing to determine whether her child would inherit the disorder. She was told she would have a girl who would not have the disorder. Instead, she gave birth to a male child with serious disabilities caused by the disorder. The likely cause of this error was maternal cell contamination, in which the laboratory examined the mother's cells rather than those belonging to the fetus (35).
- A Maryland couple who both were carriers of the cystic fibrosis gene and already had an affected child sought prenatal testing to determine whether their child would have the disease. The laboratory report indicated the fetus did not have cystic fibrosis. After the child was diagnosed with cystic fibrosis at three months of age, the laboratory issued an amended report indicating that the results had been positive for the cystic fibrosis mutation. Laboratory personnel admitted they had "misread the chromatograph" indicating the genetic mutation (36).
- A young woman who experienced several episodes of deep vein thrombosis (blood clots) was tested for the factor V Leiden genetic mutation, which is associated with an increased risk of blood clots. The laboratory indicated she had the mutation. Over the course of several years, two other laboratories reported that she was negative for the mutation. Based on these reports indicating she did not have the mutation, and seeking to conceive a child, she began to take a fertility drug known to increase the risk of blood clots. Two months later she experienced extensive blood clots. A fourth genetic test indicated she had the mutation. A case report reviewing this incident determined that the woman did in fact have the mutation and cited laboratory error (sample misidentification, test failure, incorrect interpretation, or clerical error) as possible reasons for the false negative results by two of the four laboratories (37).
- A Florida couple both tested negative for the genetic mutation that causes Tay-Sachs, a fatal childhood disease. Two copies of the mutation are required to cause the disease. The couple learned that the test results were incorrect for both parents when their son began exhibiting symptoms of Tay-Sachs shortly after birth. He died eight years later (38).
- After a middle-aged man was diagnosed with a fatal adult-onset neurological disease caused by a dominant genetic mutation, three close relatives had genetic testing by a different laboratory. The laboratory, which had failed to use a sample from the affected relative for comparison, analyzed the relatives' DNA at the wrong location of the gene and issued a report to two of the relatives indicating they were negative for the mutation. Before releasing the third relative's results, the laboratory realized its error and notified the genetic counselor. The three relatives were informed of the error and decided to be re-tested. After much additional anxiety, the two relatives again tested negative, while the third relative was found to have the mutation (39).

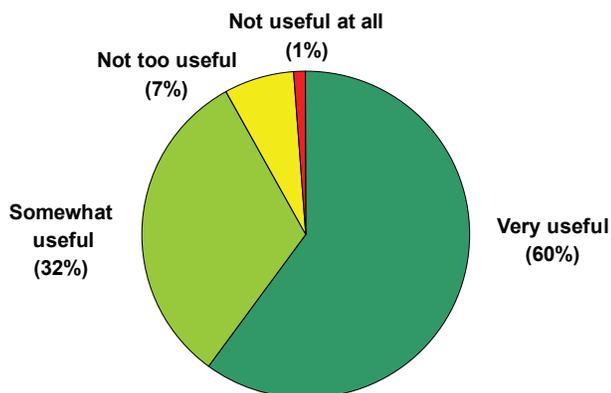
# Opinions on Oversight

The Genetics and Public Policy Center’s survey assessed laboratory directors’ attitudes toward laboratory quality and oversight. Nearly all directors found proficiency testing to be very or somewhat useful in improving the quality of genetic testing (23) (Figure 5). A majority (73 percent) of those surveyed agreed or strongly agreed that CLIA should create a genetic testing specialty for molecular and biochemical tests (23) (Figure 6).

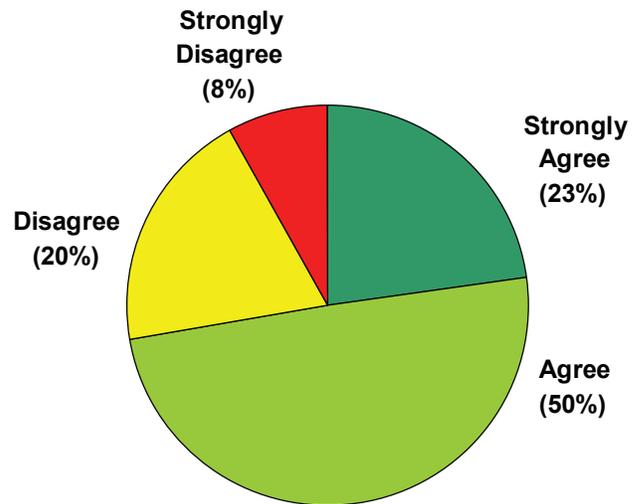
While the regulated industry supports the creation of a genetic testing specialty under CLIA, the College of American Pathologists, which accredits clinical laboratories and administers proficiency testing, consistently has opposed the creation of a genetic testing specialty (47-49).

Those who have the most to gain or lose from the accuracy and reliability of genetic testing — that is, patients — resoundingly have expressed their support for the creation of a genetic testing specialty. In February 2006, the Genetic Alliance sent a letter to CMS Administrator Mark McClellan urging him to issue a proposed rule for a genetic testing specialty under CLIA, stating that a specialty “is a necessary first step toward a regulatory system that encourages new technology and ensures

**Figure 5: Overall, how useful is proficiency testing for improving the quality of genetic testing?** (n=187)



**Figure 6: CLIA should create a genetic testing specialty for molecular and biochemical tests.** (n=186)



safety and accuracy when those technologies are implemented.”(33)

A diverse array of stakeholders also has supported a genetic testing specialty under CLIA. In June 2006, a letter signed by 75 groups comprising patient advocacy organizations, genetic testing laboratories, healthcare provider organizations, and industry urged CMS to issue a proposed rule for a specialty (50). Separately, 14 women’s health advocacy organizations also wrote CMS asking for creation of a genetic testing specialty (51).

# Conclusion: Why a Specialty is Needed

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In the 18 years since Congress enacted CLIA, genetic testing has become a critical part of clinical medicine, and among the fastest-growing areas of laboratory testing (52). In that time frame, the number of genetic tests has increased more than tenfold. New companies offering genetic tests to healthcare providers and consumers appear with increasing frequency.

Yet, because of CMS's inattention and delay in implementing CLIA, neither healthcare providers nor consumers can be confident in the oversight mechanisms in place to ensure genetic tests are accurate and reliable. While genetic science and genetic technologies have leapt into the 21<sup>st</sup> century, the agency entrusted with ensuring laboratory quality is stuck in the past.

The mandate from Congress under CLIA was clear: Laboratories must participate in proficiency testing for each test they perform unless proficiency testing cannot be developed. Congress was equally clear that the absence of proficiency-testing programs or the difficulty in establishing such programs was not an adequate reason for failing to require participation in proficiency testing. Yet CMS has not mandated participation in proficiency testing for any genetic tests, nor has it demonstrated that creation of proficiency-testing programs is not possible.

Congress was similarly clear regarding the need for transparency regarding laboratory quality. To that end, the law required CMS to create a program to make the results of proficiency-testing programs available to the public. No such program has been created. Nor does CMS make available to the public information on whether a laboratory is certified under CLIA. CMS could easily make this information available to healthcare providers and the public. Without this information, providers and patients are kept in the dark regarding the qualifications and competence of the laboratories that provide critical healthcare information.

To be sure, many genetic testing laboratories in the United States are of very high quality, and go beyond the current minimal standards to ensure the accuracy and reliability of the genetic tests they perform. But, as the Genetics and Public Policy Center's survey of genetic testing laboratory directors reveals, some laboratories are not routinely performing proficiency testing and are not following recommended quality control procedures. Moreover, the survey indicates a correlation between proficiency testing and laboratory quality. A genetic testing specialty under CLIA would provide a mechanism for mandating both formal and informal proficiency testing. Additionally, a genetic testing specialty under CLIA would standardize quality control methods to ensure adherence to the recommended standards.

Genetic testing will have an increasing impact on public health through improved diagnosis, treatment, and prevention of disease. However, the promise of genetics to improve health and healthcare will not be realized unless genetic tests provide accurate and reliable test results. Policy to require that genetic testing be accurate and reliable has not kept pace with the growth of genetic tests. In enacting CLIA, Congress was explicit regarding the need for improved quality standards. With respect to genetic testing quality, CMS has failed to meet the expectations of Congress and the public. The creation of a genetic testing specialty is a critical first step to ensuring that laboratories have demonstrated capability to perform accurate and reliable tests. The time is now for CMS to move expeditiously to protect the public's health.

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