Clinical genetic testing laboratories have come under scrutiny in the US and Europe with increasing public awareness of genomic research. Such increased publicly driven demand for quality can improve laboratories and encourage high standards of excellence. The Department of Health and Human Services Secretary’s Advisory Committee on Genetic Testing (1) was instrumental in placing genetic testing in the public eye and exerted pressure on genetic providers to organize our profession and address public concerns, particularly concerns about laboratory quality.

Are safeguards in place to prevent poor-quality genetic testing? Multiple federal and state agencies as well as professional organizations have developed guidelines, recommendations, and checklists with which laboratories must comply. In the US these include the Clinical Laboratory Improvement Amendments (CLIA) of 1988 (2), Genetic Testing Under the Clinical Laboratory Improvement Amendments (3), New York State Department of Health Laboratory Standards (4), the College of American Pathologists (CAP) checklist for molecular pathology laboratories (5), the American College of Medical Genetics (ACMG) Standards and Guidelines for Clinical Genetics Laboratories (6), and a NCCLS guideline (7). A recent review of quality assurance in genetic testing has been addressed in the ACCE [analytical validity, clinical validity, clinical utility, and ELSI (ethical, legal, and social issues of genetic testing)] report on carrier screening for cystic fibrosis, a CDC-sponsored project (8).

Internal and external quality assurance and quality-control programs have been established to ensure that laboratories can reliably produce (and reproduce) high-quality results in a timely manner and with clinical utility for patients and healthcare providers. Proficiency testing (PT) identifies weaknesses and provides guidance for improvement. The ACMG/CAP PT program has been providing a molecular genetics laboratory survey with challenges on multiple genetic disorders since 1995, and CAP has provided on-site laboratory inspection and a certification program for molecular genetics laboratories since 1993. These professionally regulated programmatic efforts undoubtedly represent an important contribution to the development of clinical molecular genetic laboratory excellence. Ongoing review of performance occurs at multiple levels, including the CAP/ACMG Biochemical and Molecular Genetics Resource Committee and the ACMG Quality Assurance/Laboratory Practice Committee. Similar to the ACMG/CAP program in the US, the European Molecular Genetics Quality Network (EMQN) provides external quality assessment for European laboratories, with a similar test menu and performance trends (9).

In contrast to these disease-specific PT programs in the US and Europe, an Italian group now reports the results of a more generic methods-based program to compare the quality of PCR amplification of genomic DNA performed by multiple laboratories (10). In this issue, Raggi et al. (10) report their survey results from 39 participating laboratories. Admirably, they monitored DNA extraction (both quality and quantity), PCR performance (specificity and efficiency), and electrophoresis results and interpretation, using valid quantitative measures to develop an overall score for each laboratory. The results presented showed that only 10% of laboratories ranked in the “excellent” category, and 33% ranked as “good”. More concerning was that 38% of laboratories ranked as only “sufficient”, 8% were “poor”, and 10% were “unacceptable”. Taken at face value, if this evaluation reflects the overall quality of genetic testing in Europe, then approximately one of five laboratories has a problem, and that seems too high. Could there be other explanations for the rankings of poor performers? A review of a similar experience in the US program may shed some light.

Approximately 200 laboratories subscribe to various aspects of the CAP/ACMG molecular genetics PT program. Laboratories can choose any or all of three disease-specific groupings or modules. This represents a subset of the ~900 laboratories that are accredited through the CAP inspection program in all areas of molecular diagnostics and for which specific proficiency surveys are offered, including, for example, nucleic acid-based tests for infectious diseases, cancer markers, and paternity testing (11). It should be further contrasted with the more than 25 000 laboratories that subscribe to CAP’s other PT programs in the broad area of pathology and laboratory medicine. Thus, although genetic testing in general, and molecular genetic testing in particular, is the target of much public and governmental scrutiny over laboratory quality and ethical concerns, it should be kept in mind that these applications represent only a small fraction of overall clinical laboratory activities and are undertaken only in specialized laboratories.

The CAP/ACMG PT program in molecular genetics has, since its inception, focused on disease-based gene targets. The first official surveys in 1995 comprised challenges for cystic fibrosis, sickle cell disease, fragile X syndrome, and Duchenne muscular dystrophy. Huntington disease was added the following year, and myotonic dystrophy and Prader-Willi/Angleman syndrome were added the year after that. At present, testing for a total of 17 diseases is offered, with the most recent additions being DNA sequencing-based challenges for familial cancers associated with MEN2 and BRCA1/2. Despite this impressive growth in disease offerings over a relatively short period, the CAP/ACMG Resource Committee has long been concerned about an inability to keep up with the growth of molecular genetic tests in the field. Given the effort it takes to develop programs, obtain mutant samples, and pilot test each new disease analyte, the menu of PT offerings will never equal or even approach the sum total of genetic diseases that can be tested at the
molecular level, let alone the wide variety of mutations possible for each disease.

In part for this reason, and also to address some more generic technical issues, the committee included in its early mailings (1995–1996) a methods-based challenge similar to the one developed by Raggi et al. (10). As in their study, the CAP participants were sent a PCR primer set along with instructions for amplification conditions. The target chosen was a short tandem repeat polymorphism, and a simple linkage problem was constructed using several of the shipped specimens. This practice was soon abandoned, however, because of unsatisfactory performance, reports of PCR amplification failures and anomalies, and complaints from the survey participants. [Other attempts involving generic Southern blot challenges, with a variable number tandem repeat (VNTR) probe supplied, met with similar outcomes.] We suspect that these problems derived from sources similar to those in the study by Raggi et al. (10). It may be too much to expect a laboratory to be challenged in a proficiency survey on an assay it has not validated or become comfortable with through years of experience. Although we supplied the PCR primers and reaction conditions, many laboratories had trouble getting the expected amplification products and sizing them accurately, probably because of lack of optimization and familiarity.

Regulatory guidelines under CLIA require that US laboratories participate in organized PT programs when available (or, when not available, some equivalent activity such as informal sample exchanges with another laboratory) for every analyte they test for, not for every method. Generic PCR or DNA extraction challenges of the type developed by Raggi et al. (10) and by CAP/ACMG early on, although potentially useful to assess proficiency in methods used for many molecular analytes, do not satisfy this requirement and therefore cannot substitute for disease-specific challenges. Moreover, poor performance on this sort of challenge does not necessarily indicate that the laboratory has poor quality or will perform poorly on real disease tests. For example, many PCR-based tests work adequately on crudely prepared, as opposed to high-purity, DNA; is it necessary or fair to require the testing laboratory to meet high standards of DNA purity as this challenge did?

All practitioners of clinical molecular genetics face the ongoing challenge of an ever-increasing number of analytes derived from disease-gene discovery under the impetus of the Human Genome Project. Regulatory and professional agencies are hard pressed to keep pace with these advances through their external quality assurance programs. The CAP/ACMG Resource Committee has been attempting to do so through modularization of PT menus and more efficient modes of mutation sample procurement, whereas the program developed by Raggi et al. (10) represents another creative approach. Both options, the expansionist approach of proliferating individual disease challenges or the reductionist approach of generic methods-based challenges, offer their own advantages and disadvantages and place their own special stress on participating laboratories. It is perhaps this last factor that we should be most mindful of, to ensure that whatever quality assurance programs we choose, they fairly assess performance of the target laboratories while not impeding their important work through unrealistic or irrelevant exercises.

We applaud efforts such as that of Raggi et al. (10) and encourage clinical laboratories to participate in such programs and support the exchange of information among programs. Through our shared experience, we envision the development of a powerful collaborative effort across continents in working toward our common goal, improving the quality of genetic testing.

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References

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