

# Issues in genetic testing for ultra-rare diseases: background and introduction

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Since 1994, at least three national advisory committees have addressed issues involving access to high-quality genetic testing for ultra-rare genetic diseases. These included the Institute of Medicine (1994), a National Institutes of Health-Department of Energy Task Force on Genetic Testing (1997), and the Secretary's Advisory Committee on Genetic Testing (2000). All identified the limited availability of high-quality testing for these rare diseases as a very high priority and a number of recommendations to improve access were made. However, little systematic progress was made as a direct result of these committee recommendations. Beginning in 2004, a series of national workshops on "Quality Laboratory Testing for Rare Diseases" was organized by a group of clinical laboratory directors experienced in rare disease testing working with the Centers for Disease Control and the Office of Rare Diseases at National Institutes of Health. These meetings included broad-based community involvement, with stakeholders from appropriate federal agencies, professional societies, patient advocacy groups as well as clinical geneticists and clinical genetics laboratory experts. Two successful outcomes of these workshops were the formation of a National Laboratory Network for Rare Disease Testing and a National Institutes of Health-funded program to aid in the translation of new genetic tests from research laboratories to Clinical Laboratory Improvement Amendments-certified diagnostic laboratories known as the Collaboration and Education in Test Translation program. This article briefly reviews the history and current status of genetic testing for ultra-rare genetic diseases in the United States, with a primary focus on molecular genetic testing by DNA sequencing. Other articles in this series provide more detailed reports on the significant progress in improving access to quality genetic testing for rare diseases within the last few years. **Genet Med 2008;10(5):309–313.**

**Key Words:** genetic testing, ultra-rare diseases, test translation, rare disease testing, CLIA, research laboratories, clinical laboratories

The pace of human gene discovery has been dramatic in the last decade, benefiting from the success of the international Human Genome Project to map and sequence the entire human genome. Among the first potential benefits of gene discovery is the opportunity for precise and accurate laboratory diagnosis by molecular genetic techniques including full gene sequencing. Until the last few years, however, there has been little progress in developing a systematic approach to facilitate translation of new gene discoveries from the research laboratory to broadly accessible clinical testing in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories. This has been especially true for ultra-rare genetic diseases (defined in this and the following articles as diseases affecting <2000 individuals in the United States) where genetic testing volume is anticipated to be very low.

This series of articles on issues in ultra-rare genetic disease testing is in part the result of a workshop on this topic held at the American College of Medical Genetics annual meeting, March 23–26, 2006, which indicated significant progress being made in the field. Since 1994, three national committees have evaluated a number of issues related to genetic testing, and each focused a part of their attention on the special issues related to ultra-rare genetic diseases. A number of recommendations were made by each of these groups, but implementation of these has only recently begun. A community effort, with support and guidance from the Centers for Disease Control (CDC) and Office of Rare Diseases (ORD) at the National Institutes of Health (NIH), has held three national workshops in the last 3 years to engage all stakeholders in this problem to work together to find practical solutions to accelerating the translation of new genetic knowledge to clinical use.

There are several real and perceived obstacles to the transition from disease gene discovery to accessible, high-quality clinical laboratory testing, the major one being the perceived lack of financial incentives for individual laboratories to invest in the development and validation of a test with very low volume. In this issue, Das et al.<sup>1</sup> discuss successful academic and commercial models for the cost-effective development and

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Disclosure: The authors declare no conflict of interest.

Submitted for publication January 18, 2008.

Accepted for publication March 4, 2008.

DOI: 10.1097/GIM.0b013e3181729d99

provision of high-quality clinical genetic testing for very rare diseases.

However, genetic testing in research laboratories has significant issues related to access and quality of testing for this important group of disorders. Often, only a few or even a single research laboratory are involved in mutation analysis of a particular rare disease gene, and may not have the capacity or interest in performing testing on all families that might benefit. There is also a lack of long-term stability to the availability of testing if the research laboratory is dependent on grant support that may not be renewed or the priorities of the funding agency (or investigator) change. Finally, in the United States, it is federal law that all individually identified laboratory results provided to physicians, patients, or medical records must be performed by CLIA-certified clinical laboratories (see below). Most research laboratories are not willing or interested in reorganizing their laboratory to comply with CLIA regulations and obtain CLIA certification.

### **CLINICAL LABORATORY IMPROVEMENT AMENDMENTS (1988)**

Many researchers and genetic professionals are still unaware of, or unsure of, the full legal and practical implications of CLIA (1988) for genetic testing ([wwwn.cdc.gov/clia/](http://wwwn.cdc.gov/clia/)). This federal legislation states that clinical tests can only be performed by CLIA-certified laboratories (Sec. 353), and defines a clinical test as any laboratory data that is communicated to a physician or patient that could be used in diagnosis, management, or patient decision-making (including reproductive planning). Many researchers are under the false impression that as long as they are not charging for mutation analysis or other molecular genetic or biochemical testing it would not be considered a clinical test. It is also not sufficient to simply qualify results with statements (verbal or written) that testing was done on a research basis if those results might be used to impact diagnosis, management, or decision-making on the part of the patient or their physician. It is not permissible to report any patient-specific results (Sec.493.3), but only *aggregate* research results to participants and to inform them if clinical testing for their disorder has become available during the course of their research participation.

Not only is there a lack of understanding of CLIA-mandated regulations regarding laboratory test results among researchers, there is also a lack of knowledge among many Institutional Review Boards (IRBs) at medical schools and universities. Often IRBs will have the well-intentioned philosophy that patients should have access to information generated from research projects for which they have participated (including donating DNA samples), especially if that information might be of some benefit to them directly or to their family members. However, this philosophy is in direct conflict with current US law under CLIA (1988) and usually does not fully consider the potential harm of an incorrect laboratory test result (which could lead to incorrect information regarding recurrence risks to future children and liability for wrongful birth).

Many clinical geneticists and genetic counselors continue to search out research laboratories that will perform mutation analysis or other genetic tests either because they are the only available laboratories performing the tests, or because they do not charge for the testing. These referrals are technically illegal, although the federal government does not have the manpower to monitor and enforce such breaches of CLIA. The focus of CLIA has been to identify laboratory concerns and provide targeted education to improve the quality of testing and patient safety.

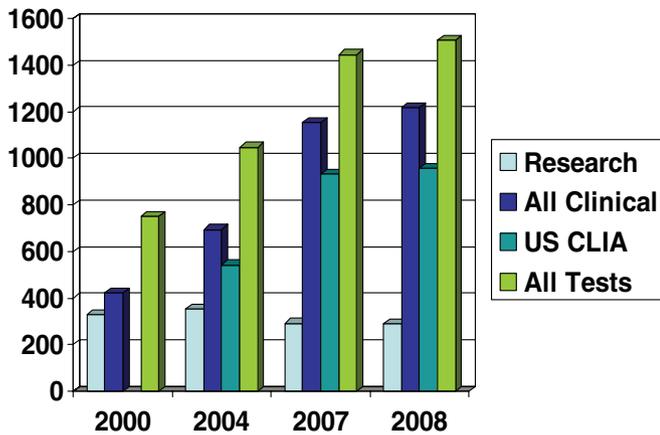
A potential risk for genetic professionals (and their institutions) of referring genetic testing to non-CLIA certified laboratories is the liability associated with an incorrect test result leading to an incorrect diagnosis or recurrence risk information (e.g., a “wrongful birth” due to incorrect carrier status or recurrence risk information). Even in clinical laboratories, significant errors occur, the majority of these being in the preanalytical phase (e.g., sample mix-up, clerical errors).<sup>2,3</sup> With less formal training in sample handling and other quality control measures,<sup>4</sup> research laboratories are likely to have a higher rate of preanalytical and postanalytical errors that may negatively impact patient care. This potential liability may also apply to most genetic testing performed in foreign laboratories, as very few laboratories outside of the United States are CLIA-certified (only four, all of which are in Canada).

The rationale for CLIA is straightforward and meritorious: to maintain quality assurance for any medically relevant laboratory testing much the same as hospitals, physicians, and other health care professionals are credentialed by appropriate inspections and testing processes. In this series of articles, research laboratory will be used to refer to any human genetics laboratory involved in the identification and characterization of human disease genes but without CLIA-certification to perform molecular genetic testing for clinical purposes. A clinical laboratory is defined as a CLIA-certified laboratory performing molecular genetics testing for the purpose of providing results to physicians and patients.

### **SCOPE OF THE PROBLEM**

Most people involved in genetics research or in patient care are aware that access to quality genetic testing for very rare diseases is problematic, but may not be aware of the scope of the problem. Although imperfect, one simple approach to evaluating the magnitude of the problem is the summary data provided at the GeneTests website ([www.geneclinics.org](http://www.geneclinics.org)). The data in GeneTests are probably quite comprehensive for clinical genetics laboratories in the United States, as most would find it beneficial to list their testing services and the data are systematically updated on an annual basis. However, research laboratories may have less incentive to submit their data to this national database and GeneTests has changed the way laboratories are classified in the past 8 years. Both factors make it difficult to assess how complete this information may be.

A comparison of the total number of genetic diseases with genetic testing available is shown from 2000<sup>5</sup> to January, 2008 (Fig. 1). The total number of diseases with tests available has



**Fig. 1.** Data on genetic tests from 2000 to 2008 compiled from GeneTests ([www.geneclincs.org](http://www.geneclincs.org)). All tests refer to the total number of genetic disorders for which a genetic test is offered in clinical or research laboratories. All clinical testing in the United States is performed in CLIA-certified laboratories, and all non-CLIA laboratory testing is categorized as research laboratory testing. Clinical testing performed outside of the United States (included in All Clinical testing category) includes laboratories certified as clinical testing laboratories by their national or local certification processes.

doubled, from 751 in 2000 to 1509 in 2008. A strong indication of progress in moving gene discovery and analysis from a research setting to clinical use is that in 2000 only 56% of all testing was performed in clinical laboratories, while in 2008 that percentage has reached 80% of the total. However, it should be noted that 20% of the clinical testing available in 2008 is outside of the United States which may still indicate that improvements in access are necessary.

## PREVIOUS NATIONAL EFFORTS TO ADDRESS VERY RARE GENETIC DISEASE TESTING

There have been three national committees since 1994 charged to evaluate a number of issues related to new genetic technologies and their safe and ethical application to genetic testing. Each of these three has included a consideration of the special issues involved with very rare genetic diseases where a significant proportion of the testing was being conducted only in research laboratories. We will briefly highlight the main considerations and recommendations of these three groups.

### Institute of Medicine Committee on Assessing Genetic Risks (1994)

The Institute of Medicine (IOM) of the National Academy of Sciences charged a Committee on Assessing Genetic Risks to evaluate the current status and future concerns related to genetic testing.<sup>6</sup> Although a primary motivation for this was the newly emerging concern over potential ethical issues related to genetic testing of healthy individuals to determine their future likelihood of developing a disease (predictive testing), the committee also considered the problems associated with rare genetic diseases. In their 1994 report, this group recommended that “tests for rare diseases be centralized in a few laboratories” and urged “the genetics community under the leadership of its professional societies to designate a small number of laborato-

ries to serve as the centralized facility.” The basis of this recommendation was the concern over quality assurance because most individual laboratories would be unlikely to perform enough tests to maintain proficiency if only serving their local referral base. However, there was no easy mechanism for the “genetics community” or its professional societies to designate the rare disease laboratories. This prescient vision of the IOM committee is now coming to reality because of a voluntary effort among the molecular genetics laboratory community in the form of the National Laboratory Network for Rare Genetic Disease Testing (NLN), described below.

### NIH-Department of Energy Task Force on Genetic Testing (1997)

The second major effort to address the special problems associated with genetic testing for very rare diseases was the NIH-Department of Energy (DOE) Task Force on Genetic Testing which met from 1995 to 1997.<sup>7</sup> This group was created by the NIH-DOE Working Group on Ethical, Legal, and Social Implications of Human Genome Research and was asked to make recommendations to promote safe and effective genetic tests. This group also addressed the special issues related to rare genetic diseases. Although they emphasized the importance of clinical tests (any laboratory data or result that might be used for diagnosis, management or patient decision-making) being performed in a CLIA-certified laboratory, they also suggested that the Clinical Laboratory Improvement Advisory Committee allow leniency for laboratories performing rare genetic disease testing in some aspects of their quality assurance programs. This topic is addressed more fully by Grody and Richards.<sup>4</sup>

### Secretary’s Advisory Committee on Genetic Testing (2000)

An advisory committee to the Secretary of Health and Human Services (D. Shalala) was appointed in June 1998 to further consider issues related to genetic testing and the appropriate federal regulatory agencies and policies in response to the reports discussed above. In their report in July, 2000, the Secretary’s Advisory Committee on Genetic Testing (SACGT) stated in the Overarching Principles “. . . the public is best served by ensuring both the adequate oversight of genetic tests and the continued development of genetic tests” (SACGT Rare Diseases Work Group, unpublished data). And it was recommended that the Food and Drug Administration evaluate the validity and clinical use of all new genetic tests. They also emphasized the importance of genetic testing being performed only in CLIA-certified laboratories and suggested that “Federal agencies should make technical assistance available to laboratories performing tests for orphan diseases or mutations to help them meet CLIA certification requirement.”

A Working Group on Rare Diseases was established as part of SACGT, but final recommendations from this group were not completed or published before disbanding of the SACGT in August, 2002.

### **CDC-NIH ORD conferences on “Quality Laboratory Testing for Rare Diseases”**

As a result of continued community interest in improving the access and quality for genetic testing in very rare diseases, a series of national workshops have been organized primarily by the CDC and NIH ORD, but with substantial input and participation by a broad base of stakeholders in this area including the Health Resources and Services Administration, the American College Medical Genetics, the American Society of Human Genetics, the Genetic Alliance, and the Department of Human Genetics, Emory University School of Medicine. The first conference was held in May, 2004 with participation from approximately 50 experts and stakeholders from government, academic institutions, professional organizations, industry, health care payers, and patient advocacy groups. An executive summary of the conference, recommendations and a detailed conference report can be found at <http://www.phppo.cdc.gov/dls/genetics/RareDiseaseConf.aspx>.

Immediate outcomes of this first meeting included the revitalization and expansion of a volunteer network of molecular genetics laboratories committed to ultra-rare disease testing, the NLN (see <http://www.rarediseasetesting.org/about.php>). Plans were made for educational efforts by the American Society of Human Genetics and other professional organizations, as well as by the Office for Human Research Protections to provide education to IRBs regarding their role in safeguarding the release of individual test results from research laboratories.

A second, much larger conference, was held in September, 2005 as an “Integration Conference” to convert the initial recommendations of the first conference into projects and action items and to develop additional recommendations. From this meeting, a model pilot process was developed to facilitate evaluation of the clinical use and readiness of new genetic tests for very rare diseases. This “CETT Program” (Collaboration and Education in Test Translation)<sup>7</sup> has already been implemented and is available to any qualified clinical genetics testing laboratory for expert assistance and potential financial assistance in rare disease test translation (see <http://www.cettprogram.org/>). Additional recommendations included education about test translation for researchers, clinical laboratories, and disease specific advocacy organizations.

A third meeting sponsored by the CDC-NIH ORD was held in October, 2006 to address issues in genetic testing for rare metabolic genetic diseases in which biochemical and/or molecular genetics laboratory methods may be used for diagnosis, carrier detection, and prenatal diagnosis. It was agreed that the CETT Program model included translation of biochemical tests and the CETT Program was encouraged to include experts with biochemical testing and clinical experience on the review board.<sup>7</sup> Meeting attendees encouraged that providing molecular testing in combination with biochemical diagnostic testing should become standard of care. A working group was formed to address improvements in quality control for biochemical testing and to develop a plan to increase the availability of quality control materials for biochemical testing in coop-

eration with the CDC program Genetic Testing Reference Materials Program (see <http://wwwn.cdc.gov/dls/genetics/rmmaterials/>).

### **POSSIBLE SOLUTIONS AND PROGRESS REPORT**

There are at least four major solutions which have been considered by previous national working groups, some of which are presented in detail in the articles to follow in this series. These include

1. CLIA exemption for research laboratories performing genetic testing for ultra-rare genetic disorders for which no CLIA-certified laboratory testing is available. This proposal, or variants thereof, was considered by the NIH-DOE panel and by the SACGT. This approach obviously raises questions regarding mechanisms for assuring quality genetic testing without the minimal quality assurance/quality control (QA/QC) standards requisite for CLIA certification, and would seem to endorse a potentially lower standard of patient care for patients and families with very rare genetic diseases. Fortunately, this solution may no longer need consideration, especially for molecular genetic testing, given the success of the alternatives solutions described below.
2. Research laboratories become CLIA certified. Historically, many clinical genetic testing laboratories evolved out of expert research laboratories performing cytogenetics, biochemical genetics, and molecular genetics research. Because of the very different training, mission and culture of research and clinical laboratory directors and staff (see Grody and Richards<sup>4</sup>), this requires a substantial commitment on the part of the research laboratory to obtain the proper training in QA/QC and other critical aspects of clinically laboratory work. This model may continue to have limited applicability in genetic testing, particularly in cases involving esoteric technologies or assays (e.g., certain enzymatic assays for metabolic disorders) available in only one or a few laboratories and not easily portable to a clinical laboratory with CLIA-certification. For most molecular genetics testing, including DNA sequencing, there are now many highly-experienced and qualified laboratories to perform testing for any disease gene.
3. Research laboratories and CLIA-certified clinical laboratories partner with each other to transfer genetic testing to a CLIA laboratory environment with the researcher’s expertise regarding the disease gene structure and function. This model works best when viewed as a team approach including the research expert, the CLIA laboratory, clinical genetics experts, genetic counselors and appropriate patient advocacy group. Successful examples of this model are described in Das et al.<sup>1</sup> for CLIA-certified laboratories in an academic medical center and in a private laboratory setting. To encourage and facilitate this expert team approach to accelerate the translation of

new gene discoveries to high-quality clinical testing, the NIH ORD has established a national program of CETT, described in detail by Faucett et al.<sup>7</sup>

4. Centralized laboratory or network of laboratories specializing in ultra-rare genetic disease testing. This model was envisioned and encouraged by the IOM committee in 1994, but was not pursued most likely due to the perception that the establishment and operation of such a network would require substantial financial subsidy and could not achieve self-sufficiency. However, as discussed in the articles by Das et al.,<sup>1</sup> it is possible in both academic and private laboratory settings to reach a self-sufficient (or even profitable) financial operation after a modest investment in the initial development and validation for each disease gene. A voluntary organization of laboratories with a commitment to ultra-rare genetic disease testing was formed in 2004 and named the NLN ([www.rare-disease.org](http://www.rare-disease.org)). The main purpose of this Network is to coordinate and facilitate the development of new genetic tests for ultra-rare genetic diseases.

The articles that follow address many of the critical issues in ultra-rare genetic disease testing, including QA/QC issues (see Grody and Richards<sup>4</sup>), models for partnership between research laboratories and CLIA-certified laboratories (see Das et al.<sup>1</sup>), the

CETT Program (see Faucett et al.<sup>7</sup>), the critical role of genetic counselors in genetic testing (see Scacheri et al.<sup>8</sup>), and issues related to gene patenting and licensing (see Ledbetter<sup>9</sup>).

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