

September 26, 2006

Mark McClellan, M.D., Ph.D.  
Administrator  
Centers for Medicare and Medicaid Services  
7500 Security Boulevard  
Baltimore, MD 21244

Petition for Rulemaking

Dear Administrator McClellan:

This Petition is submitted by the Genetics and Public Policy Center,<sup>1</sup> Public Citizen's Health Research Group,<sup>2</sup> and Genetic Alliance<sup>3</sup> pursuant to section 553(e) of the Administrative Procedure Act.<sup>4</sup> Petitioners request that the Centers for Medicare and Medicaid Services (CMS) implement the Clinical Laboratory Improvement Amendments of 1988 (CLIA)<sup>5</sup> by creating a genetic testing specialty and establishing standards for proficiency testing.

Petitioners believe this action is required under CLIA. Even if CLIA does not require this action, however, CMS has the authority to create a genetic testing specialty and should do so. Petitioners believe that creating such a specialty is critical to ensuring the quality of genetic testing in the United States and that the failure to do so poses a risk to public health.

In 2000, the Centers for Disease Control (CDC), which advises CMS on CLIA issues, published a Notice of Intent in the Federal Register announcing CMS' intent to issue a proposed rule to create a genetic testing specialty.<sup>6</sup> In April 2006, CMS placed the issuance of a proposed rule on its Semiannual Regulatory Agenda, with a target date of November 2006.<sup>7</sup> In June 2006 a CMS official testified before the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) that a proposed rule was in clearance at CMS.<sup>8</sup> However, in August 2006 officials within CMS indicated that they

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<sup>1</sup> 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.

<sup>2</sup> Public Citizen is a consumer group comprising approximately 100,000 members nationwide. Through its Health Research Group, Public Citizen advocates for the interests of consumers in health care.

<sup>3</sup> Genetic Alliance increases the capacity of genetic advocacy organizations to achieve their missions and leverages the voices of millions of individuals and families living with genetic conditions. Genetic Alliance provides leadership and infrastructure development for more than 600 disease-specific advocacy organizations, representing over 1000 diseases, affecting over 25 million Americans.

<sup>4</sup> 5 U.S.C. § 553(e).

<sup>5</sup> 42 U.S.C. § 263a.

<sup>6</sup> 65 Fed. Reg. 25,928 (May 4, 2000).

<sup>7</sup> 71 Fed. Reg. 22,537, 22,595 (Apr. 24, 2006).

<sup>8</sup> Testimony of Judith A. Yost, Director, Division of Laboratory Services, Centers for Medicare and Medicaid Services, Before the Secretary's Advisory Committee on Genetics Health and Society, June 26-

had abandoned entirely the agency's long-stated intent to create a specialty, and that current regulations are adequate to ensure the accuracy and reliability of genetic testing laboratories.<sup>9</sup> This petition seeks creation of the genetic testing specialty consistent with the government's long-stated intent.

## **I. Introduction and Action Requested**

Congress enacted CLIA in 1988 to ensure that the laboratories performing millions of tests on patient samples every year provide accurate and reliable results. In its infancy at that time, genetic testing has since become a critical part of clinical medicine, and among the fastest-growing areas of laboratory testing.<sup>10</sup> Today, genetic tests are available clinically for 1000 diseases.<sup>11</sup> Genetic testing is having an increasing impact on public health through the improved diagnosis, treatment, and prevention of disease. However, the promise of genetics to improve health and healthcare will not be realized unless laboratories performing genetic tests provide accurate and reliable test results.

CLIA mandates that the Secretary of Health and Human Services (HHS) – through CMS<sup>12</sup> – set standards for all laboratories performing clinical testing, including standards for performance of proficiency testing. CMS must establish proficiency testing standards for all tests performed by clinical laboratories unless the agency determines that a proficiency-testing program cannot reasonably be developed.<sup>13</sup>

CLIA regulations classify laboratory tests as either waived, moderate complexity, or high complexity. For moderate- and high-complexity testing laboratories, CMS has implemented the standard-setting requirements through the creation of “specialty areas.” Each specialty is tailored to a specific type of testing and sets requirements for tests in that area. These requirements may address quality assurance, quality control, personnel qualifications, and enrollment in a formal proficiency-testing program. As a practical matter, the creation of a specialty area is a prerequisite to requiring laboratories to enroll in formal proficiency-testing programs.<sup>14</sup>

Genetic tests are considered high complexity under CLIA. Yet CMS has not established a specialty area for most genetic tests. As a consequence, it has not mandated participation in proficiency testing, even for those proficiency-testing programs already

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27, 2006, at [http://www4.od.nih.gov/oba/SACGHS/meetings/June2006/transcripts/Oversight\\_Session-Yost.pdf](http://www4.od.nih.gov/oba/SACGHS/meetings/June2006/transcripts/Oversight_Session-Yost.pdf) (last visited Sept. 17, 2006) (hereinafter Yost testimony).

<sup>9</sup> Meeting between representatives of the Genetics and Public Policy Center and representatives of the Centers for Medicare and Medicaid Services, August 3, 2006.

<sup>10</sup> Frost and Sullivan, *US Genetic Diagnostic Markets*, Market Report F463-52 (2005).

<sup>11</sup> GeneTests, <http://www.genetests.org> (last visited Sept. 18, 2006).

<sup>12</sup> Although CLIA gives the Secretary of HHS the authority to implement the statute, the Secretary has delegated that responsibility to CMS. 67 Fed. Reg. 3721 (Jan. 25, 2002).

<sup>13</sup> 42 U.S.C. § 263a(f)(3)(A).

<sup>14</sup> However, creation of a specialty does not, by itself, require mandating proficiency testing; CMS may exempt tests from proficiency testing requirements if the agency finds that proficiency-testing programs cannot reasonably be developed for a particular specialty area. *Id.*

in existence.<sup>15</sup> Nor has the agency demonstrated that additional proficiency-testing programs cannot reasonably be developed.

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 recent survey of genetic testing laboratory directors reveals, some laboratories are not performing proficiency testing routinely and are not following recommended quality control procedures.<sup>16</sup> The survey also indicates a correlation between proficiency testing and laboratory quality.

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.<sup>17</sup> An accurate test result can help patients make informed decisions about their health and health care. Conversely, an inaccurate test result can result in ill-informed health care choices, needless suffering, and even death.

The creation of a genetic testing specialty enjoys wide public support,<sup>18</sup> including the support of the regulated industry. Data published by the Genetics and Public Policy Center indicate that 73 percent of laboratory directors surveyed support the creation of a specialty under CLIA.<sup>19</sup> In light of both the compelling public health need and the widespread support for the creation of a specialty with respect to genetic testing, CMS' failure to create a genetic testing specialty not only is perplexing but also unconscionable. Petitioners therefore call upon CMS to end years of delay and inattention, during which genetic tests have proliferated while oversight of genetic testing laboratories has fallen through the cracks, by issuing a proposed rule for a genetic testing specialty and moving expeditiously to finalize that rule.

## II. Background on CLIA

Congress enacted the Clinical Laboratory Improvement Amendments of 1988, referred to as CLIA, to “strengthen federal oversight of clinical laboratories to assure that the tests results are accurate and reliable.”<sup>20</sup> Congress found that laboratory testing plays 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

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<sup>15</sup> See, e.g., College of American Pathologists, 2007 Surveys & Anatomic Pathology Education Programs, Biochemical and Molecular Genetics, at 171-172, available at [http://www.cap.org/apps/docs/proficiency\\_testing/surveys\\_catalog/chapter\\_18.pdf](http://www.cap.org/apps/docs/proficiency_testing/surveys_catalog/chapter_18.pdf) (last visited Sept. 25, 2006).

<sup>16</sup> See section IV.c. *infra*.

<sup>17</sup> Gail H. Javitt and Kathy L. Hudson, *Federal Neglect: Regulation of Genetic Testing*, 22 *Issues in Science and Technology* 59 (2006).

<sup>18</sup> See section V. *infra*.

<sup>19</sup> Kathy L. Hudson et al., *Oversight of US Genetic Testing Laboratories*, 24 *Nature Biotechnology* 1083, 1088 (2006).

<sup>20</sup> H.R. REP. No. 100-899 (1988), at 8.

agencies.”<sup>21</sup> However, Congressional hearings at the time found deficiencies in laboratory quality. In particular, high numbers of false-negative results were being reported by laboratories performing Pap smears to screen women for cervical cancer.<sup>22</sup> Women with abnormal, possibly cancerous, cells were being incorrectly informed that their Pap smears were normal, leading to needless illness and death.

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.”<sup>23</sup> Proficiency testing requires a laboratory to demonstrate that it can obtain the correct answer when performing a test on a standard tissue sample; it serves as a “method of externally validating the level of a laboratory’s performance.”<sup>24</sup>

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.”<sup>25</sup> 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.”<sup>26</sup> Congress intended CLIA to remedy these shortcomings through new, more rigorous laboratory standards.

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.”<sup>27</sup>

### **III. Genetic Testing Has Become Part of Mainstream Medicine, and Errors in Genetic Testing Can Have Tragic Consequences**

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. 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.<sup>28</sup> Today there are about 1000 diseases for which genetic tests are available clinically, and several hundred more diseases for which tests

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<sup>21</sup> *Id.* at 10.

<sup>22</sup> *Id.* at 31.

<sup>23</sup> *Id.* at 12.

<sup>24</sup> *Id.* at 15.

<sup>25</sup> *Id.* at 28.

<sup>26</sup> *Id.* at 16.

<sup>27</sup> *Id.* at 13.

<sup>28</sup> *International Consortium Completes Human Genome Project*. Nat. Human Genome Res. Inst. (2003), at <http://www.genome.gov/11006929> (last visited Sept. 18, 2006).

are available in a research setting.<sup>29</sup> 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.<sup>30</sup> Identifying the genetic underpinnings for individual 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.<sup>31</sup>

The common denominator in all of these current and future applications of genetic research to human health is the tests 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. Genetic tests provide information – information about whether someone has a disease, has an increased risk of developing a disease later in life, is at risk of passing a disease onto his or her offspring, is likely to suffer an adverse reaction to a medication, or is likely to benefit from a particular therapeutic intervention. An accurate test result also can help patients make informed decisions about their health and health care. Even when no intervention is available, an accurate genetic test result can provide peace of mind or greater understanding of the causes of an illness.

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. However, errors can have devastating consequences, causing death, disability, and significant anxiety for patients and their families. Some examples of patient injury due to mistakes in genetic testing include:

- 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.<sup>32</sup>
- 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

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<sup>29</sup> GeneTests, *supra* note 11.

<sup>30</sup> Alan E. Guttmacher and Francis S. Collins, *Realizing the Promise of Genomics in Biomedical Research*, 294 JAMA 1399 (2005); Alan E. Guttmacher and Francis S. Collins, *Genomic Medicine – A Primer*, 347 New Eng. J. Med. 1512 (2002).

<sup>31</sup> Sharon Marsh and Howard L. McLeod, *Pharmacogenomics: From Bedside to Clinical Practice*, 15 Hum. Molecular Genetics R89 (2006).

<sup>32</sup> *Shirmer v. Mt. Auburn Obstetrics and Gynecological Associates*, 844 N.E.2d 1160 (2006).

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.<sup>33</sup>

- A young woman who had 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 the 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 a possible reason for the false-negative results by two of the four laboratories.<sup>34</sup>
- 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.<sup>35</sup>
- 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.<sup>36</sup>

Even with stringent quality-assurance and quality-control programs and rigorous proficiency testing, some errors will occur. However, given the significant consequences of a wrong answer to patients and their families, CMS has an obligation to implement CLIA for genetic testing in a manner that will minimize such errors. Creation of a genetic testing specialty, and establishing standards for proficiency testing, would give

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<sup>33</sup> Hood v. Lab Corp. of Am., 2006 U.S. Dist. LEXIS 36464 (D.Md. 2006).

<sup>34</sup> Edward N. Libby et al., *False-Negative Factor V Leiden Genetic Testing in a Patient with Recurrent Deep Vein Thrombosis*, 81 Am J. Hematology 284 (2006).

<sup>35</sup> *Our Stories*, Matthew Forbes Romer Foundation, at <http://www.mfrfoundation.org/stories.php> (last visited Sept. 18, 2006).

<sup>36</sup> Jennie Feiger, *Protecting Patients While Managing Lab Errors*, 25 Perspectives in Genetic Counseling 4 (2003).

the public greater assurance regarding the accuracy and reliability of the genetic tests they use to make profound medical and life decisions.

#### IV. Implementation of CLIA to Date

Under CLIA, the Secretary of HHS, through CMS, is responsible for developing laboratory standards “necessary to protect the health and safety of patients.”<sup>37</sup> Specifically, CLIA states that the Secretary of HHS “shall issue standards to assure consistent performance by laboratories issued a certificate under this section of valid and reliable laboratory examinations.”<sup>38</sup> Such standards must require laboratories to maintain quality assurance and quality control procedures “adequate and appropriate for the validity and reliability of the laboratory examinations” they perform;<sup>39</sup> maintain records, equipment, and facilities necessary for proper and effective operation;<sup>40</sup> use only personnel competent to perform the type of testing performed, based on qualifications the Secretary may establish;<sup>41</sup> and to “qualify under a proficiency testing program meeting the standards established by the Secretary under paragraph (3). . . .”<sup>42</sup>

Paragraph (3) states that the Secretary

shall establish standards for the proficiency testing programs for laboratories issued a certificate under this section which are conducted by the Secretary, conducted by an organization approved under subparagraph (C), or conducted by an approved accrediting body. The standards shall require that a laboratory . . . be tested for each examination and procedure conducted within a category of examinations or procedures for which it has received a certificate, except for examinations and procedures for which the Secretary has determined that a proficiency test cannot reasonably be developed. The testing shall be conducted on a quarterly basis, except where the Secretary determines for technical and scientific reasons that a particular examination or procedure may be tested less frequently (but not less often than twice per year).<sup>43</sup>

Although the statute provides an exception when the development of proficiency-testing standards cannot reasonably be developed, the legislative history makes clear that Congress intended this to be a very narrow exception. The House Committee on Energy and Commerce report accompanying H.R. 5150 – which became CLIA – stated that 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

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<sup>37</sup> H.R. REP. No. 100-899, at 4.

<sup>38</sup> 42 U.S.C. § 263a(f)(1).

<sup>39</sup> *Id.* § 263a(f)(1)(A).

<sup>40</sup> *Id.* § 263a(f)(1)(B).

<sup>41</sup> *Id.* § 263a(f)(1)(C).

<sup>42</sup> *Id.* § 263a(f)(1)(D).

<sup>43</sup> *Id.* § 263a(f)(3)(A).

method of proficiency testing. Rather, the Committee expects the Secretary to foster innovative approaches . . . for developing proficiency testing for analytes for which such testing is not currently available.<sup>44</sup>

**a. CMS Has Set Standards For the Vast Majority of Non-Genetic Testing Laboratories**

Regulations implementing CLIA first went into effect in 1992.<sup>45</sup> The regulations establish a “three-tier” system of regulation for clinical laboratories based on the types of tests they perform and the level of oversight required to ensure the accuracy and reliability of these tests. Laboratory tests may be categorized as waived, moderate complexity, or high complexity. Criteria for categorization include the knowledge needed to perform the test, the training and experience required, the complexity of reagent and materials preparation, and the degree of interpretation and judgment required.<sup>46</sup> 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.”<sup>47</sup> Laboratories performing only waived tests, such as dipstick or tablet urinalysis for glucose, fecal occult blood, and spun microhematocrit, are subject to only minimal regulation. They must obtain a certificate of waiver from CMS and agree to permit inspection of their facilities.

Laboratories performing tests of moderate or high complexity must, in addition to general laboratory requirements, comply with additional standards for proficiency testing, patient test management, quality control, personnel, and quality assurance. The regulations establish these standards by creating specific specialty and subspecialty areas, and mandating specialty-specific requirements.

The regulations mandate proficiency testing for the following specialties and subspecialties: 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 immuno-hematology.<sup>48</sup> The regulations specify a minimum proficiency test score that laboratories must receive for each specialty and subspecialty.<sup>49</sup>

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<sup>44</sup> H.R. REP. No. 100-899, at 29.

<sup>45</sup> 42 C.F.R. Part 493.

<sup>46</sup> *Id.* § 493.17 The complete list of criteria for complexity determination are: (1) knowledge; (2) training and experience; (3) reagents and materials preparation; (4) characteristics of operational steps; (5) calibration, quality control, and proficiency testing materials; (6) test system troubleshooting and equipment maintenance; and (7) interpretation and judgment.

<sup>47</sup> *Id.* § 493.15.

<sup>48</sup> *Id.* §§ 801-865.

<sup>49</sup> Laboratories that fail to perform successfully on proficiency testing are subject to sanctions specified in the regulations. 42 C.F.R. §§ 493.1800-493.1850. The regulations also provide that, for a laboratory’s initial unsuccessful performance, CMS may direct the laboratory to undertake training of its personnel and/or to obtain technical assistance instead of imposing sanctions unless (a) there is immediate jeopardy to

If CMS has not established a specialty or subspecialty for a type of moderate- or high-complexity test, a laboratory performing that test must “establish and maintain the accuracy of its testing procedures” and verify the accuracy of its test results at least twice a year.<sup>50</sup>

#### **b. CMS Has Not Set Specific Standards for Most Genetic Testing Laboratories**

Although CMS has made the creation of a specialty area a prerequisite for imposing test-specific standards, CMS has not established a specialty for molecular or biochemical genetics, both of which are categorized as high-complexity 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. Additionally, no proficiency testing has been mandated for cytogenetics. Thus, with the exception of cytogenetics quality control requirements, CMS has established no specific personnel or proficiency-testing requirements for any genetic tests.

In particular, the absence of a specialty area has meant that no proficiency testing is required for any laboratories performing genetic testing. Even though a limited number of proficiency-testing programs exist, in the absence of a specialty, enrollment in these programs is voluntary under the law. When formal programs are not available, laboratories can engage in informal methods of proficiency testing by, for example, swapping samples with another laboratory or splitting a sample in two and comparing the test results. However, current regulations do not require laboratories to engage in such informal proficiency testing, and, as discussed below, many do not.

CMS has taken the position that the specialties currently available under CLIA regulations are adequate to ensure the accuracy and reliability of genetic testing laboratories.<sup>51</sup> However, as discussed below, many genetic testing laboratories are not certified in *any* specialty. Moreover, requirements for other specialties have little relevance to genetic testing. For example, the proficiency-testing programs for chemistry address analytes such as glucose, cholesterol, potassium, and sodium – analytes that are not relevant to genetic testing.

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patient health and safety, (b) the laboratory fails to provide CMS with satisfactory evidence that it has taken steps to correct the problem, or (c) the laboratory has a poor compliance history. *Id.* § 493.803.

<sup>50</sup> *Id.* § 493.801(a)(2)(ii).

<sup>51</sup> *At Home DNA Tests: Marketing Scam or Medical Breakthrough? Hearing Before the Senate Special Committee on Aging*, 109<sup>th</sup> Cong., 2d sess, 2006 (hereinafter Senate Aging Committee Hearing) (statement of Thomas Hamilton, Director, Survey and Certification Group, Center for Medicaid and State Operations, Centers for Medicare and Medicaid Services).

**c. In the Absence of a Genetic Testing Specialty, Laboratory Practices are Widely Divergent and Frequently Inadequate**

Ensuring that procedures are in place to avoid and detect laboratory errors and identify laboratories whose performance is substandard is of paramount importance. To collect empirical data on laboratory practices and laboratory director attitudes regarding oversight,<sup>52</sup> the Genetics and Public Policy Center surveyed directors of molecular and biochemical genetic testing laboratories in the United States, and received 190 responses, for a 55 percent response rate.<sup>53</sup>

Results of the survey reveal wide variations in laboratory performance, as measured by the number of deficiencies<sup>54</sup> in formal proficiency testing and the number of incorrect test results reported by laboratories.<sup>55</sup> (Attachment 1). Among the survey's findings:

- Thirty-five percent of respondents offer some tests for which they perform no proficiency testing.<sup>56</sup>
- 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 perform proficiency testing for all tests they offer.<sup>57</sup> Therefore, participation in proficiency testing has a clear association with laboratory quality as measured by the number of reported deficiencies in formal proficiency-testing programs.
- The number of deficiencies reported by respondents has a clear association with the number of reported errors. Laboratories that reported two or more proficiency-testing deficiencies reported on average 10.6 errors in the last two years,

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<sup>52</sup> Although a few studies previously have examined the types of laboratory errors that occur in both genetic and non-genetic testing laboratories, or have investigated adherence to professional standards, no prior studies have surveyed the practices of genetic testing laboratories or assessed whether the creation of a genetic testing specialty could improve testing quality. See Wolfgang T. Hofgartner and Jonathan F. Tait, *Frequency of Problems During Clinical Molecular-Genetic Testing*, 112 *Am. J. Clinical Pathology* 14 (1999); Pierrangelo Bonini et al., *Errors in Laboratory Medicine*, 48 *Clinical Chemistry* 691 (2002); David L. Witte et al., *Errors, Mistakes, Blunders, Outliers, or Unacceptable Results: How Many?* 43 *Clinical Chemistry* 1352 (1997); Peter J. Howanitz, *Errors in Laboratory Medicine*, 129 *Archives Pathology Laboratory Med* 1252 (2005); Sandra C. Hollensead et al., *Errors in Pathology and Laboratory Medicine: Consequences and Prevention*, 88 *J. Surgical Oncology* 161 (2004); Margaret M. McGovern et al., *Quality Assurance in Molecular Genetic Testing Laboratories*, 281 *JAMA* 835 (1999).

<sup>53</sup> Practices and Attitudes of Laboratory Directors of Clinical Genetic Testing Laboratories. Johns Hopkins IRB No. NA-00001533 (2006).

<sup>54</sup> Deficiencies occur when a laboratory makes an error in a sample provided by a proficiency-testing program. Such errors range from incorrectly filling out a form, to switching a sample, to incorrectly interpreting the test result.

<sup>55</sup> Hudson et al., *supra* note 19, at 1087-1088.

<sup>56</sup> *Id.* at 1087.

<sup>57</sup> *Id.* at 1087-88.

compared with 4.7 errors reported by laboratories with no proficiency-testing deficiencies.<sup>58</sup>

- Laboratories that reported doing less proficiency testing also were more likely to report that their most common type of error is analytic (as opposed to pre-analytic or post-analytic). Fifty percent of laboratories performing proficiency testing on 0-24 percent of their tests reported analytic errors as their most common type of error, as compared to 26 percent of laboratories performing proficiency testing on all their tests.<sup>59</sup>
- Even when formal proficiency-testing programs are available, some laboratories do not participate; only 63 percent of directors whose laboratories do not always participate in formal proficiency-testing programs indicated it was because of the lack of availability of formal testing programs.<sup>60</sup>
- 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.<sup>61</sup>
- Genetic testing laboratories are not always certified in existing 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.<sup>62</sup>

The survey also revealed wide variation in a number of key laboratory quality assurance practices, as well as practices that are inconsistent with the American College of Medical Genetics Standards and Guidelines for Clinical Genetic Laboratories.<sup>63</sup>

Among the findings from the survey:

- Although maternal cell contamination studies are necessary to ensure that prenatal tests do not inadvertently test the mother's DNA, about 40 percent of respondents do not always include maternal cell contamination studies when performing prenatal testing. Thirteen percent never or hardly ever do such testing.<sup>64</sup>

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<sup>58</sup> Practices and Attitudes of Laboratory Directors of Clinical Genetic Testing Laboratories, *supra* note 54 (unpublished data on file with the Genetics and Public Policy Center).

<sup>59</sup> *Id.* at 1089, Table 4.

<sup>60</sup> *Id.* at 1086.

<sup>61</sup> *Id.* at 1087.

<sup>62</sup> *Id.* at 1085-86.

<sup>63</sup> *Standards and Guidelines for Clinical Genetics Laboratories*. American College of Medical Genetics (2006), available at [http://www.acmg.net/Pages/ACMG\\_Activities/stds-2002/stdmenu-n.htm](http://www.acmg.net/Pages/ACMG_Activities/stds-2002/stdmenu-n.htm) (last visited Sept. 18, 2006).

<sup>64</sup> Practices and Attitudes of Laboratory Directors of Clinical Genetic Testing Laboratories. *supra* note 54 (unpublished data on file with the Genetics and Public Policy Center).

- While performing prenatal testing in duplicate reduces the chance of a false-positive or false-negative result, 18 percent of those surveyed never or hardly ever perform prenatal testing in duplicate.<sup>65</sup>
- While bi-directional sequencing improves analytic accuracy, 23 percent of respondents do not always sequence in both directions, and about six percent never or hardly ever do it.<sup>66</sup>

Thus, in the absence of mandated standards for genetic testing laboratories, laboratories follow widely divergent, and sometimes substandard, practices. 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. It would also provide the mechanism for mandating proficiency testing, and the incentive for the development of new proficiency-testing programs. These efforts would increase the quality of the tests and hence of the medical decisions made by patients and their physicians.

#### **V. There is Broad Stakeholder Support for the Creation of a Genetic Testing Specialty**

The Genetics and Public Policy Center’s survey of genetic testing laboratory directors also assessed directors’ attitudes toward laboratory quality and oversight. Nearly all directors responded that they found proficiency testing to be very or somewhat useful in improving the quality of genetic testing.<sup>67</sup> A majority (73 percent) of those surveyed agreed or strongly agreed that CLIA should create a genetic testing specialty for molecular and biochemical tests.<sup>68</sup>

Those who have the most to gain or lose from the accuracy and reliability of genetic testing — that is, patients — have expressed their support resoundingly for the creation of a genetic testing specialty. In February 2006, Genetic Alliance sent a letter to you urging you 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 safety and accuracy when those technologies are implemented.”<sup>69</sup>

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, health care provider organizations, and industry urged CMS to issue a proposed rule for a specialty.<sup>70</sup> Separately, 14 women’s

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<sup>65</sup> *Id.*

<sup>66</sup> *Id.*

<sup>67</sup> Hudson et al., *supra* note 19, at 1088.

<sup>68</sup> *Id.*

<sup>69</sup> Letter from Sharon Terry, President and CEO, Genetic Alliance, to Mark McClellan, Administrator, Centers for Medicare and Medicaid Services (Feb. 28, 2006).

<sup>70</sup> Letter from Sharon Terry, President and CEO, Genetic Alliance, et al., to Mark McClellan, Administrator, Centers for Medicare and Medicaid Services (June 6, 2006).

health advocacy organizations also wrote CMS asking for creation of a genetic testing specialty.<sup>71</sup> This, however, is the first time a formal Petition on this subject has been filed.

## **VI. CMS Has Reneged on Its Longstanding Commitment to Create a Genetic Testing Specialty and Has Rejected the Recommendations of Numerous Expert Advisory Groups**

More than a decade ago, federal government officials realized the need for improved oversight of genetic testing, and established expert advisory bodies to make recommendations. Subsequent recommendations were far-reaching, and were addressed to multiple agencies, including the Food and Drug Administration.<sup>72</sup> However, improved oversight of clinical laboratories by CMS through the creation of a genetic testing specialty was viewed as an essential component of improved genetic testing quality. 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>73</sup> In addition to recommending that a specialty be established, the task force 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.<sup>74</sup>

In 2000, the CDC 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.<sup>75</sup> The Notice included the recommendations of the Clinical Laboratory Improvement Advisory Committee (CLIAC), an advisory group within the CDC. In the Notice, CDC 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. According to an analysis of the

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<sup>71</sup> Letter from Reproductive Technologies Project et al., to Mark McClellan, Administrator, Centers for Medicare and Medicaid Services (July 13, 2006).

<sup>72</sup> Under the Federal Food Drug and Cosmetics Act, 21 U.S.C. § 301 *et seq.*, FDA currently regulates some genetic tests as medical devices, but does not regulate directly the quality of laboratories performing genetic testing. See Genetics and Public Policy Center, *Issue Brief: FDA Regulation of Genetic Tests*, at <http://www.dnapolicy.org/policy.issue.php> (last visited Sept. 20, 2006).

<sup>73</sup> Neil Holtzman and Michael Watson eds., *Promoting Safe and Effective Genetic Testing In the United States: Final Report of the Task Force on Genetic Testing* (1997), available at <http://genome.gov/10001733> (last visited Sept. 18, 2006).

<sup>74</sup> ENHANCING THE OVERSIGHT OF GENETIC TESTING LABORATORIES: RECOMMENDATIONS OF THE SACGT (2000), available at [http://www4.od.nih.gov/oba/sacgt/reports/oversight\\_report.pdf](http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf) (last visited Sept. 18, 2006).

<sup>75</sup> 65 Fed. Reg. 25,928.

comments by the Genetics and Public Policy Center, the overwhelming majority of respondents (93 percent) 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.<sup>76</sup> 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.<sup>77</sup> However, some who submitted comments were concerned that requiring laboratories to obtain patient consent and provide genetic counseling “overreached” CLIA’s mandate by requiring laboratories to assume functions more appropriately handled by health care providers.<sup>78</sup>

The CLIAC modified its recommendations in response to the comments received,<sup>79</sup> although a modified set of recommendations was not made public, 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.<sup>80</sup>

In a September 2005 letter responding to an inquiry from the Genetics and Public Policy Center,<sup>81</sup> CMS stated that “[u]nder a Notice of Proposed Rulemaking . . . we will propose to add a specialty category for genetic testing.”<sup>82</sup> Similarly, in a January 2006 response to a Genetics and Public Policy Center inquiry,<sup>83</sup> CMS averred that “we intend to publish a Notice for Proposed Rule Making for genetic testing as quickly as feasible.”<sup>84</sup> 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.<sup>85</sup> CMS’ intent to move forward with the proposed rule was confirmed

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<sup>76</sup> Juli Murphy, Gail Javitt, and Kathy Hudson, *Creating a Genetic Testing Specialty Under CLIA: What Are We Waiting For?* at 6 (2005), Genetics and Public Policy Center, at <http://www.dnapolicy.org/resources/McClellanpaper.pdf> (last visited Sept. 18, 2006).

<sup>77</sup> *Id.* at 13-14.

<sup>78</sup> *Id.* at 11-13.

<sup>79</sup> CLINICAL LAB. IMPROVEMENT ADVISORY COMM. (CLIAC), SUMMARY REPORT, Feb. 2001, at [www.phppo.cdc.gov/dls/cliac/default.asp](http://www.phppo.cdc.gov/dls/cliac/default.asp) (last visited Sept. 18, 2006).

<sup>80</sup> CLINICAL LAB. IMPROVEMENT ADVISORY COMM. (CLIAC), SUMMARY REPORT, Jan. 2002, SUMMARY REPORT, Sept. 2002, SUMMARY REPORT, Sept. 2003, SUMMARY REPORT, Feb. 2004, SUMMARY REPORT, Sept. 2004, SUMMARY REPORT, Feb. 2005, SUMMARY REPORT, Sept. 2005, SUMMARY REPORT, Feb. 2006, at [www.phppo.cdc.gov/dls/cliac/default.asp](http://www.phppo.cdc.gov/dls/cliac/default.asp) (last visited Sept. 18, 2006).

<sup>81</sup> Letter from Gail Javitt, Law and Policy Director, Genetics and Public Policy Center, to Judith A. Yost, Director, Division of Laboratory Yost Services, Centers for Medicare and Medicaid Services (July 15, 2005).

<sup>82</sup> Letter from Judith A. Yost, Director, Division of Laboratory Yost Services, Centers for Medicare and Medicaid Services, to Gail Javitt, Law and Policy Director, Genetics and Public Policy Center (Sept. 15, 2005) (on file at the Genetics and Public Policy Center).

<sup>83</sup> Letter from Kathy Hudson, Director, Genetics and Public Policy Center, to Mark McClellan, Administrator, Centers for Medicare and Medicaid Services (Nov. 18, 2005).

<sup>84</sup> Letter from Thomas Hamilton, Director, Survey and Certification Group, Center for Medicaid and State Operations, Centers for Medicare and Medicaid Services, to Kathy Hudson, Director, Genetics and Public Policy Center (Jan. 9, 2006) (on file at the Genetics and Public Policy Center).

<sup>85</sup> 71 Fed. Reg. at 22,595.

by the testimony of a CMS official before the SACGHS in June 2006. She stated “we do have a Notice of Proposed Rulemaking in CMS clearance at this time.”<sup>86</sup>

But one month later, at a hearing of the Senate Special Committee on Aging, CMS signaled it had abruptly shifted course and abandoned its commitment to establish a genetics specialty. 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.<sup>87</sup> 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’ Survey and Certification Group made no mention of the proposed rule.<sup>88</sup> Moreover, he testified that genetic testing already is covered adequately under existing regulations.<sup>89</sup> Even more surprisingly, he testified that because genetic tests are high complexity, laboratories must “participate in an approved proficiency-testing program” three times per year.<sup>90</sup> 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, discussed above, show that in the absence of a clear mandate from CMS, many genetic testing laboratories do not enroll in available voluntary proficiency-testing programs or perform any type of proficiency testing for every genetic test they offer.<sup>91</sup>

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.”<sup>92</sup> A review of the available specialties listed in the regulations makes this claim hard to understand. The existing specialties and their associated proficiency testing requirements are scientifically irrelevant to determining proficiency for genetic testing. For example, under the Chemistry specialty, proficiency testing is mandated for serum sodium. This ability to measure this analyte has no scientific relevance to molecular or biochemical genetic testing.

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).”<sup>93</sup> 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

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<sup>86</sup> Yost testimony, *supra* note 8.

<sup>87</sup> U.S. GAO, *Nutrigenetic Testing: Tests Purchased From Four Websites Mislead Consumers*, (2006), available at <http://www.gao.gov/new.items/d06977t.pdf> (last visited Sept. 18, 2006).

<sup>88</sup> Senate Aging Committee Hearing, *supra* note 51.

<sup>89</sup> *Id.* at 8.

<sup>90</sup> *Id.* at 4.

<sup>91</sup> Hudson et al., *supra* note 19, at 1086-1087.

<sup>92</sup> Senate Aging Committee Hearing, *supra* note 51, at 8.

<sup>93</sup> *Id.*

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.<sup>94</sup> CMS' contention that the 2003 regulation adequately addresses genetic testing quality is thus incorrect.

The proposal to create a genetic testing specialty was never mentioned in CMS' July testimony. This omission, together with the assertion that existing regulations are sufficient, signaled that CMS had reversed course. A July 2006 CMS letter to Genetic Alliance also indicated the agency's policy reversal. In response to a request that CMS issue a proposed rule for a genetic testing specialty,<sup>95</sup> CMS replied that genetic testing laboratories already are covered adequately under CLIA, making no mention of the proposed rule.<sup>96</sup>

Representatives of the Genetics and Public Policy Center met with CMS officials in August 2006.<sup>97</sup> 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.

CMS' excuse that proficiency-testing programs are not available is both inaccurate and contrary to Congress' intent in passing CLIA. Proficiency-testing programs are available for some genetic tests, albeit a limited number. In the absence of a genetic testing specialty, however, CMS has no practical means of mandating that laboratories participate in these programs. With respect to tests for which formal programs are not yet available, CMS cannot abdicate its responsibility because of the failure of private entities to create them. CLIA places the burden of establishing standards for proficiency testing squarely on CMS' shoulders. CLIA therefore has the obligation to ensure the development of proficiency-testing programs, unless the agency finds such programs cannot reasonably be developed. Finally, in the absence of formal proficiency testing CMS should require informal means of conducting proficiency testing, such as sample swapping or split-sample testing. Establishing a specialty would permit CMS to mandate participation in formal or informal proficiency-testing programs.

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<sup>94</sup> The Genetics and Public Policy Center's survey asked respondents to select all of the techniques their laboratory routinely employs in genetic testing. While 82 percent of respondents selected PCR genotyping, 58 percent selected DNA sequencing, 44 percent selected Southern blot, 38 percent selected SNP genotyping, 37 percent selected QPCR, 33 percent selected STR genotyping, and 30 percent selected FISH." Other technologies were also selected by a lower percentage of respondents. Thus PCR, a predominant technology, is certainly not the only technology routinely used by a significant percentage of genetic testing laboratories. *See supra* note 54.

<sup>95</sup> Letter from Sharon Terry, *supra* note 69.

<sup>96</sup> Letter from Dennis G. Smith, Director, Center for Medicaid and State Operations, Centers for Medicare and Medicaid Services (July 17, 2006).

<sup>97</sup> Meeting between representatives of the Genetics and Public Policy Center and representatives of the Centers for Medicare and Medicaid Services, *supra* note 9.

## **VII. Conclusion**

Making sure that laboratories can accurately and reliably perform genetic tests is a fundamental requirement for the success of genetic medicine, and a fundamental obligation of CMS under CLIA. However, because of CMS' inattention regarding laboratories performing genetic tests, neither health care providers nor consumers can be confident in the oversight mechanisms in place to ensure that laboratories performing genetic tests provide accurate and reliable test results.

Therefore, for the reasons discussed in this petition, the undersigned Petitioners request that CMS issue a proposed rule for a genetic testing specialty within 90 days, and finalize that rule within 180 days, after allowing a reasonable period for public comment.

Yours sincerely,

### **Signature on File**

Kathy Hudson, Ph.D.  
Director  
Genetics and Public Policy Center

### **Signature on File**

Sharon Terry  
President and CEO  
Genetic Alliance

### **Signature on File**

Peter Lurie, M.D., M.P.H.  
Deputy Director  
Public Citizen's Health Research Group

cc: Secretary Mike Leavitt