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Frequency of Participation in External Quality Assessment Programs Focused on Rare Diseases: Belgian Guidelines for Human Genetics Centers

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Abstract

Background

Participation in quality controls, also called external quality assessment (EQA) schemes, is required for the ISO15189 accreditation of the Medical Centers of Human Genetics. However, directives on the minimal frequency of participation in genetic quality control schemes are lacking or too heterogeneous, with a possible impact on health care quality.

Objective

The aim of this project is to develop Belgian guidelines on the frequency of participation in quality controls for genetic testing in the context of rare diseases.

Methods

A group of experts analyzed 90 EQA schemes offered by accredited providers and focused on analyses used for the diagnosis of rare diseases. On that basis, the experts developed practical recommendations about the minimal frequencies of participation of the Medical Centers of Human Genetics in quality controls and how to deal with poor performances and change management. These guidelines were submitted to the Belgian Accreditation Body and then reviewed and approved by the Belgian College of Human Genetics and Rare Diseases and by the National Institute for Health and Disability Insurance.

Results

The guidelines offer a decisional algorithm for the minimal frequency of participation in human genetics EQA schemes. This algorithm has been developed taking into account the scopes of the EQA schemes, the levels of experience, and the annual volumes of the Centers of Human Genetics in the performance of the tests considered. They include three key principles: (1) the recommended annual assessment of all genetic techniques and technological platforms, if possible through EQAs covering the technique, genotyping, and clinical interpretation; (2) the triennial assessment of the genotyping and interpretation of specific germline mutations and pharmacogenomics analyses; and (3) the documentation of actions undertaken in the case of poor performances and the participation to quality control the following year. The use of a Bayesian statistical model has been proposed to help the Centers of Human Genetics to determine the theoretical number of tests that should be annually performed to achieve a certain threshold of performance (eg, a maximal error rate of 1%). Besides, the guidelines insist on the role and responsibility of the national public health authorities in the follow-up of the quality of analyses performed by the Medical Centers of Human Genetics and in demonstrating the cost-effectiveness and rationalization of participation frequency in these quality controls.

Conclusions

These guidelines have been developed based on the analysis of a large panel of EQA schemes and data collected from the Belgian Medical Centers of Human Genetics. They are applicable to other countries and will facilitate and improve the quality management and financing systems of the Medical Centers of Human Genetics.

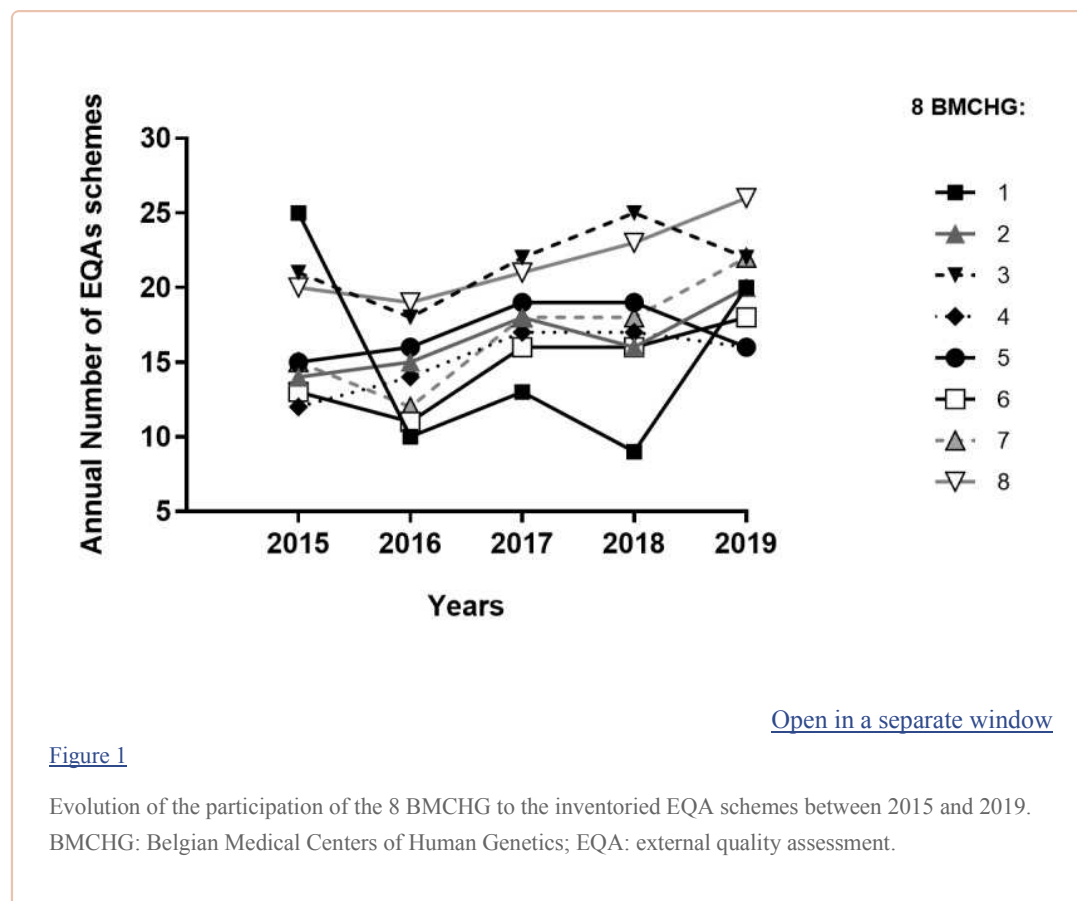
Keywords: human genetics, external quality assessment, quality control, proficiency testing, frequency, genetic testing, rare diseases, cost-effectiveness, surveillance, public health authorities, public health, health informatics, medical informatics, genetics, human genetics, algorithm

Introduction

Rare diseases are life-threatening or chronically debilitating conditions affecting less than 5 per 10,000 people [1]. At least 80% of them have a genetic origin and 50% to 75% affect children [2,3]. Despite the discovery of more than 200 new genes every year, the diagnosis of rare diseases often remains delayed because of their complexity and low prevalence [1,4-6].

There is a willingness of European governments to develop harmonized guidelines to improve the quality of genetic testing, particularly by stimulating medical laboratories to acquire accreditation and to participate in external quality assessments (EQAs) [7,8]. Indeed, the participation in EQA schemes is efficient for assessing and improving health care quality, as it allows performance comparisons and the identification of specific problems, areas for improvement, and training needs [9-11]. Besides, it

enables monitoring of the compliance with best practice guidelines and is required for the accreditation of medical laboratories according to the ISO 15189 standard [12-14]. It has been shown that the quality of genetic services in Europe can still improve [10,15]. Nevertheless, several recent studies performed in European laboratories for cancer testing have pointed out the positive influence of participation in EQAs on laboratories' performance [16-18]. In several countries such as in Belgium, the accreditation of the genetic laboratories is a requisite for reimbursement of the diagnostic tests. However, the EQA of the laboratories is still hampered by a lack of a harmonized European framework (numerous and heterogeneous quality schemes, lack of reference systems, and different Member State regulations) [19,20]. Similar concerns have been raised in a recent Belgian study focusing on the frequency of participation in EQA schemes in the fields of molecular microbiology, hematology, and pathology [20]. The authors proposed to harmonize the frequency of participation to quality controls [20]. Indeed, the ISO 15189 standard states that "the laboratory shall participate in an inter-laboratory comparison program (such as an EQA program or proficiency testing program) appropriate to the examination and interpretations of examination results," but does not give precise instructions [13]. This lack of clear national and international directives leads to uneven participation of the Medical Centers of Human Genetics in quality controls [21]. [Figure 1](#) illustrates this phenomenon with the participation of the Belgian Medical Centers of Human Genetics (BMCHG) in EQAs between 2015 and 2019.



To address this lack, we have developed Belgian guidelines about the minimal frequency of participation in EQA schemes for hereditary rare diseases, with reference to international recommendations and national laboratory practices.

Methods

Context of the Study

In the context of the Belgian National Plan for Rare Diseases, the Belgian National Institute for Health (Sciensano [22]) is responsible for the harmonization of the quality management system for rare disease diagnostics within the BMCHG.

Data Collection

In 2018, Sciensano performed a preliminary inventory of 90 EQA schemes related to rare diseases and that the BMCHG participate in. Of note, in the case of cancers, only EQA schemes for rare hereditary cancers were considered, while schemes for somatic mutation detection were excluded. In 2019, Sciensano collected retrospective data about the annual participation of the BMCHG in the inventoried EQA schemes between 2015 and 2019.

Guidelines for the Participation to Genetic EQA Schemes

To structure and harmonize the frequency of participation of the BMCHG in EQA schemes focused on the genetic diagnosis of rare diseases, a working group composed of two representatives for each of the 8 BMCHG was established by Sciensano in 2019, in consultation with the Belgian College of Human Genetics and Rare Diseases [23].

The working group developed recommendations about the minimal frequency of participation of the BMCHG in quality controls. These recommendations were accompanied by a decisional algorithm to help the BMCHG to plan their future participations in quality controls based on their own experience in the performance of the tests considered and the scopes of the available EQA schemes. Besides, attention was paid to recommendations on actions that should be undertaken in case of poor performance to EQA schemes and to the continuous follow-up and surveillance of the participation of the BMCHG to EQA schemes.

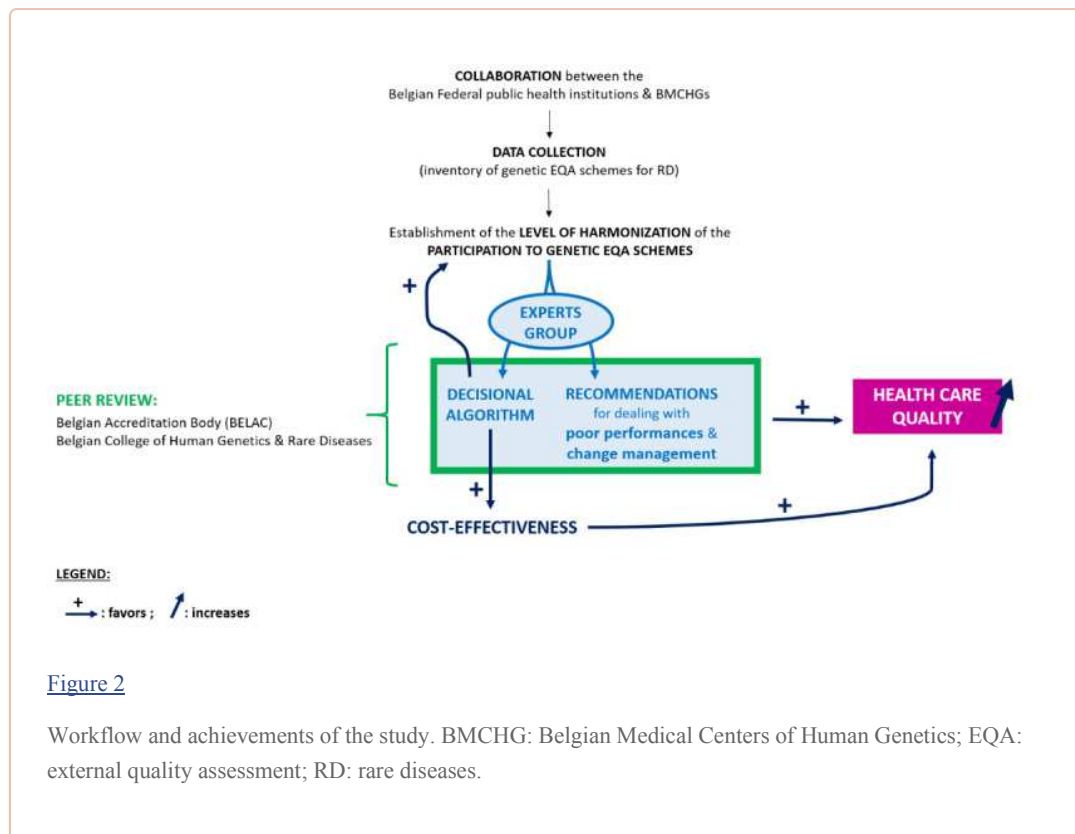
Validation of the Guidelines

The inventory of 90 genetic EQA schemes focused on rare diseases was used by the working group for the validation of the decisional algorithm based on the routine BMCHG practice.

Besides, the opinion of three accreditation managers from the Belgian Accreditation Body regarding the whole guidelines' draft was requested. The final version of the guidelines was submitted in 2020 to the Belgian College of Human Genetics and Rare Diseases for evaluation and endorsement.

Study Workflow

The global study workflow is illustrated in [Figure 2](#).



Statistical Analysis

For some rare disorders, only a few requests are obtained on an annual basis. Due to this low number, the question now arises whether the number of routine analyses can be used as an indicator of performance. Indeed, in genetic testing, errors have a great impact on the patients' and their relatives' lives. It is therefore important to maintain a high quality level, even if every laboratory is subject to underlying errors. To this aim, an error rate of 1% has been set by the working group as the maximal error threshold to define the quality of the performance of genetic tests. This threshold has been determined based on the following:

- The error rate reported in May 2020 by the EQA provider European Molecular Quality Network [24] for its global data for the germline schemes organized by this provider during the past 5 years (2016-2020); mean analytical error rate 1.37% (unpublished data): This percentage is based on the assessment of more than 33,132 genotypes during 11,044 participations in fully operational EQA schemes for germline mutation testing (technical, molecular pathology, and pilot schemes were excluded; each scheme assesses 3-4 samples). Of note, the mean analytical error rate is defined as any genotyping error that would lead to patient harm.
- Data published in the scientific literature: Indeed, error rates between 0.1% and 1% have been reported for high-throughput DNA sequencing technologies (eg, next generation sequencing) [25,26]. Raw data about error rate percentages published in 5 other peer-reviewed scientific papers for different types of situations (diseases, techniques, etc) [27-31] were also analyzed. Mean error rates and SDs with the number of scenarios investigated by the authors and confidence intervals are reported in Table 1. Based on this analysis it appears that the mean error rates fluctuate approximately between 0% and 4%.

Table 1

Data analysis about error rate percentages published in peer-reviewed papers for different types of situations.

Bibliographic references	Investigated scenarios, n ^a	Error rate
Hofgartner et al, 1999 [27]	8	0.38 (0.34)
Ewen et al, 2000 [28]	7	0.89 (0.82)
Bonin et al, 2004 [29]	4	2.20 (1.10)
Hoffman and Amos, 2005 [30]	8	0.35 (0.19)
Gilles et al, 2011 [31]	2	0.80 (0.38)



[Open in a separate window](#)

^aNumber of investigated scenarios for different types of situations reported in the literature.

To determine the sufficient number of analyses needed to have a maximal error rate of 1%, assuming that the laboratory is performing well, the distribution of possible error rates for a certain performance statistic was modeled using the *proportion* library of R software (version 3.6.1; R Foundation for Statistical Computing).

A Bayesian model with noninformative prior was used for having a rate of 100% correct analyses for a certain number of analyses and a rate of $(n - 1) / n$ correct analyses for a certain number of analyses n . Details concerning the statistical model can be found in [Multimedia Appendix 1](#).

Results

Scope of Guidelines

As this study was funded by a grant dedicated to the improvement of the quality of the genetic testing in the BMCHG in the context of rare diseases, all developed guidelines are related to human genetics EQA schemes for rare hereditary diseases, including germline predispositions to cancers and adverse drug effects resulting from pharmacogenomic variants [32].

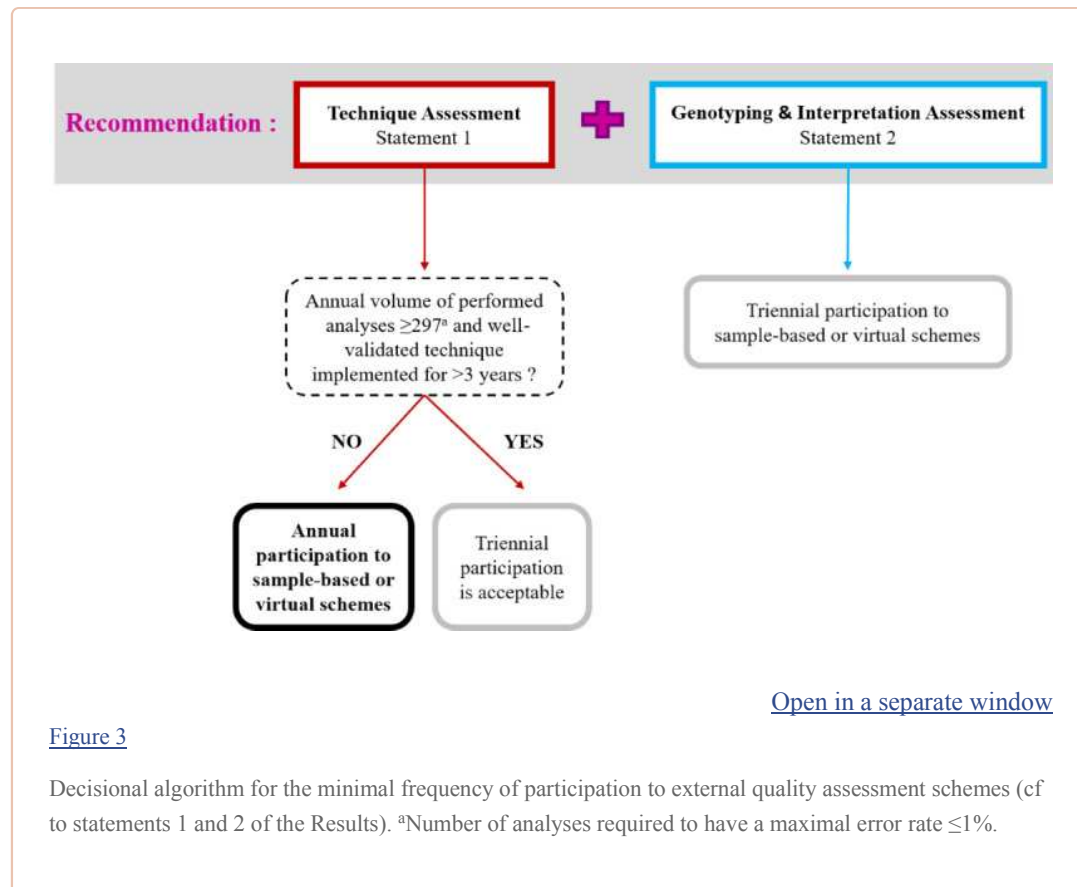
EQA Schemes Inventory

The EQA schemes inventoried during the preliminary phase of the study and considered by the working group for the establishment of the guidelines are mentioned in [Multimedia Appendix 2 \[24,33-38\]](#).

They are focused on the diagnosis of 72 different rare diseases or specific genetic variants involved in rare diseases. For each scheme, we have reported the aspects that are assessed (technique, genotyping, and interpretation of the results). The majority ($n=65$, 72%) of the EQA schemes are assessing the technique, genotyping, and interpretation. A total of 21 (23%) of the schemes are assessing both the technique and genotyping. A few of the schemes are covering both the genotyping and interpretation ($n=1$, 1%), only the technique ($n=1$, 1%), only the genotyping ($n=1$, 1%), or only the interpretation ($n=1$, 1%). Of note, for 15 selected rare diseases or genetic variants, EQA schemes are offered by 2 or 3 providers, which increases the total number of inventoried EQA schemes ($n=90$) used for the percentage calculations described here. These EQA schemes are marked with an asterisk in [Multimedia Appendix 2](#).

Guidelines

These guidelines on the minimal frequency of participation in EQA schemes can be divided into three pillars: (1) general recommendations that constitute the backbone of the guidelines and cover the majority of situations encountered (statements 1-2 and [Figure 3](#)), (2) how to address poor performances (statements 3-4), and (4) follow-up and surveillance (statements 5-6).



General Recommendations The quality of all diagnostic tests offered by the BMCHG should be frequently assessed. Indeed, the annual rate of some specific analyses (eg. performed in the context of rare diseases) may be very low. However, given the large number of genetic diseases and the low frequency of most of them, an annual participation in all possible EQA schemes is neither feasible nor economically defensible. It is therefore important to run a quality assessment in a comprehensive, rather than an exhaustive way, to assess the quality of services offered to the patients. We also took into account that the same techniques are applied for analyses of different rare disorders.

Statement 1: Annual Assessment of All Techniques The quality of all techniques and technological platforms used by the BMCHG should be annually assessed, even with EQA schemes only based on mock clinical cases, virtual images or variant call format files, or raw data sets. As mentioned by Brookman et al [39], if visual inspections are needed in daily practice, virtual schemes are useful to test postanalytical performances, notably in the case of fluorescence in-situ hybridization and karyotype analysis.

If different EQA schemes exist to cover the same technique, the centers are free to implement a turnover between those EQAs as long as the technique is covered every year and the clinical indications at least every 3 years (cf statement 2).

An exception is made for well-validated methods implemented for more than 3 years (*in-house* or using a commercial CE [European Conformity]-labelled kit) and for which at least 297 tests per year are performed, meaning that the maximal error rate of the analysis is between 0% and 1%. If those specific conditions are met, a triennial participation to an EQA is sufficient to evaluate a specific technique, as long as the methodology does not change. Of note, the number of tests have been deducted from the

Bayesian statistical model performed for the distribution of the maximal error rates (see [Multimedia Appendix 1](#)). The rationale for triennial participation has to be properly documented in the center's quality management system [40].

Statement 2: Genotyping and Interpretation Assessment A triennial assessment of the genotyping and interpretation for the detection of specific germline mutation diseases and pharmacogenomics is considered sufficient as long as the technique involved is covered (cf statement 1). This is also true when EQA schemes only assess the clinical interpretation based on virtual clinical cases or images.

How to Address Poor Performances

Statement 3: Identification of Errors' Origins Poor EQA performances because of analytical or clerical errors (eg, copy and paste mistakes) have to be discussed internally. All actions (cause analysis, corrective, and preventive actions) carried out in response to the poor evaluation must be properly documented according to the center's quality management system procedures.

Statement 4: Poor Performances With an Impact on the Diagnosis In case of poor EQA performance due to genotyping or critical interpretation errors that impacts the diagnosis, the center has to participate in an EQA the following year. Actions taken to avoid future errors have to be documented in the quality management system of the centers.

Follow-up and Surveillance

Statement 5: Management of Changes in Activities and EQA Schemes' Availability It is the responsibility of the Medical Centers of Human Genetics to regularly review and adapt their participation to EQA schemes based on the present guidelines, changes in activities or infrastructure (eg, significant changes in the annual volume of tests and gene panels or modifications in the technique or analytical equipment), and new schemes introduced on the market. This should be notified in their quality management system.

Statement 6: Implication of Public Health Authorities Public health authorities can play a key role in the improvement and follow-up of the activities, quality, and cost-effectiveness of medical laboratories such as the Medical Centers of Human Genetics. For instance, the Belgian National Institute for Health, called Sciensano, will annually coordinate the participation of the BMCHG to EQA schemes focused on rare diseases and hereditary cancers, ensure the reimbursement of participation fees, and monitor the outcomes. To provide this service, the data regarding the participation of BMCHG will be used to forecast the annual global budget dedicated to the reimbursement of participation fees. This information will then be communicated to the Belgian health care authorities. Besides, Sciensano and the working group will also regularly review and update the Belgian guidelines according to the evolution of the centers' activities, scientific developments, and EQAs' availability.

In the coming years, the collected data about the participation frequencies of the BMCHG in EQA schemes will be included into the Belgian genetic tests database, developed by Sciensano, in collaboration with the BMCHG.

Impact of the Guidelines on Health Care Costs

We have studied the impact that the establishment of harmonized guidelines on the minimal frequency of participation of the BMCHG in EQA schemes may have on national health care and genetic centers' expenditures. To this aim, three different scenarios have been compared:

1. The cost estimation if the BMCHG would annually participate to all EQAs included in their assessment scope among the inventoried EQA schemes focused on 72 rare diseases or genetic variants (fictitious scenario)
2. The participation costs of the BMCHG to the same EQAs as in 2019 (in absence of guidelines)
3. The prediction of the annual BMCHGs participation costs (mean over 2020, 2021, and 2022) for the EQAs included in their assessment scope, following the participation frequencies proposed in the guidelines

Based on the costs of the different EQA schemes, the estimated annual expenditures in these three scenarios were €117,400 (~US \$140,444), €82,000 (~US \$98,096) and €70,600 (~US \$84,458), respectively.

These estimations show that the rationalization of the frequency of participation proposed in these guidelines (third scenario), based on the types of EQA schemes and results of previous participation, enables a reduction in global annual participation costs of 14% for the 8 BMCHG.

Based on the developed guidelines on the minimal frequency of participation and current commercial EQA prices, we were able to estimate that a mean annual budget of €9000 (~US \$10,900) is required for each BMCHG to cover the fees requested by the provider to participate in the EQA schemes included in their assessment scope.

Discussion

Principal Results and Strengths

A regular participation in quality controls is mandatory for the accreditation of medical laboratories under the ISO 15189 standard [12,14,40]. Accreditation itself is a requisite for the reimbursement of genetic tests in Belgium. However, no Belgian instructions on the required frequency of participation in rare diseases diagnostic and genetic testing EQAs were available prior to this study. This study can be considered as the first Belgian harmonized quality update in terms of frequency of participation in proficiency testing in the field of human genetics.

These guidelines present six main strengths. First, they are based on European recommendations [41-43] and on the clinical and laboratory practice to make them as broad and consistent as possible. Second, they have been developed by a working group composed of representatives of all BMCHG to ensure a harmonization at the national level. Besides, these members have different professional backgrounds and tasks that enabled us to collect the opinions of all stakeholders involved in the performance of different types of genetic tests (molecular, cytogenetic, and biochemical), quality management, and in the interaction with the Belgian health care authorities. Third, a distinction was made based on the aspects assessed by the EQA schemes (technique, analysis, or interpretation) to draft guidelines as relevant as possible. Fourth, a large number of available genetic EQA schemes from accredited providers has been considered. This emphasizes the importance of assessing the quality of highly specific tests performed at a relatively low annual volume in the context of rare diseases. Fifth, a statistical model was used to estimate the probability of a laboratory to make a mistake according to the number of analyses that are performed per year. This new model may help other laboratories to define the minimal number of analyses required to indicate that the experience of a laboratory can be taken into account as a reliable performance indicator. Finally, the guidelines have been approved by the Belgian College of Human Genetics and Rare Diseases and are in accordance with the statements of the ISO 15189 standard referring to the validation of analytical methods [13]. This ensures their clinical relevance and legal accreditation aspects.

Participating in a large number of different EQAs for rare diseases is worthwhile, as it has a role in controlling performance and guarantees permanent education. Furthermore, participating in international EQA schemes enables the performances of a large number of the Centers of Human Genetics to be compared and evaluated by a wide range of international experts. However, taking part in a large number of EQAs is a lot of work and time-consuming. Hence, a balance had to be sought between usefulness and burden. These new Belgian guidelines will improve the harmonization and structuring of the BMCHG quality management system and help the laboratories to identify the EQA schemes that they should participate in based on the evolution of their activities and type of EQA schemes considered. They might also serve as basis for the Belgian Accreditation Body for accreditation assessments and for the Belgian health care authorities to estimate the necessary budget that should be foreseen and attributed by the National Institute for Health and Disability Insurance to the BMCHG to cover participation fees.

Comparison With Prior Work

Similar recommendations have already been developed by other countries, for instance, Dutch, Slovenian, and Estonian laboratories have to participate in a minimum of one EQA scheme for each accredited analysis of their scope during an accreditation cycle (during 3 years, till the suspension of the accreditation, and during 5 years, respectively), while other (eg, Lithuanian) laboratories are requested to participate twice during this period of time or every year for specific fields [43]. It is unfortunate that no European consensus exists at this time [19]. However, we hope that the development of guidelines on this topic in different European countries should be a catalyst to the initiation of a general reflection on the harmonization of the quality assessment of genetic testing at a European level.

Our guidelines reflect the opinion that the scope of quality controls should be broad enough to cover all methods, technologies, and tests included in the scope of the centers. It is not acceptable that a laboratory would only be accredited for a (small) fraction of its testing offers and thus avoid EQA participation.

Limitations

Regarding the limits of this study, we have to mention that these guidelines only concern EQA schemes from accredited providers. Ring tests [44] to which BMCHG may also participate in with a small number of other Belgian or foreign genetic centers were excluded. Nonetheless, the preliminary phase of the study revealed that approximately 30% of the quality controls to which the BMCHG participate in are ring tests. They were not considered in this study because we wanted to give priority to EQAs offered by accredited providers. Ring tests are often highly specific and involve a limited number of participants. The difficulty to get enough test material for all participants make the standardization of their organization difficult. However, this opens the door to future improvements in the harmonization process of the quality management of human genetic analyses when no formal EQA scheme is available.

Another limitation is that the majority of the EQAs considered are specific for hereditary rare diseases and not for all diseases.

Finally, the guidelines have been developed at the Belgian level, without asking the opinions of foreign experts. However, several members of the working group act as assessors in international schemes and have good insights into practice, evaluation, and (poor) performance management.

Conclusion

These first Belgian guidelines will help the BMCHG to improve their quality management system with recommendation on the frequency of participation in EQA schemes and on dealing with poor performance and change management. Moreover, they help the Belgian health care authorities to estimate the budget required to cover the participation of the BMCHG in EQAs. We are convinced that these Belgian guidelines could be used by foreign human genetics medical centers and can serve as a starting point for discussion about the harmonization of quality processes at a broader level.

Acknowledgments

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All authors confirmed they have contributed to the intellectual content of this paper, and they have met the following four requirements: (1) substantial contributions to the conception or design of the study, or the acquisition, analysis, or interpretation of data for the study; (2) drafting the study or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved.

Abbreviations

BMCHG	Belgian Medical Centers of Human Genetics
CE	European Conformity
EQA	external quality assessment

Appendix

Multimedia Appendix 1

Statistical modeling of the maximal error rates when performing genetic analyses for rare diseases.

[Click here to view.](#) ^(62K, docx)

Multimedia Appendix 2

List of the inventoried external quality assessment schemes considered for the establishment of the guidelines. EQA schemes offered by several providers are marked with an asterisk.

[Click here to view.](#) ^(66K, docx)

Footnotes

Conflicts of Interest: None declared.

References

1. Evangelista T, Hedley V, Atalaia A, Johnson M, Lynn S, Le Cam Y, Bushby K. The context for the thematic grouping of rare diseases to facilitate the establishment of European Reference Networks. *Orphanet J Rare Dis.* 2016 Feb 24;11:17. doi: 10.1186/s13023-016-0398-y. <https://ojrd.biomedcentral.com/articles/10.1186/s13023-016-0398-y>. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
2. Bavissetty S, Grody WW, Yazdani S. Emergence of pediatric rare diseases: review of present policies and opportunities for improvement. *Rare Dis.* 2013;1:e23579. doi: 10.4161/rdis.23579. <http://europemc.org/abstract/MED/25002987>. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
3. Mazzucato M, Visonà Dalla Pozza L, Minichiello C, Manea S, Barbieri S, Toto E, Vianello A, Facchin P. The epidemiology of transition into adulthood of rare diseases patients: results from a population-based registry. *Int J Environ Res Public Health.* 2018 Oct 10;15(10):2212. doi: 10.3390/ijerph15102212. <https://www.mdpi.com/resolver?pii=ijerph15102212>. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
4. Boycott KM, Rath A, Chong JX, Hartley T, Alkuraya FS, Baynam G, Brookes AJ, Brudno M, Carracedo A, den Dunnen JT, Dyke SOM, Estivill X, Goldblatt J, Gonthier C, Groft SC, Gut I, Hamosh A, Hieter P, Höhn S, Hurler ME, Kaufmann P, Knoppers BM, Krischer JP, Macek M, Matthijs G, Olry A, Parker S, Paschall J, Philippakis AA, Rehm HL, Robinson PN, Sham P, Stefanov R, Taruscio D, Unni D, Vanstone MR, Zhang F, Brunner H, Bamshad MJ, Lochmüller H. International cooperation to enable the diagnosis of all rare genetic diseases. *Am J Hum Genet.* 2017 May 04;100(5):695–705. doi: 10.1016/j.ajhg.2017.04.003. [https://linkinghub.elsevier.com/retrieve/pii/S0002-9297\(17\)30147-7](https://linkinghub.elsevier.com/retrieve/pii/S0002-9297(17)30147-7). [PMC free article] [PubMed] [CrossRef] [Google Scholar]

5. Gainotti S, Mascalcioni D, Bros-Facer V, Petrini C, Florida G, Roos M, Salvatore M, Taruscio D. Meeting patients' right to the correct diagnosis: ongoing international initiatives on undiagnosed rare diseases and ethical and social issues. *Int J Environ Res Public Health*. 2018 Sep 21;15(10):2072. doi: 10.3390/ijerph15102072. <https://www.mdpi.com/resolver?pii=ijerph15102072>. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
6. Dharssi S, Wong-Rieger D, Harold M, Terry S. Review of 11 national policies for rare diseases in the context of key patient needs. *Orphanet J Rare Dis*. 2017 Mar 31;12(1):63. doi: 10.1186/s13023-017-0618-0. <https://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0618-0>. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
7. Berwouts S, Fanning K, Morris MA, Barton DE, Dequeker E. Quality assurance practices in Europe: a survey of molecular genetic testing laboratories. *Eur J Hum Genet*. 2012 Nov;20(11):1118–26. doi: 10.1038/ejhg.2012.125. <http://europepmc.org/abstract/MED/22739339>. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
8. Content sheet 10-1: overview of External Quality Assessment (EQA) *World Health Organization*. 2011. Jan 01, [2021-06-16]. https://terrance.who.int/mediacentre/data/ebola/training-packages/LOMS/10_b_eqa_contents.pdf.
9. Alkhenizan A, Shaw C. Impact of accreditation on the quality of healthcare services: a systematic review of the literature. *Ann Saudi Med*. 2011;31(4):407–16. doi: 10.4103/0256-4947.83204. https://www.annsaudimed.net/doi/10.4103/0256-4947.83204?url_ver=Z39.88-2003&rft_id=ori:rid:crossref.org&rft_dat=cr_pub%3dpubmed. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
10. Cassiman J. Can (should) molecular diagnostic labs improve the quality of their services? *Eur J Hum Genet*. 2012 Nov;20(11):1103–4. doi: 10.1038/ejhg.2012.126. <http://europepmc.org/abstract/MED/22739345>. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
11. Tembuyser L, Tack V, Zwaenepoel K, Pauwels P, Miller K, Bubendorf L, Kerr K, Schuurin E, Thunnissen E, Dequeker EMC. The relevance of external quality assessment for molecular testing for ALK positive non-small cell lung cancer: results from two pilot rounds show room for optimization. *PLoS One*. 2014;9(11):e112159. doi: 10.1371/journal.pone.0112159. <https://dx.plos.org/10.1371/journal.pone.0112159>. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
12. Claustres M, Kožich V, Dequeker E, Fowler B, Hehir-Kwa JY, Miller K, Oosterwijk C, Peterlin B, van Ravenswaaij-Arts C, Zimmermann U, Zuffardi O, Hastings RJ, Barton DE, European Society of Human Genetics Recommendations for reporting results of diagnostic genetic testing (biochemical, cytogenetic and molecular genetic) *Eur J Hum Genet*. 2014 Feb;22(2):160–70. doi: 10.1038/ejhg.2013.125. <http://europepmc.org/abstract/MED/23942201>. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
13. ISO 15189:2012 Laboratoires de biologie médicale — Exigences concernant la qualité et la compétence. *International Organization for Standardization*. 2012. Nov, [2020-10-22]. http://www.iso.org/iso/fr/catalogue_detail?csnumber=56115.
14. ILAC policy for participation in proficiency testing activities. *International Laboratory Accreditation Cooperation*. 2014. Jun, [2020-10-22]. https://ilac.org/latest_ilac_news/ilac-p9062014-published/
15. Dequeker E. Quality assurance in genetic laboratories. In: Patrinos GP, editor. *Molecular Diagnostics*. Amsterdam, Netherlands: Elsevier Ltd; 2017. pp. 493–500. [Google Scholar]
16. Tack V, Ligtenberg MJL, Siebers AG, Rombout PDM, Dabir PD, Weren RDA, van Krieken JHJM, Dequeker EMC. RAS testing for colorectal cancer patients is reliable in European laboratories that pass external quality assessment. *Virchows Arch*. 2018 May;472(5):717–725. doi: 10.1007/s00428-017-2291-z. [PubMed] [CrossRef] [Google Scholar]

17. Keppens C, Dufraing K, van Krieken HJ, Siebers AG, Kafatos G, Lowe K, Demonty G, Dequeker EMC. European follow-up of incorrect biomarker results for colorectal cancer demonstrates the importance of quality improvement projects. *Virchows Arch*. 2019 Jul;475(1):25–37. doi: 10.1007/s00428-019-02525-9. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
18. Keppens C, Tack V, Hart N, Tembuyser L, Ryska A, Pauwels P, Zwaenepoel K, Schuurin E, Cabillic F, Tornillo L, Warth A, Weichert W, Dequeker E, EQA assessors expert group A stitch in time saves nine: external quality assessment rounds demonstrate improved quality of biomarker analysis in lung cancer. *Oncotarget*. 2018 Apr 17;9(29):20524–20538. doi: 10.18632/oncotarget.24980. <https://www.oncotarget.com/lookup/doi/10.18632/oncotarget.24980>. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
19. Cassiman J. EuroGentest NoE, the ESHG, and genetic services. *Eur J Hum Genet*. 2017 Dec;25(s2):S47–S49. doi: 10.1038/ejhg.2017.155. <http://europepmc.org/abstract/MED/29297885>. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
20. Dufraing K, Lierman E, Vankeerberghen A, Franke S, Dequeker E. External quality assessment for molecular diagnostic laboratories in Belgium: can we improve it? *Accred Qual Assur*. 2019 Nov 25;25(1):39–49. doi: 10.1007/s00769-019-01410-x. [CrossRef] [Google Scholar]
21. Matthijs G, Limaye N. Belgian Medical Centers for Human Genetics. *Belgian Society for Human Genetics*. 2021. [2021-06-16]. <https://www.beshg.be/partners/centers>.
22. *Sciensano*. 2021. [2021-06-16]. <https://www.sciensano.be/>
23. *Collège belge de Génétique*. 2021. [2021-06-16]. <https://www.college-genetics.be/>
24. *European Molecular Genetics Quality Network*. [2021-06-16]. <https://www.emqn.org>.
25. Salk JJ, Schmitt MW, Loeb LA. Enhancing the accuracy of next-generation sequencing for detecting rare and subclonal mutations. *Nat Rev Genet*. 2018 May;19(5):269–285. doi: 10.1038/nrg.2017.117. <http://europepmc.org/abstract/MED/29576615>. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
26. Petrackova A, Vasinek M, Sedlarikova L, Dyskova T, Schneiderova P, Novosad T, Papajik T, Kriegova E. Standardization of sequencing coverage depth in NGS: recommendation for detection of clonal and subclonal mutations in cancer diagnostics. *Front Oncol*. 2019;9:851. doi: 10.3389/fonc.2019.00851. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
27. Hofgärtner WT, Tait JF. Frequency of problems during clinical molecular-genetic testing. *Am J Clin Pathol*. 1999 Jul;112(1):14–21. doi: 10.1093/ajcp/112.1.14. [PubMed] [CrossRef] [Google Scholar]
28. Ewen KR, Bahlo M, Treloar SA, Levinson DF, Mowry B, Barlow JW, Foote SJ. Identification and analysis of error types in high-throughput genotyping. *Am J Hum Genet*. 2000 Sep;67(3):727–36. doi: 10.1086/303048. [https://linkinghub.elsevier.com/retrieve/pii/S0002-9297\(07\)63258-3](https://linkinghub.elsevier.com/retrieve/pii/S0002-9297(07)63258-3). [PMC free article] [PubMed] [CrossRef] [Google Scholar]
29. Bonin A, Bellemain E, Bronken Eidesen P, Pompanon F, Brochmann C, Taberlet P. How to track and assess genotyping errors in population genetics studies. *Mol Ecol*. 2004 Nov;13(11):3261–73. doi: 10.1111/j.1365-294X.2004.02346.x. [PubMed] [CrossRef] [Google Scholar]
30. Hoffman JI, Amos W. Microsatellite genotyping errors: detection approaches, common sources and consequences for paternal exclusion. *Mol Ecol*. 2005 Feb;14(2):599–612. doi: 10.1111/j.1365-294X.2004.02419.x. [PubMed] [CrossRef] [Google Scholar]
31. Gilles A, Meglécz E, Pech N, Ferreira S, Malausa T, Martin J. Accuracy and quality assessment of 454 GS-FLX Titanium pyrosequencing. *BMC Genomics*. 2011 May 19;12:245. doi: 10.1186/1471-2164-12-245. <https://bmcgenomics.biomedcentral.com/articles/10.1186/1471-2164-12-245>. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

32. Roden DM, Wilke RA, Kroemer HK, Stein CM. Pharmacogenomics: the genetics of variable drug responses. *Circulation*. 2011 Apr 19;123(15):1661–70.
doi: 10.1161/CIRCULATIONAHA.109.914820. <http://europepmc.org/abstract/MED/21502584>.
[PMC free article] [PubMed] [CrossRef] [Google Scholar]
33. Our EQAs. *GenQA*. 2021. [2021-06-16]. <https://www.genqa.org/eqa>.
34. *Biomedical Quality Assurance KU Leuven*. Leuven: KU Leuven Biomedical Quality Assurance; 2020. [2021-06-16]. <https://eqascheme.org/> [Google Scholar]
35. 2020 surveys and anatomic pathology education programs. *College of American Pathologists*. 2020. [2021-06-16]. <https://www.cap.org/laboratory-improvement/catalogs-ordering-and-shipping>.
36. *United Kingdom National External Quality Assessment Service*. [2021-06-16].
<https://www.ukneqash.org/>
37. Schellenberg I, Spannagl M, Hunfeld KP. EQAS Program 2021. *INSTAND*. 2021. Mar 01, [2021-06-16]. <https://www.instand-ev.de/en/instand-eqas/eqas-program-2021/>
38. Ringversuche. *Referenzinstitut für Bioanalytik*. 2021. [2021-06-16].
<https://www.rfb.bio/cgi/surveys>.
39. Brookman B, Butler O, Koch M, Noblett T, Örnemark U, Patriarca M, van Putten K, Robouch P. Proficiency testing in analytical chemistry, microbiology and laboratory medicine: discussions on current practice and future directions. *Accred Qual Assur*. 2015 Apr 8;20(4):339–344.
doi: 10.1007/s00769-015-1120-9. [CrossRef] [Google Scholar]
40. *FPS Economy*. Brussels: BELAC; 2011. Feb 01, [2020-10-22]. Essais d'aptitude (proficiency testing): lignes directrices en matière de participation et évaluation des performances dans le cadre des adultes d'accréditation. <https://economie.fgov.be/sites/default/files/Files/Publications/files/Belac-FR/2-106-FR.pdf>. [Google Scholar]
41. *Organisation for Economic Co-operation and Development*. Paris: OECD; 2007. [2021-06-16]. OECD guidelines for quality assurance in molecular genetic testing.
<http://www.oecd.org/science/emerging-tech/38839788.pdf>. [Google Scholar]
42. EA-4/18 rev.00 – Guidance on the level and frequency of proficiency testing participation. *Accredia*. 2010. Jun, [2021-06-16]. <https://www accredia.it/en/documento/ea-418-rev-00-guidance-on-the-level-and-frequency-of-proficiency-testing-participation/>
43. Örnemark U, Fostel H, Straub R, van de Kreeke J. Policies, requirements and surveys concerning frequency for participation in proficiency testing schemes. *Accred Qual Assur*. 2004 Sep 4;9(11-12):729–732. doi: 10.1007/s00769-004-0858-2. [CrossRef] [Google Scholar]
44. Vandeveldel NM. Strategies to improve the quality of reference networks for rare diseases. *Translational Sci Rare Dis*. 2020 Aug 03;5(1-2):59–79. doi: 10.3233/trd-190032. [CrossRef] [Google Scholar]