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ARTICLE

Quality assurance practices in Europe: a survey of molecular genetic testing laboratories

Sarah Berwouts[1,4], Katrina Fanning[1,4], Michael A Morris[2,4], David E Barton[3,4] and Elisabeth Dequeker*[,1,4]

In the 2000s, a number of initiatives were taken internationally to improve quality in genetic testing services. To contribute to and update the limited literature available related to this topic, we surveyed 910 human molecular genetic testing laboratories, of which 291 (32%) from 29 European countries responded. The majority of laboratories were in the public sector (81%), affiliated with a university hospital (60%). Only a minority of laboratories was accredited (23%), and 26% was certified. A total of 22% of laboratories did not participate in external quality assessment (EQA) and 28% did not use reference materials (RMs). The main motivations given for accreditation were to improve laboratory profile (85%) and national recognition (84%). Nearly all respondents (95%) would prefer working in an accredited laboratory. In accredited laboratories, participation in EQA ($P<0.0001$), use of RMs ($P=0.0014$) and availability of continuous education (CE) on medical/scientific subjects ($P=0.023$), specific tasks ($P=0.0018$), and quality assurance ($P<0.0001$) were significantly higher than in non-accredited laboratories. Non-accredited laboratories expect higher restriction of development of new techniques ($P=0.023$) and improvement of work satisfaction ($P=0.0002$) than accredited laboratories. By using a quality implementation score (QIS), we showed that accredited laboratories (average score 92) comply better than certified laboratories (average score 69, $P<0.001$), and certified laboratories better than other laboratories (average score 44, $P<0.001$), with regard to the implementation of quality indicators. We conclude that quality practices vary widely in European genetic testing laboratories. This leads to a potentially dangerous situation in which the quality of genetic testing is not consistently assured.
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INTRODUCTION

By their very nature, genetic tests can have profound health consequences for patients and their families. They can confirm a genetic disorder, prevent or predict the risk of a future disorder, assist in therapy decisions or influence reproductive decision making. Consequently, incorrect results can lead to inappropriate or delayed treatment, or misdiagnosis resulting in, for instance, unnecessary mastectomy or termination of pregnancy. In addition, genetic tests are typically only performed once in an individual's lifetime, increasing the consequences of eventual errors. It is thus of utmost importance that systems are in place to assure accurate and reliable test results.

The most complete system of laboratory quality assurance (QAu) system is accreditation, for which an authoritative independent body gives formal recognition that the laboratory is competent to carry out specific tasks.[1] ISO 17025 and ISO 15189 are the major standards for accreditation.[2,3] Certification is a further quality management system, typically based on ISO 9001.[4] Certification is a procedure by which a third party gives written assurance that the laboratory conforms to specific management requirements. Although certification has value, it is less stringent than accreditation because there is no obligatory review of technical competence. A third system, licensing, is distinct from accreditation and certification, can be mandatory and government imposed for healthcare providers and laboratories, and at least in some cases has no quality management or assurance requirements. For laboratories and users of laboratory services, there has been a persistent misunderstanding of the terms accreditation, certification and licensing.[5,6] Consequently, the words are commonly used inaccurately and interchangeably. The final critical mechanism of QAu is external quality assessment (EQA). Participation in EQA, or other forms of inter-laboratory comparisons, objectively and independently assesses laboratory performance and is a requirement for accreditation.[7]

In the early 2000s, concerns were raised with regard to QAu practices in Europe and beyond as the rapid expansion of genetic testing.[8–10] The European Science and Technology Observatory Network and the Organization for Economic Cooperation and Development (OECD) conducted studies to determine the state of quality systems within genetic testing services, identifying an urgent need for better and more consistent QAu practices.[11,12] As a result, initiatives were taken to improve the quality of genetic testing laboratories. EQA providers such as the Cystic Fibrosis Network and the European Molecular Genetics Quality Network received support from the European Commission (BMH4-CT96-0462, QLK3-CT99-00241 and SMT4-CT98-7515).[13,14] Another initiative was the CRMGEN project, which aimed to develop certified reference materials (RMs) for molecular genetic tests (G6RD-CT-

[1]Department of Public Health, Biomedical Quality Assurance Research Unit, KU Leuven, Leuven, Belgium; [2]Molecular Diagnostic Laboratory, Service of Genetic Medicine, University Hospitals, Geneva, Switzerland; [3]National Centre for Medical Genetics, UCD School of Medicine and Medical Sciences University College Dublin, Our Lady's Children's Hospital, Crumlin, Dublin, Ireland
[4]EuroGentest.
*Correspondence: Professor E Dequeker, Department of Public Health, Biomedical Quality Assurance Research Unit, KU Leuven, Campus Gasthuisberg, Herestraat 49, box 602, 3000 Leuven, Belgium. Tel: +32 16 34 58 81; Fax: +32 16 34 79 49; E-mail: els.dequeker@med.kuleuven.be
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2001-00581).[15] In 2005, a network of networks was established named EuroGentest.[16] After 2 years, the OECD published Guidelines for Quality Assurance in Molecular Genetic Testing.[17] In the United States, the Centers for Disease Control and Prevention formulated recommendations for improving QAu of molecular genetic testing laboratories and efforts were made to create a genetic testing specialty under the Clinical Laboratory Improvement Amendments.[18,19]

However, little updated information has been collected on the status of QAu practices since the projects discussed above. Such data are crucial to evaluate the projects and initiatives implemented and to identify the areas where improvements are still required. The objective of our survey was to provide an overview of the current state of QAu in human molecular genetic testing (HMGT) laboratories in Europe. We also aimed to investigate the perception and knowledge of HMGT laboratories on QAu and accreditation. The target population was European laboratories that conduct nucleic acid-based HMGT for molecular genetic hereditary disease testing (constitutional), molecular oncology (somatic) and pharmacogenetics. We excluded laboratories that test only for molecular microbiology, infectious diseases, cytogenetics or biochemical genetics.

MATERIALS AND METHODS

Sample

We selected personnel registered as responsible for at least one diagnostic test in the field of molecular genetics in Orphanet (http://www.orpha.net), or registered as laboratory director, department director or quality manager in a laboratory registered in Orphanet with at least one diagnostic test, in the field of molecular genetics. Orphanet has the most reliable and up-to-date list of European genetic testing laboratories. Duplicate e-mail addresses were removed, as well as laboratories from non-European countries. This resulted in a final sample of 2337 individuals from 926 HMGT laboratories in 31 European countries. Orphanet estimated they were missing at least 129 laboratories (Hungary: 38, Czech Republic: 35, Germany: 25, Slovakia: 20, Italy: 8, Bulgaria: 2 and Denmark: 1). Our sample thus represented at most 88% (926/1055) of European HMGT laboratories.

Study design

The web-based survey was created using SurveyMonkey (http://www.surveymonkey.com). Questions were based on focussed discussions with opinion leaders who were in the study population and on the questionnaire used by OECD for developing the Guidelines for Quality Assurance in Molecular Genetic Testing.[12] The survey was validated by means of cognitive interviews, using the 'thinking aloud method', and pre-tests to assess perception, usefulness, ambiguity and interpretation of each question by professionals from accredited and non-accredited HMGT laboratories in different countries.[20] The final questionnaire had 70 open-ended and closed questions, including Likert scales,[21] arranged in different sections: characteristics of the laboratory, sample numbers and sample flow, quality indicators, certification and accreditation, EQA and RMs. Contact information was requested to filter for double responses. A total of 10 questions were mandatory. This allowed respondents, depending on the answer choices, to pass over nonrelevant questions. Definitions for quality manager, quality management, certification, accreditation, EQA and RM were provided in the relevant sections.[1,3,7,22]

Survey administration

On 7 June 2010, an introductory e-mail, explaining that a survey would be distributed, was sent to the sample list. After 2 days, an invitation e-mail was sent, providing a uniform resource locator (URL) to the survey. Embedded within that URL was a unique identifier. The unique identifier allowed us to eliminate double responses. The invitation informed respondents that the survey would take $\sim$40 min to complete, that completion was voluntary and that responses would be treated with strictest confidence. It also stated that they could return to the survey to check and modify data at any time before submission, that they could withdraw from the study using the 'opt-out' button and that if they wanted a colleague to respond they could forward a general URL. We also posted the general URL on the EuroGentest website (www.eurogentest.org). Non-respondents were sent e-mail reminders 8 and 15 days after the initial invitation. The closing date for responses was 30 June 2010.

Response rate (RR), bias and EuroGentest collaboration score

The RR was calculated using the American Association for Public Opinion Research (AAPOR) standard definitions.[23] The AAPOR RR 2 was used, which allows for the inclusion of both complete and partial, but useful, questionnaires ($n=291$). RR 2 divides the number of respondents by the number of respondents and non-respondents. Non-respondents are cases that did not return a survey ($n=574$), cases that chose to opt out ($n=5$), cases that submitted a partial questionnaire with insufficient information ($n=16$) and cases for which an e-mail delivery failure ($n=24$) was received. RR 2 does not include in the denominator cases that are known to be ineligible – those who reported not to perform HMGT and/or not to release diagnostic results ($n=16$), duplicate responses ($n=52$) and anonymous responses ($n=81$). Duplicate responses were removed in accordance with a predefined hierarchy that was based on the completeness of the response, the function of the respondent in the laboratory and the year the respondent started working in the laboratory. Potential response bias was evaluated in two ways. First, we checked whether accredited laboratories, ie, laboratories that are expected to have affinity with quality issues and recognize the importance of the questionnaire, were more likely to answer the survey. We compared the accreditation status, reported by the respondents, with data provided by the national accreditation bodies.[24–26] Second, we verified whether a higher EuroGentest collaboration score (countries with laboratories that collaborated with the authors within EuroGentest (1 point when involved in the EuroGentest project, 2 points when involved in the EuroGentest unit on quality management) or that attended training courses provided by EuroGentest (1 point)) was associated with a higher RR.

Data analysis

Responses were downloaded from SurveyMonkey and transferred into Microsoft Office Excel. Data were analyzed by frequency and percentage distributions. We ignored missing values and counted only valid answers to a question, which resulted in slightly different sample sizes between questions.

Number of samples and number of people working in the laboratory. Some questions asked respondents to select a range that contained numeric values (eg, number of samples received or number of people working in the laboratory). For these types of responses, we presented grouped mean values. The grouped mean values were calculated by multiplying the midpoint value of each range by the frequency of responses for each range, adding up all of the ranges, then dividing by the total frequency. For the questions on the number of samples received or sent to other laboratories, the median and quartiles were calculated.

Certification and accreditation status. We validated the answers to the questions 'Is your laboratory certified?' and 'Is your laboratory accredited?' by checking websites of certification and accreditation bodies and responding laboratories. If we undoubtedly found that the laboratory indicated a wrong status, we corrected it. When the answer to the questions was 'no' or 'do not know', we initially did not validate the response and accepted that the laboratory had responded: 'no certification' ($n=174$), 'no accreditation' ($n=184$) and 'do not know certification status' ($n=5$). A few laboratories indicated they were not certified ($n=11$) or not accredited ($n=2$), however, on further investigation we ascertained that they were accredited or certified and we changed the status. Among 91 laboratories that reported to be certified, only 69 truly were. In parallel, among 102 laboratories that reported to be accredited, only 63 truly were. Six laboratories had both certification and accreditation. For the analysis in this manuscript, we placed them in the accredited group.

EQA and RMs. Respondents were asked to suggest up to three disorders or markers for which new RMs and EQA schemes were urgently needed. They

were not asked to rank their suggestions, so all suggestions were pooled into a single list for counting and analysis. There was much diversity in the descriptive terms and disease names provided. Answers were therefore coded for analysis, using a single code to group synonymous or similar responses. For example, suggestions for 'HNPCC', 'MSH6' and 'Lynch' were all coded as 'colorectal cancers'.

Actions upon receipt of EQA results and accompanied score. Respondents indicated that actions were performed upon receipt of EQA results. These actions were divided into three categories: 1/ document handling (results are read, results are filed); 2/ communication (results are made available to laboratory personnel, results are presented to laboratory personnel, results are presented to management); and 3/ quality improvement (results are evaluated, actions for improvement are considered, actions are implemented in case of an error). Scores were calculated per category as a percentage going from 0, when no single action within a certain category was performed, to 100 when all actions were performed.

Quality implementation score. We assessed the degree of implementation of different technical and management quality indicators, covered by the ISO 15189 accreditation standard.[3] A QIS was calculated per laboratory. A score of 3 was given for each indicator that was fully implemented in the laboratory; a score of 2 was given for the 'advanced' stage, 1 for 'just started' and 0 for 'not started'. The QIS of a laboratory was expressed as a percentage calculated by dividing the sum of the scores of the different indicators by the maximum score in case all indicators were fully implemented. Similarly, we calculated a sub score for the management indicators (management QIS) and one for the technical indicators (technical QIS).

Statistical methodology

The χ^2 test was used to investigate the relationship between two discrete variables; in cases of small cell frequencies, the Fisher exact test was used. For pairwise comparisons on discrete variables, a logistic regression model was used. The Kruskal–Wallis test was used for investigating the relationship between a discrete and a continuous variable, or the Mann–Whitney *U*-test when the discrete variable is binary. Pairwise comparisons (discrete + continuous variable) were based on the Mann–Whitney *U*-test. The relationship between two continuous variables was based on the Spearman correlation. Regression analysis was used to examine whether there were factors independently associated with a higher QIS. We included both accreditation and the specific factor in the regression model. Some discrete variables had multiple levels with an intrinsic order. These variables were given a score going from 1 to the number of levels. These variables were analyzed both as discrete and continuous. The analysis with a continuous variable is more powerful if the relationship is linear. It concerned the following variables: number of samples (eight levels), full-time equivalent (FTE; six levels), EuroGentest collaboration score (four levels), rating importance EQA (five levels) and qualification of the laboratory director (five levels). Statistical significance was evaluated at the 0.05 level. All analyses have been performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA) of the SAS System for Windows.

RESULTS

RR and collaboration score

Of 910 eligible laboratories, 291 returned a useful response (RR of 32%). The responding laboratories were located in 29 European countries. Countries with higher EuroGentest collaboration scores were not associated ($P = 0.11$) with a higher RR (Table 1).

Table 1 Country responses and EuroGentest collaboration score

Country	*Number of eligible laboratories contacted*	*Number of laboratories responded*	*EuroGentest collaboration score*
Belgium	15	6 (40%)	3
Germany	126	32 (25%)	3
Switzerland	42	13 (31%)	3
United Kingdom	50	15 (30%)	3
Czech Republic	23	6 (26%)	2
France	190	56 (29%)	2
Ireland	2	1 (50%)	2
Italy	192	69 (36%)	2
Portugal	17	7 (41%)	2
Spain	94	27 (29%)	2
The Netherlands	18	7 (39%)	2
Austria	21	3 (14%)	1
Croatia	4	1 (25%)	1
Denmark	12	5 (42%)	1
Finland	10	7 (70%)	1
Greece	23	9 (39%)	1
Hungary	4	1 (25%)	1
Norway	4	3 (75%)	1
Poland	16	6 (38%)	1
Serbia	3	2 (67%)	1
Sweden	4	1 (25%)	1
Bulgaria	3	0 (0%)	0
Cyprus	6	2 (33%)	0
Estonia	4	2 (50%)	0
Latvia	2	1 (50%)	0
Romania	3	1 (33%)	0
Slovakia	4	2 (50%)	0
Slovenia	5	2 (40%)	0
The Former Yugoslav Republic of Macedonia (FYROM)	1	1 (100%)	0
Turkey	10	3 (30%)	0
Ukraine	2	0 (0%)	0
Total	910	291 (31%)	

Eligible laboratories included European laboratories that conduct nucleic acid-based HMGT for molecular genetic hereditary disease testing (constitutional), molecular oncology (somatic) and pharmacogenetics.
EuroGentest collaboration score: countries with laboratories that collaborated with the authors within EuroGentest (1 or 2 points) or that attended training courses provided by EuroGentest (1 point).

Characteristics of the study population

Table 2 gives an overview of the characteristics of the study population. The majority of surveyed laboratories were in the public sector (81%), affiliated with a university hospital (60%). A small number of laboratories (11%) described themselves as research laboratories, although releasing diagnostic test results. We found that independent and research laboratories were more likely to associate with an external clinical geneticist than non-university and university hospitals, which were more likely to associate with an internal clinical geneticist ($P = 0.0069$). More than half of laboratories (59%) used the equivalent of 1–10 full-time people (FTE, including dedicated technical and administrative support). Laboratories with a higher number of FTEs were more likely to have a quality manager used ($P = 0.007$). We identified a significant positive correlation between the number of FTEs and the number of samples received by the laboratory ($r = 0.556$, $P < 0.0001$).

Sample numbers and sample flow

In all, 233 of 291 laboratories reported receiving samples from other laboratories (Table 2). Among them, 220 reported an amount per year: 25% received 20 samples or fewer (lower quartile), 50% received 50 samples or fewer (median) and 75% received 200 samples or fewer (upper quartile). Similarly, 178 laboratories, among 195 laboratories that referred samples to other laboratories, reported an amount with

lower quartile: 10, median: 20 and upper quartile: 100. Two-third of laboratories received samples from laboratories outside the country and half of laboratories referred samples to laboratories in other countries (Table 2). Most important reasons for referring samples included that the test was not performed in the laboratory (prenatal testing, rare disease testing, additional testing and specialized testing) (78%) and referral for verification of results or validation of tests and methods (13%). Although it was difficult to be precise, we estimated that the mean number of all samples received per laboratory was 2560 in 2010. If we accepted that there were at least 1055 HMGT laboratories in Europe, the total number of samples received by HMGT laboratories in 2010 in Europe would be estimated at 2.7 million. The number of samples received by research laboratories was significantly lower than by other affiliations ($P<0.001$). For example, research laboratories ($n=31$) received on average 529 samples per year *vs* 2663 samples received by university hospitals ($n=172$) and 3635 by independent laboratories ($n=33$). There were no significant differences between number of samples received in private or public laboratories ($P=0.083$).

Table 2 Characteristics of the study population

Characteristic	*Number of respondents*
Sector	
Public	81% (235)
Private	19% (55)
Affiliation	
University hospital	60% (174)
Independent laboratory	12% (34)
Non-university hospital	11% (31)
Research laboratory	11% (31)
Other (eg, National Health Service, IVF clinic ...)	7% (21)
Clinical geneticist	
Yes, internal	66% (190)
Yes, external	16% (47)
No	18% (51)
Qualification laboratory director (highest degree, ranked from 'high' to 'low')	
PhD and Doctor of Medicine (MD)	31% (83)
MD	27% (72)
PhD	37% (101)
Pre-doctoral degree (Master, Bachelor)	5% (14)
Full-time equivalent	
1–5	32% (94)
6–10	27% (77)
11–20	22% (64)
21–50	16% (45)
51–100	3% (8)
Quality manager	
Yes, supported by others	49% (139)
Yes, not supported by others	19% (54)
No	32% (90)
Number of samples received every year	
1–50	5% (15)
51–200	13% (37)
201–500	16% (47)
501–1000	14% (39)
1001–2000	23% (65)
2001–5000	14% (39)
5001–10 000	10% (30)
>10 000	5% (15)
Samples are received from other laboratories	80% (233)
Within the country	94% (218)
In other countries	66% (153)
Samples are referred to other laboratories	67% (195)
Within the country	90% (175)
In other countries	47% (92)

Current state of certification and accreditation

Only half of European HMGT laboratories were inspected by official bodies in 2010: 22.6% ($n=65$) were accredited (Figure 1) and a further 25.7% ($n=74$) were certified. Among laboratories that were not accredited at the time of the survey, 105 declared they were preparing for accreditation (Figure 1), 58 will start preparing within the next 5 years and 21 were not planning to go for accreditation within the next 5 years.

We asked the accredited laboratories how many years they needed from the decision to prepare for accreditation to being accredited (Figure 2a). Estimating that all laboratories that were preparing will achieve accreditation within 5 years, a further 105 laboratories would be accredited by 2015. Laboratories were accredited according international ISO standards (66%, $n=41$) and national accreditation standards (34%, $n=21$; Figure 2b). Remarkably, when we questioned about the awareness of the existing national accreditation body in the country, 12% ($n=33$) of the respondents indicated that there was no such body in their country, and 16% ($n=45$) indicated that they did not know whether there was an accreditation body in their country. Every country in Europe has a recognized national accreditation body.

Profile of accredited laboratories

Laboratories affiliated with a university hospital and independent laboratories were more likely to be accredited ($P=0.0036$).

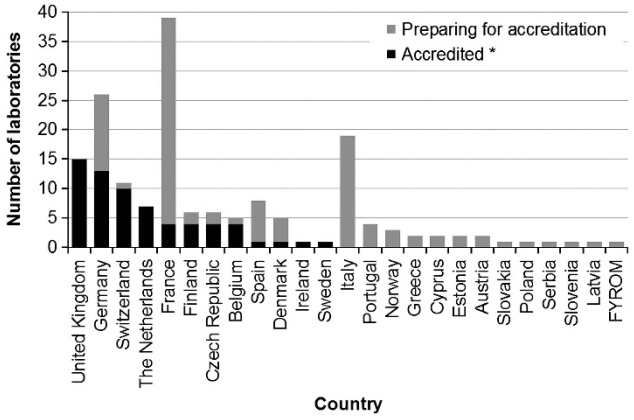


Figure 1 Overview of the countries in which accredited laboratories ($n=65$) and in which laboratories preparing for accreditation ($n=105$) were located. *We categorized for this study the following standards and programs under accreditation: ISO 15189, ISO 17025, Clinical Pathology Accreditation and Coördinatie Commissie ter bevordering van de Kwaliteitsbeheersing van het Laboratoriumonderzoek. The following standards and programs were not categorized under accreditation: ISO 9001, Haute Autorité de Santé, Clinical Laboratory Improvement Amendments, Joint Commission International, European Molecular Genetics Quality Network and licensing by national health systems.

For example, among the accredited laboratories, 65% were affiliated with university hospitals and 17% were independent laboratories, compared with 6% of laboratories affiliated with a non-university hospital and none of the research laboratories. Larger laboratories (higher number of FTEs and higher number of samples received) were more likely to be accredited than smaller laboratories ($P<0.001$). The average FTE in accredited laboratories was 23, compared with 12 in non-accredited laboratories. Average number of samples received in accredited laboratories was 5773, compared with 1755 in non-accredited laboratories. Sector (private or public, $P=0.52$) and qualification of the laboratory director ($P=0.051$) were not significantly associated with accreditation.

Triggers and barriers for, and perception of, accreditation

All respondents, except those that were not planning to prepare for accreditation, indicated the reasons for accreditation ($n=219$). The main trigger was that accreditation would improve the laboratory profile (85%). National (84%) and international recognition (76%) were also key factors. Accredited laboratories agreed significantly more with the following statements than the other laboratories (preparing + will prepare): 'accreditation would give national recognition' ($P=0.012$; 90% *vs* 81%), 'the laboratory wanted to be accredited' ($P=0.013$; 81% *vs* 63%) and 'because of reimbursement reasons' ($P=0.019$; 30% *vs* 16%). In contrast, 'preparing' and 'will prepare' laboratories agreed significantly more than accredited laboratories with the statement 'accreditation will be a legal requirement' ($P=0.0008$; 68% *vs* 42%). A few laboratories did not plan to go for accreditation ($n=21$). The reasons for their decision were cost (94%, 16/17), time (82%, 14/17) and because it is not mandatory (79%, 15/19).

We surveyed the personal view of people working in HMGT laboratories on different statements ($n=280$, Figure 3). For the statement 'I believe that in an accredited laboratory development of new techniques is restricted' non-accredited laboratories agreed significantly more than accredited laboratories ($P=0.023$; 32.6% *vs* 15.6%). A significant difference was also observed for the statement 'I believe that in an accredited laboratory work satisfaction is improved', for which non-accredited laboratories agreed more than accredited laboratories ($P=0.0002$; 51.6% *vs* 26.6%).

If respondents had access to all the necessary resources, 95% ($n=261$) would prefer working in an accredited laboratory. Furthermore, all respondents working in an accredited laboratory, except one, would recommend accreditation to another laboratory (58/59).

External quality assessment

Accredited laboratories were more likely to participate in EQA than non-accredited laboratories ($P<0.0001$). In all, 22% (62/277) of the surveyed laboratories did not participate in a single EQA scheme.

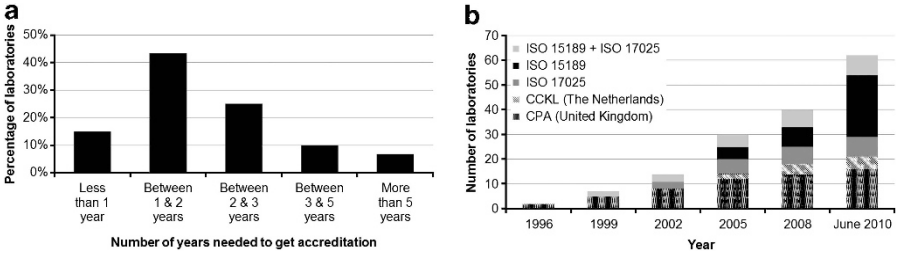


Figure 2 (**a**) Number of years the laboratories ($n=60$) needed from decision to prepare for accreditation to being accredited. (**b**) Accreditation standards implemented over the years ($n=62$) in Europe. For laboratories with both ISO 15189 and ISO 17025 accreditation, we took the year of ISO 17025 implementation, which corresponded with the initial year for accreditation.

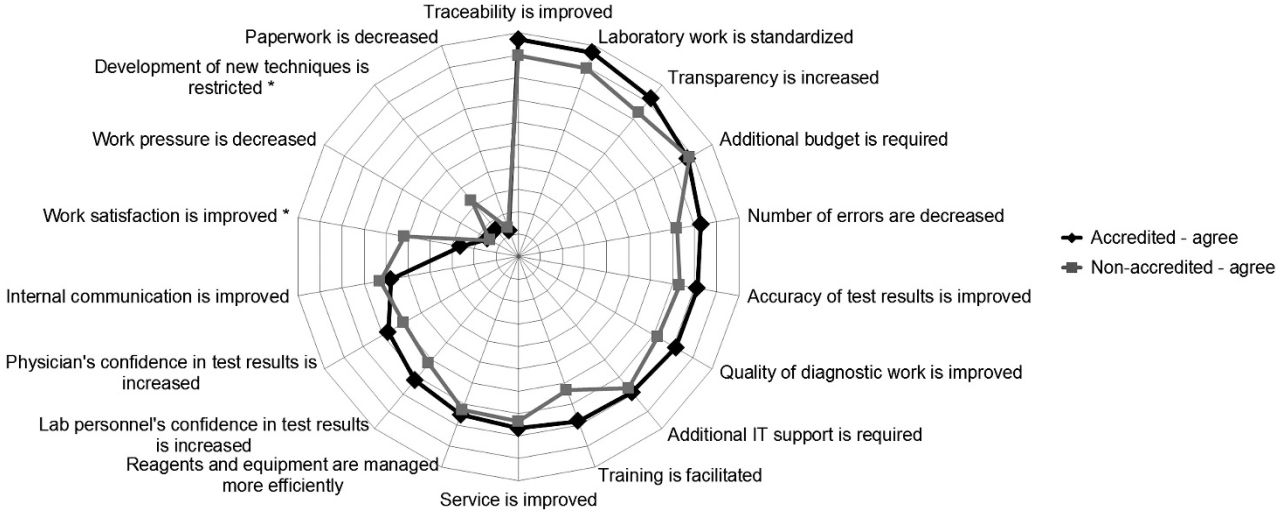


Figure 3 Personal views of people working in accredited and non-accredited HMGT laboratories on different statements (I believe that in an accredited laboratory…). The inner circle correlates with 10% agree and the outer circle correlates with 100% agree. *A Significant difference between accredited and non-accredited laboratories ($P<0.05$).

Notably, we found that 73% ($n=158$) of the EQA participating laboratories, also conducted tests for which there were no formal schemes available and of these, 24% ($n=38$) never participated in another form of inter-laboratory comparison. Respondents were asked to list new EQA schemes for which there was a need in their laboratory. In total, 215 suggestions were received from 102 respondents. The most common suggestions (of 65 responses) are shown in Supplemental Table 1 along with the current availability of EQA schemes. Notably, 97% (208) of laboratories participating in EQA rated EQA as essential or very important, compared with 78% ($n=47$) of remaining laboratories. Laboratories that participated in EQA rated the importance of EQA significantly higher than those that did not participate in EQA ($P<0.001$). Further, 26% ($n=72$) of the respondents indicated that at least one person in the laboratory was involved in the organization or assessment of an EQA scheme. There was a positive association between involvement in EQA as an assessor or organizer and the accreditation status of the laboratory ($P<0.0001$), for example, involvement in EQA in 50% ($n=32$) of the accredited laboratories *vs* involvement in EQA in 19% ($n=40$) of the non-accredited laboratories. The 'quality improvement' actions taken upon receipt of EQA results (results are evaluated, actions for improvement are considered, actions are implemented in case of an error) were positively associated with accreditation status: the score was 94 for accredited laboratories *vs* 83 for non-accredited laboratories ($P=0.007$). No significant differences were observed for the categories 'document handling' ($P=0.071$) and 'communication' ($P=0.078$).

Reference materials

The majority of respondents (72%, $n=198$) used RMs (samples of defined genotypes obtained from external sources) including materials from colleagues (69%, $n=136$), previous EQA material (46%, $n=92$), certified RM (40%, $n=80$), cell lines (30%, $n=59$) and synthetic material (12%, $n=23$). RMs were used for test validation (86%, $n=170$), regular use as internal quality control (70%, $n=139$), test development (61%, $n=120$), test calibration (43%, $n=85$) and annual/occasional use (16%, $n=32$). Accredited laboratories were more likely to use RMs ($P=0.0014$) than non-accredited laboratories. Respondents were asked to list disorders/markers for which they see the most urgent requirement for new RM. In total, 181 suggestions were received from 79 respondents. The most common suggestions (of 87 responses) are shown in Supplemental Table 2 along with the current availability of RMs.

Continuous education

CE on specific tasks in the laboratory ($P=0.0018$), broader medical/scientific subjects ($P=0.023$) and QAu ($P<0.0001$) was more readily available in accredited laboratories than in non-accredited laboratories. CE on specific tasks was available in 95% ($n=60$) of accredited laboratories and in 78% ($n=155$) of non-accredited laboratories. CE on medical/scientific subjects was available in 81% ($n=51$) of accredited laboratories and in 66% ($n=131$) of non-accredited laboratories. CE on QAu was available in 76% ($n=48$) of accredited laboratories and in 42% ($n=83$) of non-accredited laboratories. Almost all accredited laboratories (94%, $n=61$) maintained records of CE, compared with 67% ($n=142$) of non-accredited laboratories.

Quality indicators and QIS

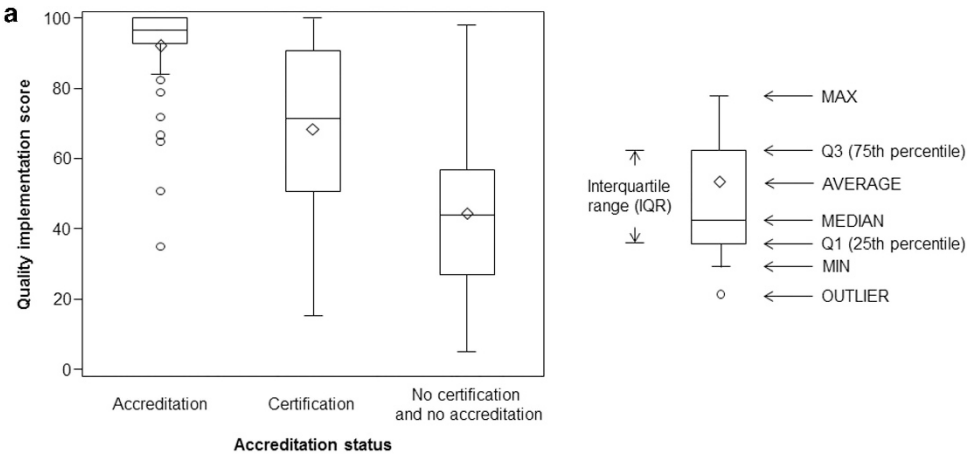
All laboratories ($n=280$), both accredited, certified and others, indicated the degree of implementation of different management and technical quality indicators (as required by the ISO accreditation standards) (Table 3). SOPs, document control, recording complaint response times, internal quality control and validation of methods were equally implemented in accredited and certified laboratories (* in Table 3). Participation in EQA was the single aspect equally implemented in certified laboratories and in laboratories without accreditation or certification (** in Table 3).

The average QIS for accredited laboratories (QIS = 92, $n=64$) was, as expected, significantly higher ($P<0.001$) than the average QIS for certified laboratories (QIS = 69, $n=74$) (Figure 4a). The average QIS for certified laboratories was significantly higher ($P<0.001$) than the average QIS of the remaining laboratories (QIS = 44, $n=144$). About half of the laboratories (48%, 137/284) obtained a QIS <60. We observed also a significantly higher ($P<0.001$) management QIS and technical QIS for the accredited laboratories (average 94 and 91) than for the certified laboratories (average 69 and 70) and a higher management QIS and technical QIS was observed for the certified laboratories compared with the non-accredited and non-certified laboratories (average 44). Factors associated with a higher QIS are shown in Figure 4b. Most factors were independently associated with a higher QIS when correcting for accreditation, except the use of RMs ($P=0.14$) and the number of FTEs ($P=0.63$).

Table 3 Degree of implementation of different management and technical quality indicators in accredited and non-accredited laboratories

	Degree of implementation (%)			P-*value*		
Quality indicator	*Acc*	*Cert*	*None*	*Acc vs Cert*	*Acc vs None*	*Cert vs None*
Management						
SOPs	100	99	69	1.00*	≤0.01	≤0.01
Document control	100	93	62	0.06*	≤0.01	≤0.01
Diagnostic log books	98	82	58	≤0.01	≤0.01	≤0.01
Quality manual	98	78	43	≤0.01	≤0.01	≤0.01
Maintenance/calibration log books	98	77	50	≤0.01	≤0.01	≤0.01
Training records	98	76	37	≤0.01	≤0.01	≤0.01
Following turnaround times	97	76	46	≤0.01	≤0.01	≤0.01
Recording of nonconformities	97	76	46	≤0.01	≤0.01	≤0.01
Recording complaints and compliments	97	71	40	≤0.01	≤0.01	≤0.01
Documented internal audits	97	66	18	≤0.01	≤0.01	≤0.01
Recording diagnostic errors	95	77	61	≤0.01	≤0.01	0.02
Recording complaint response times	78	66	31	0.18*	≤0.01	≤0.01
Technical						
Participation in EQA	100	77	65	≤0.01	≤0.01	0.09**
IQC	98	91	55	0.07*	≤0.01	≤0.01
Validation of instruments	97	84	54	≤0.01	≤0.01	≤0.01
Systematic corrective/preventive actions	97	73	46	≤0.01	≤0.01	≤0.01
Performing internal audits	97	68	21	≤0.01	≤0.01	≤0.01
Validation of methods	95	86	66	0.08*	≤0.01	≤0.01
Performing annual management reviews	94	66	19	≤0.01	≤0.01	≤0.01

Abbreviations: Acc, accredited laboratories; cert, certified laboratories; EQA, external quality assessment; IQC, internal quality control; none, non-accredited and noncertified laboratories.
*No significant difference between accredited and certified laboratories ($P>0.05$).
**No significant difference between certified laboratories and laboratories with no certification and no accreditation ($P>0.05$).



b

Factors associated with a higher QIS	P-value (Spearman correlation)	P-value when correcting for accreditation
Private sector	p<0.001	p<0.001
Higher number of samples received	p<0.001 (r=0.34 => moderate)	p<0.001
Presence of quality manager	p<0.001	p<0.001
Accreditation status vs certification status	p<0.001	_
Certification status vs no accreditation and no certification	p<0.001	_
Continuous education related to specific tasks in the laboratory	p<0.001	_
Continuous education related to quality assurance	p<0.001	_
Participation in EQA	p<0.001	p=0.028
Higher rating importance EQA	p<0.001	_
Affiliation	p<0.001	p<0.001
Independent laboratories vs research laboratories	p<0.001	_
Independent laboratories vs laboratories in university hospitals	p<0.001	_
Independent laboratories vs laboratories in non-university hospitals	p=0.023	_
Use of RMs	p=0.002	p=0.14
Involvement of somebody in the lab in the organisation or assessment of EQA	p=0.003	_
Association with an internal clinical geneticist	p=0.012	p=0.025
Higher number of FTEs	p=0.012 (r=0.15 => weak to very weak)	p=0.63
'Lower' qualification of the laboratory director	p=0.013 (r=-0.15 => weak to very weak)	_
Pre-doctoral (BSc + MSc) vs PhD	p=0.24	_
Pre-doctoral (BSc + MSc) vs MD	p=0.081	_
Pre-doctoral (BSc + MSc) vs MD + PhD	p=0.0062	_

Figure 4 (**a**) Graphical representation of the QIS for accredited laboratories, certified laboratories and non-accredited plus noncertified laboratories. (**b**) Factors associated with a higher QIS. '_': not analyzed.

DISCUSSION

Principal findings

This survey was the first large comprehensive update of the quality status in European genetic testing laboratories since projects and literature published that aimed to improve QAu practices in the early 2000s. The previous most recent study had been conducted in 2003, and included 15 European countries.[27] In contrast, we contacted 31 countries, exclusively in Europe, using the updated registry, resulting from a long-term collaboration between Orphanet and EuroGentest, of genetic testing laboratories.

In previous studies, responses with regard to accreditation status must be interpreted with care, principally because of the confusion between accreditation, certification and licensing: the rates of 54% of accredited/certified laboratories in the European Science and Technology Observatory Network study and 56% in the OECD study were almost certainly overestimations.[5,27,28] To overcome these challenges we validated and, where necessary, corrected the answers to the questions 'Is your laboratory certified?' and 'Is your laboratory accredited?', identifying 39 laboratories mistakenly declaring themselves as accredited.

We found that the implementation of accreditation in European HMGT laboratories was poor (23%). It is, however, very encouraging that the number of accredited laboratories doubled over the last 5 years. It is of concern that 22% of responding laboratories did not participate in EQA at all. Further, 28% of laboratories did not use RMs, which are crucial for the development, validation and monitoring of assays and thus for enhancing the quality of genetic testing.[29]

A limitation of this study was that we did not obtain answers from all HMGT laboratories. Therefore, we must be careful when making assumptions for the whole population. To verify whether the proportion of accredited laboratories was representative of the whole, we requested data from the national accreditation bodies. The bodies of 17/29 countries responded, including those of 9/12 countries with accredited HMGT laboratories. From these data, we estimate that the

proportion of accredited laboratories in Europe in 2010 was at least 26% (275/1055), compared with 23% in our study. Consequently, non-accredited laboratories may be slightly overrepresented in our data.

The QIS was not determined independently, but was based on self-assessment, and so may not be entirely accurate; however, the comparison between different groups is interesting. The average QIS indicated a suboptimal situation with regard to implementation of QAu practices in non-accredited genetic testing laboratories. Although the certified laboratories had an average QIS of 69, efforts are required to improve the implementation of internal auditing, systematic corrective and preventive actions, and participation in EQA. In parallel, non-accredited and noncertified laboratories (average QIS of 44) lacked the implementation of aspects that ensure continuous improvement and evaluation of competency, which raises major concerns. Unexpectedly, a higher QIS was associated with a 'lower' qualification of the laboratory director. However, the association was very weak ($r = -0.15$). When we compared qualifications against each other, only a significant difference in QIS was found between Bachelor + Master and MD + PhD. In addition, the number of laboratory directors with a Bachelor or Master degree was only 14, so it is possible that by chance the non-accredited laboratories with a laboratory director with a Bachelor or Master degree did not respond. There was no correlation between accreditation and the qualification of the laboratory director.

This study is the first to evaluate perceptions of accreditation of personnel in HMGT laboratories. The perception was largely very positive: although about 90% of individuals (in both accredited and non-accredited laboratories) considered accreditation to require additional budget, 95% wanted to work in an accredited laboratory, if money was not an issue. It was also intriguing that non-accredited laboratories were more pessimistic about the potential restriction of the development of new tests, and more optimistic about the improvement of work satisfaction than accredited laboratories.

Challenges and key considerations

This study reveals that the implementation of QAu practices in European genetic testing services is incomplete, and that implementation of ISO 15189 has been slow. The fact that accredited laboratories were identified in only 12 European countries is striking. A challenge will be to continue to improve QAu practices and to continue to support laboratories in achieving accreditation, especially seen the changing landscape of genetic testing with the arrival of new technologies such as microarray and next-generation sequencing.[30] Therefore, it is worth considering two approaches for the future. First, accreditation of HMGT laboratories could become mandatory. The prime example is the national initiative in France, where all medical laboratories must by law be accredited by the Comité français d'accréditation by November 2016.[31] To extend this to the European level, compulsory accreditation could be regulated, for example, by the European Council adopting the OECD Guidelines for Quality Assurance in Molecular Genetic Testing. These guidelines require all clinical results to be issued by accredited laboratories, and participation in EQA for every disease tested. A second approach would be a model where accreditation is not mandatory, but incentive-driven; an example is Belgium, where accreditation progressively becomes a requirement for reimbursement of laboratory tests, as is the case yet for Factor V Leiden, Factor II and fetal Rhesus genotyping testing.[32] Networks have to be established and maintained with local authorities and governments. An effective approach is implemented in Switzerland, where human genetic testing laboratories are obliged to report annually to the federal government for which diseases they test, for which diseases they perform EQA, the results of the EQA and their accreditation status. The government has the responsibility and the authority to collect and analyze the results, and to intervene in case of irregularities or insufficiencies of QAu. To provide the broadest assurance of the quality of genetic testing in Europe, data could be transferred from national bodies to an European body that is competent to monitor activity and, in case of poor performance, to intervene, for example, by audit, CE and potential sanctions.

The need for a comprehensive database of genetic testing laboratories is important, not only in performing research, but also for healthcare providers when referring samples (47% of laboratories referred samples to laboratories in other countries) and for patients. Although the Orphanet database is the most complete database available, at least 129 laboratories were missing, and the number of missing laboratories was unclear for at least 18 countries. To improve the accuracy and usefulness of the database, it is essential to identify all missing HMGT laboratories.

Furthermore, as the uptake of accreditation increases in Europe, EQA and RM provision will need to keep pace with demand. According to our study, there is also a need for new EQA schemes and new RMs, and for better diffusion of information about existing offers. EQA scheme providers should anticipate the increase and additional efforts might be needed to remain sustainable. In addition, a huge increase of accreditation requests will place a heavy burden on the accreditation bodies, which need to have sufficient trained and competent technical experts to perform external audits; the experts must have knowledge of the ISO requirements for medical laboratories as well as expertise in human genetic testing.

To aim for improved QAu practices in Europe, it is essential that laboratories are first aware of what is available to support them and where to find it. Our validation of the answers concerning laboratories' certification/accreditation status revealed that there is still a lack of understanding of the differences between accreditation, certification and licensing. This is not merely a semantic question, but is fundamental to the value and reputation of accreditation and, like the poor awareness of the existence of national accreditation bodies, should be addressed by the accreditation bodies themselves. Poor awareness of the availability of EQA schemes and RMs was similarly apparent. It is important to increase awareness and to make the currently available resources more visible and accessible. This would require the involvement and support of organizations at national and international levels.

CONCLUSION

Although both accreditation of laboratories and participation in EQA are accepted as effective and important tools to improve the accuracy and reliability of genetic testing, they are very rarely mandatory and are implemented only patchily in the HMGT community in Europe. The fact that quality of testing is not assured at all times leads to potential risks for patient safety and quality-of-care. We suggest specific improvements as follows:

- Accreditation should be actively encouraged by incentives or, ideally, by legislation.
- Consequently, participation in inter-laboratory comparisons such as EQA will be encouraged or become mandatory.
- A competent European body should monitor the QAu of the laboratories (accreditation status, participation in and results of EQA schemes).

- European or national mechanisms should be established to take appropriate actions in cases of noncompliance or poor performance.
- An accurate, reliable and complete European database is essential for patients and healthcare professionals. A system for continuous support should be established to improve and maintain the existing Orphanet database.
- EQA and RM providers should be prepared for an increased demand, and should provide schemes and materials according to the highest quality standards (ISO 17043 accreditation; certified RMs).
- Continued efforts are needed to ensure that laboratories are aware of and have access to the relevant information available with regard to QAu.

This study provides important information for national and international decision makers, governments, laboratories, EQA providers, national accreditation bodies and others. All interested parties should reflect on the needs and challenges described and act in a concerted manner to improve QAu practices in European genetic testing services more in the near future, for the benefit of the patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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