

Genetics and Public Policy Center

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March 18, 2008

The Honorable Michael O. Leavitt
Secretary of the Department of Health and Human Services
Hubert Humphrey Bldg.
200 Independence Ave., SW
Room 615F
Washington, DC 20201

Dear Mr. Secretary,

On behalf of the Genetics and Public Policy Center, we would like to commend you for your leadership on the issue of genetic testing oversight. Your inclusion of quality testing oversight as a key priority for your Personalized Medicine Initiative demonstrates your recognition that test quality is a key prerequisite for the success of personalized medicine. In furtherance of this Initiative, last April you requested that the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) review the oversight of genetic testing and make recommendations for improved oversight. We were pleased to have the opportunity to participate in the development of these recommendations, both through Task Force membership, testimony before the SACGHS, and the submission of comments. We believe the process of developing the recommendations spurred much needed discussion on many issues, and resulted in a comprehensive set of recommendations that, if implemented, will help to create a regulatory environment conducive to innovation of validated genetic tests and pharmaceuticals to foster personalized medicine.

In particular we wanted to address Rec 4-1, 1., which states: "CMS should require PT of all nonwaived laboratory tests for which PT products are available. For tests without PT products, laboratories must use alternative assessment methods, as required under current CLIA regulations." The Genetics and Public Policy Center has had longstanding concerns about the absence of proficiency testing (PT) requirements for genetic testing laboratories under the Clinical Laboratory Improvement Amendments (CLIA). Proficiency testing is a means to assess whether the laboratory reliably can perform and interpret tests correctly. Data from our survey of genetic testing laboratories¹ demonstrates that, in the absence of a requirement to enroll in proficiency testing programs, many laboratories do not perform proficiency testing, and that those laboratories that report performing more proficiency testing also report fewer analytic errors. We therefore strongly support this recommendation.

¹ Hudson K., J. Murphy, D. Kaufman, G. Javitt, S. Katsanis, and J. Scott. 2006. Oversight of US Genetic Testing Laboratories. *Nature Biotechnology* 24 (9): 1083-1090.

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As the public comments to SACGHS reflect, a broad coalition of stakeholders including industry also supports mandating proficiency testing for genetic testing laboratories. In addition to providing greater assurance of laboratory quality, mandating proficiency testing performance would also create an economic incentive for the creation of additional proficiency testing programs, enabling a wider range of genetic testing laboratories to participate.

We believe that implementing Recommendation 4-1, 1 would require only minor modification to current CLIA regulations. We have drafted a Model Notice of Proposed Rulemaking (NPRM) for your consideration. This approach would effectively implement the SACGHS recommendation and would be of tremendous benefit to ensuring laboratory quality and thereby helping to foster the era of personalized medicine.

We have enclosed the Model NPRM for your review and would like to request a meeting with you to discuss it further.

Sincerely,



Kathy Hudson

Director



Gail Javitt

Law and Policy Director

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Medicare and Medicaid Services

AGENCY: Centers for Medicare and Medicaid Services (CMS), HHS

42 CFR Part 493

[CMS-XXXX-X]

CLIA Program; Proficiency Testing for Analytes Not Covered by a Specialty or
Subspecialty

[XX FR XXXX]

DATE: [Day, Date, Year]

ACTION: Proposed Rule

SUMMARY: This proposed rule would extend the requirement to participate in proficiency testing to clinical laboratories performing non-waived testing on analytes for which proficiency testing is not required under an existing specialty or subspecialty. It would require all clinical laboratories performing nonwaived testing that are not covered by a specialty or subspecialty under 42 CFR Subpart I to enroll in available approved proficiency testing programs for the analytes they test, unless the laboratory has received an exemption from CMS.

DATES: To be assured consideration, comments must be received at one of the addresses provided below, no later than 5 p.m. on [Day, Date, Year]

ADDRESSES:

FOR FURTHER INFORMATION CONTACT:

SUPPLEMENTARY INFORMATION:

I. Background

Congress enacted the Clinical Laboratory Improvement Amendments of 1988 (CLIA), Public Law 100-578, on October 31, 1988. CLIA established a new section 353 of the Public Health Service Act (PHS) to replace the existing section 353. New section 353 required the Department of Health and Human Services (HHS) to establish certification requirements for clinical laboratories.

CMS issued final regulations implementing CLIA in 1992 (57 FR 7002, Feb. 28, 1992). The regulations establish three levels of tests by complexity as well as criteria for determining complexity level. Laboratories performing only low complexity tests are granted a Certificate of Waiver and are not subject to routine inspection and are exempt from the subparts of the regulations addressing proficiency testing, patient test management, quality control, laboratory information systems, personnel, and quality assurance. Using the criteria established, the 1992 regulations selected eight tests for the waived category; the list was amended in 1993 (58 FR 5221) and currently includes nine tests.

Tests classified as moderate or high complexity are required to meet the applicable requirements of the subparts relating to certificates of accreditation or registration, patient test management, quality control, quality assurance, personnel, proficiency testing, and inspection

Under the 1992 regulations, CMS established categories (called “specialties”) and subcategories (called “subspecialties”) of tests that were moderate or high complexity. Some specialties included both moderate and high complexity subspecialties. In all, the 1992 regulations established the following specialty and subspecialty areas: histocompatibility, including the subspecialties transplant and nontransplant; microbiology, including the subspecialties bacteriology, mycobacteriology, mycology, parasitology, and virology; diagnostic immunology, including the subspecialties syphilis serology and general immunology; immunohematology, including the subspecialties ABO Group and Rh Group, antibody detection, compatibility testing, and antibody identification; pathology, including the subspecialties histopathology, oral pathology, and cytology; radiobioassay; and clinical cytogenetics.

Tests within these specialty and subspecialties are subject to additional, specialty-specific requirements. In particular, for many of these tests the regulations mandate that the laboratory enroll in approved proficiency testing programs that meet specified criteria. Laboratories performing such tests must typically participate in three proficiency testing events per year. Currently there are 83 analytes for which the laboratory must enroll in an approved PT program.

The list of specialties and subspecialties has remained largely the same since it was first implemented. In the intervening years, an entirely new field of molecular and biochemical genetics has arisen and become a well-recognized part of laboratory practice. However, because molecular and biochemical genetic testing is not covered by a specialty or subspecialty, laboratories are not required under CLIA to enroll in approved proficiency testing programs for these tests. Instead, they are subject only to the regulatory requirement to “establish and maintain the accuracy of” their testing procedures and to “verify the accuracy of” their test results at least twice a year.

Recognizing that growth of genetic testing would bring with it both potential benefits and risks, in 1995 the National Institutes of Health-Department of Energy (NIH-DOE) Joint Working Group on the Ethical, Legal and Social Implications (ELSI) of Human Genome Research launched the Task Force on Genetic Testing. The mission of

the Task Force was to “evaluation of the current state of genetic testing technologies in the United States” and to examine critical issues, including how the quality of laboratories performing genetic tests would be ensured.

The Task Force released its report and recommendations in 1997.¹ The Task Force tests determined that proficiency testing was an essential element of ensuring the quality of genetic testing. The Task Force recommended that a genetic testing specialty be created under CLIA and that laboratories performing genetic testing thereafter be required to enroll in available proficiency testing programs.

Based on the recommendations of the Task Force, the Clinical Laboratory Improvement Advisory Committee (CLIAC), a CDC group that advises CMS on CLIA implementation, took up the task of developing a genetic testing specialty. These recommendations were published in the Federal Register in 2000 as a “Notice of Intent” (65 FR 25928). The Notice of Intent announced CMS’s intention to create a genetic testing specialty and requested public comment on the CLIAC’s recommendations.

The CLIAC’s recommendations for a genetic testing specialty were comprehensive and far-reaching. They addressed, among other things, the definition of genetic testing, informed consent, genetic counseling, personnel standards, analytical and clinical validation, reporting of results, and proficiency testing.

HHS received 57 comments in response to the Notice of Intent. Many commenters raised concerns that some of the CLIAC’s recommendations would impose significant new and unwarranted burdens on clinical laboratories. There were also concerns about the proposed definition of molecular and biochemical genetic tests. There was, however, strong support, in principle, for the creation of a specialty area to cover molecular and biochemical genetic tests, and little opposition to the proposal regarding proficiency testing.

Since the CLIAC issued its recommendations, new data have emerged that underscore the importance of proficiency testing in ensuring the analytic accuracy of tests. A 2006 study by *Hudson et al.*² surveyed 190 directors of molecular and biochemical genetic testing laboratories and found that many laboratories do not enroll in available approved proficiency testing programs. It also found that laboratories that performed PT on all their tests were less likely to identify analytic errors as their most frequent cause of error. The overwhelming majority of respondents (92 percent) agreed that proficiency testing was useful in improving laboratory test quality.

An international laboratory survey by the Organization for Economic Cooperation and Development (OECD) similarly confirms the importance of proficiency testing for laboratory quality.³ The OECD surveyed 18 member countries including the United States to document and compare quality assurance practices in clinical molecular genetic testing laboratories. The data collected were intended to inform the development of international standards and guidelines to ensure genetic testing quality. The survey, published in 2005, found that participation in proficiency testing is associated with higher quality laboratories. In 2007 the OECD adopted guidelines for quality assurance in

molecular genetic testing, which state that laboratories “should participate in a proficiency testing scheme for every disease for which they test, where such schemes are available.”⁴

CMS believes that proficiency testing is a critical part of ensuring quality laboratory services. Currently the College of American Pathologists offers 25 separate surveys for molecular or biochemical genetic tests. CMS is troubled that many laboratories performing molecular and biochemical genetic testing appear not to enroll in such programs when they are available. CMS believes that laboratories performing molecular and biochemical genetic testing should be required, consistent with CLIA, to enroll in CMS-approved proficiency testing programs. Further, CMS believes that entities offering proficiency testing programs for these tests should have the ability to apply for HHS approval of these programs in the same manner as they do for other clinical laboratory tests.

CMS has struggled for a long time with the issue of establishing a genetic testing specialty. In light of the significant challenges in defining the specialty, and opposition to many of the specific proposals of the CLIAC, CMS has decided not to create a genetic testing specialty. However, CMS has also determined that creation of a genetic testing specialty is not a prerequisite to requiring that laboratories performing molecular and biochemical genetic tests participate in available CMS-approved proficiency testing programs. The Clinical Laboratory Improvement Amendments of 1988 does not require the creation of specialty areas as a condition of requiring proficiency testing; rather, the law states that the Secretary “shall establish standards for the proficiency testing programs for laboratories issued a certificate” and that such standards shall require that a laboratory issued a certificate under this section 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.” 42 U.S.C. § 263a(f)(3). While the creation of specialty areas was a convenient means to implement CLIA in 1992, it is not a prerequisite to requiring proficiency testing for tests developed after that date.

In the proposed rule, CMS is proposing to require that all laboratories performing non-waived testing enroll in available, approved proficiency testing programs. CMS believes that this requirement primarily will affect laboratories performing molecular and biochemical genetic tests, since (1) many of these tests were developed following the implementation of CLIA in 1992, (2) they represent the fastest growing area of laboratory medicine, and (3) there are existing proficiency testing programs for many of these tests that are eligible for CMS approval. CMS specifically requests feedback on what tests other than molecular and biochemical genetic tests will be affected by this change.

In the proposed rule, CMS is also proposing to allow entities offering proficiency testing programs for tests and analytes for which criteria have not been established under subpart I the opportunity to receive HHS approval. Entities offering such programs will be required to meet the applicable requirements currently specified in 42 C.F.R. §

493.901 and 493.903 and will also be required to demonstrate that they have the capability accurately to measure, evaluate, and grade a laboratory's proficiency for the particular test being performed. CMS specifically requests feedback from proficiency testing programs regarding criteria that CMS should consider in evaluating requests for approval from entities offering proficiency testing programs for tests not currently subject to proficiency testing requirements under an existing specialty or subspecialty.

II. Proposed Rule

§493.801 is amended as follows [**PROPOSED TEXT IN BOLD CAPS**]:

Each laboratory must enroll in a proficiency testing (PT) program that meets the criteria in subpart I of this part and is approved by HHS. The laboratory must enroll in an approved program or programs for each of the specialties and subspecialties for which it seeks certification. **IF THE LABORATORY PERFORMS NON-WAIVED TESTS FOR WHICH PROFICIENCY TESTING IS NOT REQUIRED UNDER SUBPART I, AND A PROGRAM HAS BEEN APPROVED BY HHS FOR THE TESTS PERFORMED BY THE LABORATORY, THEN THE LABORATORY MUST ENROLL IN SUCH PROGRAM FOR EACH TEST FOR WHICH A PROGRAM HAS BEEN APPROVED.** The laboratory must test the samples in the same manner as patients' specimens. . . .

(a) Standard; Enrollment. The laboratory must --

(1) Notify HHS of the approved program or programs in which it chooses to participate to meet proficiency testing requirements of this subpart.

(2)(i) Designate the program(s) to be used for each specialty, subspecialty, and analyte or test to determine compliance with this subpart if the laboratory participates in more than one proficiency testing program approved by CMS; and

(ii) For those tests performed by the laboratory that are not included in subpart I of this part, a laboratory must **ENROLL IN A PROGRAM IF SUCH PROGRAM HAS BEEN APPROVED FOR ANY TEST PERFORMED BY THE LABORATORY. IF NO PROGRAM HAS BEEN APPROVED, THE LABORATORY MUST** establish and maintain the accuracy of its testing procedures, in accordance with § 493.1236(c)(1).

§ 493.803 is amended as follows: [**PROPOSED TEXT IN BOLD CAPS**]:

(a) Each laboratory performing nonwaived testing must successfully participate in a proficiency testing program approved by CMS **FOR EACH TEST PERFORMED BY THE LABORATORY FOR WHICH A PROGRAM IS AVAILABLE.**

§ 493.901 is amended as follows: [**PROPOSED TEXT IN BOLD CAPS**]:

....

(c) Meet the specific criteria for proficiency testing programs listed by specialty, subspecialty, and analyte or test contained in §§ 493.901 through 493.959 for initial approval and thereafter provide HHS, on an annual basis, with the information necessary to assure that the proficiency testing program meets the criteria required for approval. **IF NO SPECIFIC CRITERIA HAVE BEEN ESTABLISHED, A PROGRAM MAY APPLY FOR APPROVAL TO OFFER PROFICIENCY TESTING PROGRAMS FOR ANY NONWAIVED TEST. CMS SHALL APPROVE PROGRAMS THAT OTHERWISE MEET THE REQUIREMENTS OF §§ 493.901 and 493.903 AND THAT DEMONSTRATE CAPABILITY TO MEASURE, EVALUATE, AND GRADE A LABORATORY'S PROFICIENCY.**

....

§ 493.1236 is amended as follows: **[PROPOSED TEXT IN BOLD CAPS]:**

....

(c) At least twice annually, the laboratory must verify the accuracy of the following:

(1) Any test or procedure it performs that is not included in subpart I of this part **OR THAT IS NOT OTHERWISE COVERED BY AN APPROVED PROFICIENCY TESTING PROGRAM.**

(2) Any test or procedure for which compatible proficiency testing samples are not offered by a CMS-approved proficiency testing program.

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¹Holtzman, Neil and Michael Watson, eds. 1997. Promoting Safe and Effective Genetic Testing in the United States: Final Report of the Task Force on Genetic Testing. National Human Genome Research Institute.

² Hudson K., J. Murphy, D. Kaufman, G. Javitt, S. Katsanis, and J. Scott. 2006. Oversight of US Genetic Testing Laboratories. *Nature Biotechnology* 24 (9): 1083-1090.

³ Organization for Economic Co-operation and Development, Quality Assurance and Proficiency Testing for Molecular Genetic Testing: Summary Report of a Survey of 18 OECD Member Countries (2005).

⁴ Organization for Economic Co-operation and Development, OECD Guidelines for Quality Assurance in Molecular Genetic Testing (2007).