Oversight of US genetic testing laboratories

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Despite the boom in genetic tests available in US laboratories, oversight remains patchy. A survey of laboratory directors suggests that mandatory proficiency testing would result in fewer errors.

Today, genetic tests for close to 1,000 diseases are clinically available, with hundreds more under development[1]. Results from these tests can lead to profound, life-changing decisions, such as whether to undergo prophylactic mastectomy, terminate a pregnancy or take a particular drug or dosage of a drug. An incorrect test result can lead to misdiagnosis and inappropriate or delayed treatment; therefore, it is imperative that results from genetic tests be accurate and reliable.

To explore whether creation of a genetic testing specialty with specific proficiency testing (PT) standards could improve the quality of genetic testing, we have examined not only the relationship between participation in PT for genetic testing and laboratory quality but also the attitudes of laboratory directors toward current genetic testing regulation, the value of a genetic testing specialty and the value of PT in ensuring quality testing. The data from our survey clearly demonstrate that participation in PT correlates with test quality. What's more, most laboratory directors support moves to create formal registration under a genetic testing specialty for centers that carry out such analyses.

Genetic testing without quality control may be cause for concern. (Source: Genetics and Public Policy Center, Washington, DC.)

The testing landscape

Over the past three decades, genetic testing has played an increasingly important role in clinical medicine. The first genetic test, for the prenatal diagnosis of sickle cell disease, was developed in 1978 and signaled the birth of modern clinical molecular genetics[2]. What began as a handful of academic laboratories performing genetic testing for rare and often debilitating diseases has grown into a multimillion-dollar commercial industry[3]. Fueled by information gained from the Human Genome Project, new genetic tests are quickly transitioning from the research bench to clinical practice (**Fig. 1**).

Currently, a patchwork of oversight mechanisms is in place to help ensure the quality of genetic testing. Only a few genetic tests—those marketed by companies as 'test kits'—require FDA premarket review. Most tests are developed in-house by clinical laboratories (so-called home brews) and are not subject to government review before they are made clinically available.

In 1988, the US Congress enacted the Clinical Laboratory Improvement Amendments (CLIA) in response to reports of rampant errors and poor quality laboratory testing services, particularly with regard to Pap smear results. Any laboratory performing testing on human specimens and reporting patient-specific results must be certified under the provisions of CLIA and adhere to general requirements for quality control (QC) standards, personnel qualification and documentation/validation of test procedures[4]. Research laboratories are exempt only if they "do not report patient-specific results for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of individual patients" (**Box 1**).

Laboratories performing tests categorized as high complexity under CLIA must enroll in the appropriate specialty area, if one is available. Specialty areas provide more detailed requirements than the general CLIA regulations. In particular, many specialties require enrollment in a CLIA-approved PT program. However, a specialty area for molecular and biochemical genetic testing has not yet been created, so there are no specific QC, personnel or PT

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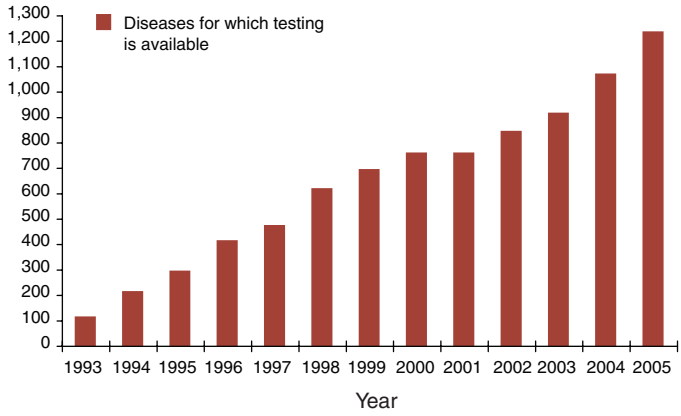

Figure 1 Growth of genetic testing, including both clinical and research testing. (Source: Gene Tests database 2005, http://www.genetests.org/.)

standards required by CLIA for these kinds of tests. In the absence of a formal PT program, CLIA states that "a laboratory must establish and maintain the accuracy of its testing procedures" and "have a system for verifying the accuracy of its test results at least twice a year." Thus, CLIA does not require genetic testing laboratories to enroll in a formal PT program, although some accrediting entities do (e.g., New York State requires laboratories located in New York State or doing business in New York State to participate in PT programs if they are available). Moreover, formal PT programs are available for only a small fraction of the genetic tests offered today. When a laboratory cannot or chooses not to enroll in a formal PT program, it can perform PT by exchanging samples with other laboratories performing similar testing, retesting archived specimens or splitting samples and comparing results.

Few empirical data exist on genetic testing laboratory errors and testing quality, and no data have been made available that directly assess the relationship between the extent of participation in formal and informal PT programs and the types or frequency of genetic testing errors. A review of the literature from both genetic[5,6] and nongenetic[7–10] testing laboratories finds that although error rates can vary widely from study to study, the distribution of errors across the pre-analytic, analytic and post-analytic phases of testing remains remarkably consistent for all types of clinical laboratory testing, including genetic testing. The majority of reported laboratory errors occur in either the pre-analytic (e.g., mislabeling specimens, incorrect test ordering) or post-analytic phases of testing (e.g., transcription or interpretation errors). Analytic errors, which are the types of errors that CLIA was intended to address, are estimated to account for 4%–32% of all laboratory errors[7]. In a 1999 survey of 42 molecular genetic testing laboratories, analytic errors accounted for only 6.1% of all reported problems[5].

Another survey of 245 molecular genetic testing laboratories found that participation in PT was a leading indicator of higher quality assurance scores[6]. Quality assurance scores were assigned based on the number of American College of Medical Genetics (ACMG; Bethesda, MD, USA) standards for proper procedures met by a laboratory; the study did not assess laboratory errors. The study's conclusions were based only on the potential for laboratory errors to occur.

In the survey of laboratory directors presented below, we study the quality of genetic testing laboratories, as measured by the level of participation in PT programs, the number of PT deficiencies, the number of incorrect test reports issued and the percent of laboratory directors who cite an analytic error as the laboratory's most common problem. In addition, we document attitudes of laboratory directors toward current CLIA regulation, the value of a genetic testing specialty and the value of PT in ensuring quality testing.

Box 1 How CLIA works

CLIA defines a clinical laboratory as "a facility for the biological, microbiological, serological, chemical, immunohematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or assessment of the health of a human being." (United States Code, Title 42 Section 263a.)

Under CLIA, laboratory tests are categorized based on their degree of complexity. Tests are graded based on seven criteria: (i) knowledge, (ii) training and experience, (iii) reagents and materials preparation, (iv) characteristics of operational steps, (v) calibration, quality control and PT materials, (vi) test system troubleshooting and equipment maintenance and (vii) interpretation and judgment. Tests requiring higher skills and knowledge to perform and interpret, such as tests for HIV, other infectious diseases, or molecular diagnostics, are categorized as "moderate" or "high complexity" tests. For these tests CLIA develops specialty areas (e.g., virology, toxicology) that provide additional QC, personnel and other standards specific to that type of testing. CLIA also requires laboratories performing moderate or high complexity testing to enroll in approved PT programs for each specialty in which the laboratory is certified, to provide an independent, external assessment of how well a laboratory is able to perform that type of testing (commonly referred to as a formal PT program). Laboratories enrolled in these formal PT programs periodically receive blinded specimens from the program to be tested in the same manner as samples received from patients. The PT program determines how often a laboratory obtains and reports correct results on these tests, which helps laboratories identify procedural problems and take corrective actions. Proficiency test results are graded as either satisfactory or unsatisfactory depending on how many deficiencies (errors) are detected. Unsatisfactory performance is reported to the CLIA-accrediting organization, and laboratories that consistently perform poorly risk losing their accreditation and CLIA certification.

Survey results

Overall, 190 laboratory directors responded to our survey (see **Box 2** for methodology). They provided information on CLIA certification and specialty, their use of formal or informal PT methods, the effect of PT on laboratory quality, the overall number and type of incorrect test results and their enthusiasm for more stringent oversight of the testing sector.

Demographics. Of the 190 respondents, 55% worked in laboratories that perform only clinical testing, 42% in laboratories that offered both clinical and research testing, and 3% in laboratories that perform only research testing, but provided test results to patients and

providers. When respondents worked in a setting that offered research testing, we asked them to consider only the research testing they did that resulted in a report back to the patient or provider.

Nearly one in four respondents (23%) was the director of a commercial or independent laboratory, half were at a university or medical school laboratory and 22% were in other hospitals. More than half of the directors (58%) were PhDs, whereas 22% held an MD or DO degree, 18% were MD/PhDs and the remainder (2%) held another degree. Most directors (77%) reported that their laboratories perform molecular genetic tests, whereas 5% reported that their laboratories perform biochemical genetic tests and 17% reported performing both types. The number of distinct tests offered, the estimated yearly volume of tests performed and other characteristics are found in **Table 1**.

CLIA certification and specialty. Laboratory directors were asked, "By which organizations is your laboratory accredited or licensed as a molecular or biochemical diagnostic laboratory?" A laboratory was considered CLIA certified if it was accredited by either CLIA or one of three 'deemed' accrediting organizations (the Joint Commission on Accreditation of Healthcare Organizations, the College of American Pathologists Laboratory

Box 2 Survey methodology

In the absence of a comprehensive directory of US genetic testing laboratory directors, our search strategy for potential participants was designed to cast a wide net and capture as many genetic testing laboratory directors as possible.

Survey design. A list of 680 potential participants was compiled using the current GeneTests Clinic Directory[1] ($n = 226$), the Association for Molecular Pathology membership directory[15] ($n = 274$), New York State Department of Health's online directory of certified biochemical[16] and molecular genetic[17] testing laboratories ($n = 120$), laboratories participating in the 2005 National Tay-Sachs and Allied Diseases' Quality Control Program[18] ($n = 79$), the Canavan Foundation's laboratory directory[19] ($n = 91$), Washington G-2 Reports' 2005 Lab Outreach Buyer's Guide: Providers of Laboratory Outreach Products and Services[20] ($n = 57$) and Veteran Administration hospital laboratories selected from the Veterans Administration website[21] ($n = 8$), as well as potential participants from laboratories identified in Google searches using a variety of search terms ($n = 9$). Many potential participants appeared on more than one of these lists.

All 680 potential participants were mailed an initial invitation to participate in an online survey of genetic testing laboratory directors. This was followed several days later by an e-mail invitation. To be eligible to complete the survey, a potential participant had to identify himself or herself as the director of a molecular or biochemical testing laboratory that reports test results to patients or providers. Potential participants were excluded if they were not laboratory directors, were directors of laboratories that did not provide results to patients or providers or were directors of laboratories that test only for paternity, identity, ancestry, cytogenetics, infectious diseases tissue typing or newborn screening. Up to eight periodic mail, e-mail and phone call reminders were made to nonresponders over a three-month period.

Of 680 potential participants, 404 responded. Of these, 199 respondents were ineligible based on the above criteria and were not offered the survey, whereas 190 were eligible and completed the survey. Fifteen additional eligible laboratory directors began the survey but did not complete it, and were excluded from analyses. No response was received from the remaining 276 potential participants. To calculate a response rate among eligible laboratory directors, we estimated the total number of eligible laboratory directors in our list of 680 potential participants by extrapolating the proportion of respondents who were eligible to the 276 nonrespondents[22] (**Supplementary Methods** online). In this way, we estimated that 345 of our potential participants had been eligible for the survey, for a valid response rate of 190/345, or 55%.

A 65-question survey, qualified by the Johns Hopkins University Institutional Review Board as exempt (Application no. NA_00001533), was developed to collect data on the current laboratory practices and opinions of molecular and biochemical genetic testing laboratory directors in the United States. A small pretest was conducted with directors of six genetic testing laboratories, and feedback was incorporated into the final survey instrument.

The survey collected data about the laboratory setting, types of testing performed (molecular or biochemical or both; research or clinical or both), the qualifications of the laboratory director, laboratory accreditation and certification, test volume and menu, quality control practices, the nature and frequency of laboratory errors, and PT practices.

Knowledge Networks, a survey research firm in Menlo Park, California, administered the Web-based instrument. The data provided to the Genetics and Public Policy Center were anonymized with respect to respondents' identifying information. Potential participants were told that data collected from the survey would be reported only in aggregate, and that analyses would not identify any particular laboratory or director. An incentive in the form of a $25 donation to one of four organizations (College of American Pathologists Foundation, American College of Medical Genetics Foundation, American Red Cross or America's Second Harvest) was offered in exchange for a laboratory director's participation.

Survey analyses. Analyses included examination of the relationship between laboratory characteristics and the level of participation in both formal and informal PT programs, the number of deficiencies reported in formal PT programs, the number of incorrect test reports and the types of errors observed. Data on annual laboratory test volume were collected by asking respondents to choose a range corresponding to the number of biochemical genetic tests and the number of molecular genetic tests the laboratory performs in a year (ranges provided for both questions were 0, 1–249, 250–999, 1,000–4,999, 5,000–9,999, 10,000–14,9999, ≥15,000). To create an estimate of the total annual genetic test volume for a given laboratory, we added the midpoint of the range for the number of molecular tests to the midpoint of the range for the number of biochemical tests. These sums fell into four clusters, resulting in categories of 1–1,999, 2,000–5,999, 6,000–14,999 and ≥15,000 total tests performed annually. Observations based on these ranges should be interpreted with the understanding that they are estimates of laboratory volume. To assess the relationship between survey variables, we implemented general linear, Poisson and logistic regression models using SAS version 9.1. Key variables used in regression are listed in column 1 of **Table 1**.

Table 1 Extent of CLIA certification, specialty certification and proficiency testing among laboratories

Type of laboratory		*N*	Percent	Percent of labs that are CLIA certified	Percent of CLIA certified labs with no specialty certification	Percent of tests subjected to proficiency testing (formal or informal)*				
						0–24%	25–74%	75–99%	100%	<100%
All respondents		190	100	95	16	8	8	18	65	35
Clinical or research testing	Clinical only	104	55	98	13	6	7	19	68	32
	Clinical and research	80	42	98	19	9	10	19	63	37
	Research only	6	3	17	100	33	17	0	50	50
Setting	Commercial	43	23	98	25	7	12	12	70	30
	Univ./medical school	101	53	92	17	10	7	23	60	40
	Other hospital	46	24	100	7	4	9	15	72	28
Director's education (one missing)	MD or DO	41	22	98	6	10	10	20	61	39
	PhD	119	58	95	23	7	9	17	66	34
	MD/PhD	34	18	97	7	6	6	21	68	32
	Other	5	3	80	0	20	0	20	60	40
Estimate of annual test volume (one missing)	1–1,999	65	34	86	13	15	8	9	68	32
	2,000–5,999	71	38	100	18	4	7	25	63	36
	6,000–14,999	35	19	100	9	6	6	17	71	29
	15,000+	18	10	100	35	0	22	22	56	44
Number of distinct tests offered (one missing)	1–4	45	24	87	7	13	4	4	78	21
	5–19	77	41	96	8	7	8	21	65	35
	20+	67	35	100	29	6	12	25	57	43
Molecular or biochemical testing	Molecular	147	77	94	20	7	6	17	70	30
	Biochemical	10	5	100	20	30	20	10	40	60
	Both	33	17	100	0	6	15	27	52	48

*Row totals may not add up to 100% due to rounding.

Accreditation Program, the Commission on Office Laboratory Accreditation), or held a New York State clinical laboratory permit. Ninety-five percent of respondents indicated that their laboratory was CLIA certified (**Table 1**). All of the laboratories that were not CLIA certified were low volume laboratories that process <2,000 tests yearly; 86% of these low volume laboratories were CLIA certified, compared to 100% of laboratories that perform ≥2,000 tests annually ($p = 0.0001$). Additionally, certification rates increased significantly as the menu of different tests offered increased ($p = 0.006$). The majority of laboratories that performed only research testing and reported patient-specific results were not CLIA certified.

Nearly all CLIA-certified laboratories (97%) were certified for high complexity testing. However, 16% reported no specialty area certification. Approximately a third of laboratories with the highest test volumes (35%) and largest test menus (29%) reported having no specialty certification (**Table 1**). Among CLIA-certified laboratories, 41% were certified in a single specialty area, and 43% listed multiple specialties. The most common specialty certifications were pathology (48%), chemistry (46%) and clinical cytogenetics (41%).

Participation in formal PT. All respondents were asked, "Does your laboratory participate in a formal external proficiency testing program?" Two-thirds of directors said their laboratory participated in "all available formal external proficiency testing programs," whereas 17% said, "Yes, for some formal, external proficiency testing programs." Sixteen percent indicated they do not participate in any formal PT programs. Significantly more laboratory directors at university sites (66%, $p = 0.03$) and other hospitals (82%, $p = 0.01$) than commercial laboratory directors (56%) reported using all of the formal external PT programs available to them, after excluding directors who said no formal programs were available for the tests they offer ($n = 19$).

The 43 directors who responded either that their laboratory did not participate in formal external PT programs or that their laboratory participated in only some formal programs were asked to select up to five possible reasons for their nonparticipation. Sixty three percent of respondents indicated they did not participate because of "the lack of availability of formal testing programs." Another 17% responded that internal PT is adequate. Very few laboratory directors responded that "formal external proficiency testing is too expensive" (7%) or "formal external proficiency testing does not provide timely feedback" (2%). Twenty-four percent selected "another reason" in response to this question and were provided the opportunity to type in their response. Other reasons provided were that the laboratory was for research or teaching purposes only, that the diseases tested for were too rare, that a formal testing program for rare diseases was being established or that other informal means of PT were used. Some respondents indicated that they would participate if PT programs were available.

Use of informal PT methods. For tests where no formal external proficiency test is available, CLIA requires that the laboratory "have a system for verifying the accuracy of the test result at least twice a year." All respondents were asked, "When a formal external proficiency testing program is not available, does your laboratory perform proficiency testing using some other

mechanism?" A majority of respondents said "yes" for all (77%) or some (15%) tests whereas 8% said "no." Respondents whose laboratories offer 1–4 different tests were twice as likely as those offering a larger menu of tests to say that they used no additional informal PT methods (16% versus 8%, $p = 0.02$). Half of the laboratories that perform only research testing used no informal PT methods.

Respondents ($n = 42$) whose laboratories did not always perform informal PT on tests when no external program was available were asked "Which of the following, if any, are reasons your lab does not perform proficiency testing using some other mechanism when a formal program does not exist?" The most common response (53%) was "We use competency testing to document our laboratory proficiency." Forty percent answered, "We are the sole source of the test"; 21% said, "Our test volume is too low to justify developing a proficiency testing program"; and 3% said, "Proficiency testing is not necessary for the types of tests we perform."

Overall extent of PT use. We also asked respondents, "For what percentage of the genetic tests offered by your laboratory do you conduct some sort of proficiency testing?" More than one-third of respondents (35%) offered some genetic tests for which they perform no PT at all, including 8% who conducted either formal or informal PT on less than a quarter of the tests they offer (**Table 1**). Three percent conduct no PT for any of their tests. Nearly two-thirds of participants (65%) said that their laboratory performs either formal or informal PT on every test offered (**Table 1**).

After adjusting for key variables, laboratories that perform only molecular genetic tests were significantly more likely to complete either formal or informal PT on all their tests, compared to directors of laboratories using any biochemical genetic tests (70% versus 49%, $p = 0.006$). Additionally, the smaller the menu of tests offered, the more likely laboratories were to perform some type of PT on all of their tests ($p = 0.02$). No significant differences in any of the other key variables modeled were noted with respect to the extent of PT employed.

Influence of PT on laboratory test quality. A laboratory participating in a formal external proficiency program is given a deficiency if the laboratory is unable to ascertain and report the correct test results in a timely manner. Among laboratories that participate in formal external proficiency programs ($n = 159$), 78% reported that their laboratory had no deficiencies over the past two years, 16% reported one deficiency during that period and 7% reported two or more. **Table 2** shows that as the percentage of tests on which formal or informal PT is done in a laboratory increased, the number of formal deficiencies decreased. In addition, laboratories that do not perform formal or informal PT on all of their tests were eight times as likely to report multiple deficiencies (16% versus 2%, $p = 0.001$).

After adjusting for key variables, the percentage of tests on which formal or informal PT is done was the strongest predictor of the number of formal PT deficiencies reported over the past two years ($p = 0.004$), that is, the number of deficiencies decreased with increasing use of PT. After adjusting for extent of PT participation, only annual test volume was significantly related to the number of reported PT deficiencies. Laboratories that performed >2,000 tests annually reported significantly

Table 2 Frequency of proficiency test deficiencies and incorrect test reports issued

				"How many times in the past 2 years has your lab been found to be deficient in any way on a formal external proficiency test?"			"What is your best estimate of how many incorrect test reports were issued by your lab in the past 2 years?"		
Type of laboratory		*N*	%	Never (%)	1 time (%)	2+ times (%)	None (%)	1–3 (%)	4+ (%)
All respondents		190	100	78	16	7	28	37	35
Clinical or research testing	Clinical only	104	55	79	17	3	23	38	39
	Clinical and research	80	42	75	13	12	29	38	32
	Research only	6	3	—	—	—	83	17	0
Setting	Commercial	43	23	77	17	6	28	25	48
	Univ./medical school	101	53	76	18	6	27	44	29
	Other hospital	46	24	83	10	7	30	34	36
Estimate of annual test volume	1–1,999	65	34	86	12	2	41	44	15
	2,000–5,999	71	38	73	18	10	25	45	30
	6,000–14,999	35	19	82	15	3	18	21	61
	15,000+	18	10	71	18	12	12	12	77
Number of distinct tests offered	1–4	45	24	79	14	7	48	35	18
	5–19	77	41	79	16	6	25	44	32
	20+	67	35	76	16	7	19	32	49
Percent of tests subjected to proficiency testing (formal or informal)	0–24%	15	8	50[a]	33[a]	17[a]	54	31	15
	25–74%	16	8	67	8	25	27	33	40
	75–99% PT	35	18	70	18	12	15	42	42
	100% PT	124	65	84	14	2	28	37	35
	<100% PT	66	35	67	16	16	26	38	36
Number of PT deficiencies in the past 2 years (35 missing)	None	121	78	—	—	—	28	36	35
	1	24	15	—	—	—	9	48	43
	2+	10	7	—	—	—	0	40	60

Row totals may not add up to 100% because of rounding.
[a]This category excludes those performing no PT, because they cannot have PT errors.

more PT deficiencies than low volume laboratories. Findings did not differ when the six directors whose laboratories perform only research testing were excluded.

Incorrect test results. All respondents were asked to provide their best estimate of how many incorrect test reports were issued to patients or providers by their laboratory over the past two years (**Table 2**). Among respondents (n = 177), 28% said no incorrect test reports had been issued by their laboratory during that period, 37% reported between one and three incorrect reports and 35% reported four or more incorrect reports. The average number of incorrect reports reported over the past two years was 5.1.

Not surprisingly, the number of incorrect test reports increased significantly with the volume of testing ($p < 0.0001$). However, adjusting for key variables, the number of incorrect test reports detected also increased significantly with the number of deficient proficiency tests in the same period. A 20% increase in the number of incorrect test reports is associated with each additional PT deficiency ($p = 0.03$). This finding did not differ when laboratories that perform only research testing were excluded.

Types of laboratory errors reported. All respondents were provided a list of seventeen types of laboratory errors and asked to indicate which had been observed in their laboratory over the last two years. Respondents were then asked to select the most common type of error seen in their laboratory. These were grouped into pre-analytic, analytic and post-analytic errors (**Table 3**).

The most commonly observed errors occurred during the pre-analytic phase of testing; 45% of the most common errors were pre-analytic, 30% were analytic and 24% were post-analytic. Adjusting for key variables, the strongest predictor of whether the most commonly observed error occurred during the analytic phase of testing was annual testing volume. Lower-volume laboratories were more likely than those in higher-volume laboratories to identify an analytic error as the most common error ($p = 0.03$). The second strongest predictor of whether a laboratory's most common error was analytic was the percentage of tests on which formal or informal PT is performed (**Table 4**). The odds that the most common error was analytic increased 40% with each decrease in level of PT completed ($p = 0.06$, **Table 4**). When analysis was restricted to laboratories that complete ≥2,000 tests annually, those that do not perform some form of PT on all of their genetic tests were significantly more likely than those who complete PT on all tests to identify an analytic error as the most common type ($p = 0.02$). This finding did not differ when the laboratories that perform only research testing were excluded.

Table 3 Type and frequency of laboratory errors

Test phase	Error	Percent of directors that reported detecting this type of error during the past two years	"Which was the most common type of error over the past 2 years?"
Pre-analytic errors	Referrer ordered incorrect test	74	27
	Referrer labeled specimen incorrectly	68	10
	Contamination before receipt by laboratory	19	4
	Transcription error at specimen receipt	32	2
	Sample switch at specimen receipt	16	2
	Error in written protocol	7	1
	Patient's transfusion not reported by referrer	13	0
	Total pre-analytic		45
Analytic errors	Faulty reagent	52	13
	Equipment failure	52	11
	Human error in data analysis	44	3
	Contamination during specimen testing	18	2
	Sample switch during specimen testing	27	1
	Total analytic		30
Post-analytic errors	Typographical error on test report	55	17
	Data transcription error	42	5
	Misinterpretation of data	19	1
	Wrong results reported to patient/provider	20	1
	Software error in data analysis	8	0
	Total post-analytic		24
Other	Other	4	1

Laboratory directors' attitudes. A majority of respondents (73%) agreed or strongly agreed that "CLIA should create a genetic testing specialty for molecular and biochemical tests." Directors of laboratories that perform testing for both clinical and research purposes showed somewhat greater approval for a new specialty (79%) than directors of laboratories that provide only clinical genetic testing (66%, $p = 0.07$). There was no difference in support for a new CLIA specialty based on setting (commercial, academic, other), test volume or on the type of testing performed.

Sixty percent of respondents found PT to be "very useful" to "improve the quality of genetic testing performed by the laboratory industry" and another 32% said PT was "somewhat useful." The perceived value of PT was similarly high in both clinical and research laboratories, in laboratories that do and do not perform biochemical testing, and across laboratory settings and annual test volume. Respondents whose laboratories conducted some type of PT on fewer than half their tests also showed high support for PT in general: 47% said it was very useful and 40% said it was somewhat useful ($p = 0.35$).

Discussion

Results of this survey indicate that participation in PT—whether through a formal program or through other measures—has a clear association with laboratory quality as measured by the number of reported deficiencies and the frequency of reported analytic errors. In this survey, the number of reported deficiencies decreased as the percentage of tests for which any PT was performed increased. In addition, the number of incorrect test reports

Table 4 Relationship between extent of proficiency testing and type of most common error

		Type of most common error (%)		
		Pre-analytic	Analytic	Post-analytic
Percent of tests on which some PT is done	0–24 PT	29	50	21
	25–74 PT	53	33	13
	75–99 PT	37	34	29
	100 PT	48	26	26
All respondents		45	30	24

Row totals may not add up to 100% because of rounding.

increased 20% with each additional reported deficiency. Furthermore, laboratories that perform PT on a lower percentage of tests were more likely to report that their most common error occurred during the analytic phase of testing, which is the phase of testing that PT is intended to evaluate.

A limitation of our study stems from the fact that there are no comprehensive baseline data describing the numbers, types and sizes of genetic testing laboratories in the United States that would allow us to determine whether the study sample is representative. Therefore, the extrapolation of the results to the universe of US genetic testing laboratories should be made with some caution. Respondents may over-represent laboratory directors with strong opinions, or under-represent those reluctant to share information about their attitudes or practices. In addition, because we collected data regarding the annual volume of tests and the size of the test menu as ranges (e.g., 250–999 test requisitions per year), we could not completely account for the effect of differences in volume and menu size on respondents' answers to other questions.

The significant rates of nonparticipation in PT reported by directors of laboratories of all sizes demonstrates that merely being certified under CLIA is insufficient to ensure quality: nearly a third of respondents reported that their laboratories perform PT for only some tests they offer. Mandating participation in PT (formal or informal) would increase the number of laboratories performing PT and thereby enhance the quality of genetic testing.

Genetic testing has become an increasingly integral component in the diagnosis, treatment, management and prevention of numerous diseases and conditions. Information gained from genetic test results can have a significant impact on medical decision making. Incorrect test results stemming from laboratory errors can lead to misdiagnosis, inappropriate and/or delayed treatment, anxiety and in rare cases, even death. Thus, it is critical that mechanisms are in place to detect and reduce laboratory errors and to ensure that the laboratories performing genetic testing are of high quality.

Since the mid-1990s a number of federal government advisory groups have questioned the adequacy of US regulatory oversight of both genetic tests and the laboratories performing them. In 2000, the US Centers for Disease Control recommended that the Centers for Medicare and Medicaid Services (CMS), the agency that oversees CLIA, create a genetic testing specialty area under CLIA[11]. Nearly three out of four respondents to this survey approved of such a measure. To date, CMS has not issued a rule for the creation of a genetic testing specialty. Although the US Department of Health and Human Services placed the issuance of a proposed rule for a genetic testing specialty on its regulatory agenda[12] in April, with a target publication date of November 2006, more recent statements by CMS officials indicate the agency believes a specialty is not needed.

In enacting CLIA, the US Congress stated that PT "should be the central element in determining a laboratory's competence, as it provides a measure of actual performance on laboratory test procedures rather than only gauging the potential for accurate outcomes"[13]. The importance of PT in evaluating and monitoring laboratory quality is underscored by the fact that errors can be difficult to detect, and self-reported error rates may not accurately reflect the actual occurrence of errors in the laboratory or the quality of the laboratory. A laboratory may be making errors but not have mechanisms in place to detect them, whereas another laboratory may rarely make errors but detect them more often as a result of redundant checks and balances that have been instituted in the laboratory. Thus, PT is a useful and objective means of evaluating a laboratory's ability to get the correct test result and to identify potential sources of error.

Creation of a genetic testing specialty under CLIA by CMS is a prerequisite to mandating enrollment in specified, CLIA-approved PT programs for genetic testing laboratories. In the absence of CLIA-approved PT programs, laboratories have adopted different practices with regard to PT. Some laboratories enroll in all available formal PT programs, whereas others do not. When a formal external PT program is not available, some laboratories seek to comply with CLIA's general requirement to ensure accuracy through alternative PT methods, whereas others do not. Lack of availability of formal PT programs was a key reason cited by respondents for failure to perform PT. In the absence of formal PT programs, some laboratory directors use competency testing as a means to assess proficiency. However, competency testing is not a comparable substitute as it assesses an individual laboratory employee's performance and not the actual ability of a laboratory to get the correct test result.

In a recent US Senate hearing, CMS stated that genetic tests are adequately covered by other specialties[14]. However, the survey data show 16% are not certified in any specialty, including one-third of high volume laboratories. Furthermore, the most common specialty certifications held by genetic testing laboratories have questionable relevance to establishing quality for genetic testing.

Establishing additional formal PT programs for genetic testing laboratories and requiring enrollment as a condition of CLIA certification would require additional resources. Even so, more than nine out of ten laboratory directors surveyed regard PT as useful for improving the quality of the genetic testing performed by the laboratory industry and almost no one said cost is a driver of nonparticipation in programs. Furthermore, a majority of laboratory directors support creation of a genetic testing specialty under CLIA. Given these observations, and the demonstrated association between PT and laboratory quality, we conclude that the creation of a genetic testing specialty and the associated requirement to enroll in specified CLIA-approved PT programs would improve the quality of genetic testing laboratories.

Note: Supplementary information is available on the Nature Biotechnology website.

ACKNOWLEDGMENTS

The Genetics and Public Policy Center is supported at Johns Hopkins University by The Pew Charitable Trusts. The opinions expressed in this report are those of the authors and do not necessarily reflect the views of The Pew Charitable Trusts. The authors are grateful to Linda Bradley, Michele Caggana, Wayne Grody and Michele Schoonmaker for their helpful review of an earlier draft of this manuscript, and to GeneTests for providing their Clinic Directory.

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