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Editors

Quality Issues in Clinical Genetic Services

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Foreword

Initially genetic disorders were all considered as rare diseases. At present, in the mid of 2009, the OMIM catalogue contains information on more than 12,000 entries of which about 6,700 have a proven or suspected Mendelian based phenotype. Of these, about 2,500 are available for clinical testing based on the identification of the responsible gene defect. Further, altogether it has been estimated that the cumulative prevalence for rare diseases is about 8% of which most have a strong, i.e. single gene background. Adding to that, it is estimated that most other diseases have a genetic component, which will determine who will be at a higher than average risk for a certain disorder. Further it is postulated that in the near future, this genetic profiling could become useful in selecting an appropriate therapy adapted to the genetic constitution of the person. Thus, genetic disorders are not rare.

Measuring quality of heath care related processes became an issue in the 1990s, mainly in laboratory medicine, but also for hospitals and other health care systems. In many countries national authorities started to implement recommendations, guidelines or legal procedures regulating quality of health care delivery. In laboratory medicine, in parallel, the use of accreditation as a method assuring high quality standards in testing came in use. With the increasing possibilities of performing molecular genetic testing, genetic laboratories needed to become involved in this process.

Early on international organisations like the European Union became aware of the need of harmonising quality recommendations and have during the last 15 years sponsored several initiatives from clinical and laboratory genetic stakeholders, of which the Network of Excellence EuroGentest received a 10M grant under the 6th framework programme for the 2005–2010 to further harmonise and develop quality issues in Europe.

As many genetic disorders are rare, most laboratories worldwide offered analysis for a specific set of disorders, and, therefore, very early on a transborder flow of samples occurred. While international quality criteria (ISO) have been in existence for a number of years, the regulation of quality issues still may differ between countries. As a blood sample transferred between countries is regarded as "tradable goods", the OECD in year 2000 took the initiative to a workshop on quality issues in molecular genetic testing which was followed by setting up an expert group to develop quality guidelines. Based on this work, the OECD council in 2007

adopted “Recommendations for quality assessment in molecular genetic testing”. This was followed in 2009 by the Council of Europe document “Additional Protocol to the Convention on Human Rights and Biomedicine”, concerning Genetic Testing for Health Purposes.

Based on their personal experience in the varying fields of quality research and clinical implementation of quality criteria in genetic services the authors of this book share their experience and give examples of the implementation of quality issues in national quality systems world wide. This book, which is the result of the effort of many persons, is destined, to aid laboratory managers and counsellors, health care managers and other stakeholders in national or international health care service to improve the services to the benefit of patients with suspected genetic disorders.

We, the editors, hope that this book will be helpful in increasing the quality of the genetic service, and also contribute to maintain it high.

Lund — Ulf Kristoffersson
Hannover — Jörg Schmidtke
Leuven — Jean-Jacques Cassiman

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Improving Quality and Harmonization of Standards in Clinical Genetic Services in Europe: The EuroGentest Network of Excellence

Jean-Jacques Cassiman

Key Points

The most important contributions of the EuroGentest NoE can be summarized as follows:

- European diagnostic labs are moving towards accreditation under ISO 15189, hereby helped by training workshops in quality management and accreditation; integration and harmonization of the three EQA schemes in Europe and new Best practice guidelines for the labs. The Orphanet database has been overhauled and expanded. It now also provides information on the degree of quality assurance of many registered labs
- Gene cards containing information on the clinical validity and utility of 32 different molecular tests are available. Different aspects of the clinical utility of genetic tests have been critically analyzed
- A technology platform for the validation of emerging technologies is in place and generic SOPs for the validation of these technologies have been drafted
- A context-dependent definition of genetic testing, important for any official or legal document, is being finalized and a review of the legislation pertaining to patient's rights in each Member State is already available for 15 countries and minimal criteria for quality genetic counseling have been defined and tools to evaluate performance are available
- Core competences for health professionals have been defined and leaflets explaining to families different aspects of a visit to a genetic clinic are freely available in 27 languages

Keywords Genetic testing · EuroGentest · Quality issues

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Introduction

The way the European Union (EU) is structured and functions, in particular with regard to the provision of genetic services to its citizens and to the support of research in genetics is not well understood by most of its citizens and probably even less by most non-EU scientists.

The EU executive is formed by the members of the EU Commission, appointed by the Member States (MS) based on a political consensus between the different parties represented in the EU Parliament. The parliament, composed of members elected in the different MS, legislates by Directives, which have to be translated into National laws within a limited number of years.

At present the majority of all new legislation in a country actually originated in the EU parliament. Nevertheless, under the principle of subsidiarity, the MS are still responsible to a large extent for the organization of the health services, for medical specialty recognition and public or private health insurance, leading to a fairly heterogeneous landscape. Some MS have extensive legislation and well organized genetic services. Others, leave the services essentially open to whomever feels competent to provide them, whether private or public organizations. Some countries have worked out a comprehensive system for the organization of the genetic services, including the reimbursement of the costs, while others leave it essentially to their citizens or private insurances to cover these costs. To add to the complexity, some MS have a strong regional organization, leaving most of the decisions on how the services are organized or reimbursed to regional authorities or regional health insurance companies.

European research is funded for about 85% with the money and on decision of the MS or private charity organizations. The remaining 15% is contributed by the MS to the EU. The different Directorate Generals (DG) of the EU Commission have their specific research budget, which has been approved by the EU parliament for periods of 5–7 years, called Framework Programs (FP). Each of these FPs is prepared after extensive consultation of experts, MS representatives and the general public. At present we are in the 7th FP.

Applications for research projects can only be submitted on selected topics defined in regular calls by the commission. Research in genetics is mainly covered by DG Research and DG Sanco. The first, with the largest budget, covers about any field in research, provided it is a collaboration between groups from at least two different MS. The second is focused on health and consumer protection and supports more policy type research e.g. support for rare disease management and the Orphanet database. Finally, in an attempt to liberate more MS funds for European research, the EU also supports projects which are funded directly by two or more MS, the European research Area or ERA-NET. In recent years, a European Research Council was created, which supports applications from individuals. The EU also created a series of Joint Research Centers (JRC) where specific expertise is concentrated. The IRMM (Institute for Reference Materials and Measurements) in Geel, Belgium and IPTS (Institute for Prospective Technological Studies) in Sevilla, Spain are involved as partners in EuroGentest.

It is not surprising, in view of the heterogeneous health systems in Europe, that the genetic services lacked harmonized structures and procedures. Moreover, while based on high quality scientific know-how, they suffer to some extent from technical errors and poor reporting (Ibarretta et al. 2004). Similar problems were identified in a more recent study of the preimplantation diagnostic services (Corveleyn et al. 2008). This has been mainly due to a lack of structuring and complementarity at the European level and the absence of a common European objective to provide quality services to all its consumers now and in the future. Diverse and heterogeneous quality schemes, lack of reference systems, have added to the overall disorganization and fragmentation of services.

Nevertheless, genetic services face an ever-increasing number of requests for testing, while widespread susceptibility testing and pharmacogenetic tests are lurking on the horizon.

This combination of a perceived opportunity to become involved in shaping healthcare policy in Europe, and as well as recognition of a need to structure existing services on a more uniform basis led leading stakeholders within the European genetics community to propose the EuroGentest initiative to the EU in 2004.

The *EuroGentest NoE*, a Network of Excellence funded for 5 years under the EU 6th Framework program by DG research started officially on January 1, 2005 (Cassiman 2005). Its aims were to develop the necessary infrastructure, tools, resources, guidelines and procedures leading to the establishment of harmonized, quality genetic testing services in Europe, which can interact with, stand as a model for, or help to achieve similar services on other continents.

To achieve these aims it planned to bring together, in a real long-term partnership, experts and expert genetic centers available in Europe engaged on different aspects of testing, including researchers and clinical geneticists, small and medium enterprises (SMEs), testing laboratories, quality management and public health experts, ethicists, lawyers, sociologists, educational authorities and consumers/patient and family organizations (www.EuroGentest.org).

To achieve its aims and efficiently monitor its progress, the 36 official participants in the NoE were assigned to 6 functional units each with specific aims and objectives, clear milestones and deliverables. The six themes under which these units developed their activities were: quality assurance issues; databases; clinical genetics and public health; new technologies; ethical, legal and social issues; education and information.

Quality Assurance

Testing for genetic diseases has moved progressively from a predominantly research-based context into specialized clinical genetic laboratories. Concomitantly, there has been increased need for Quality Control (QC) and Quality Assurance (QAu), particularly with respect to External Quality Assessment (EQA) and accreditation. To support the genetic services in this effort, the NoE developed different activities around these issues.

EQA Schemes

In the past there has been limited co-operation and bi- or multi-lateral discussions between European and National EQA schemes for cytogenetics, molecular and biochemical genetics. During a series of meetings between the EQA organizers ERNDIM (European Research Network for evaluation and improvement of screening, Diagnosis and treatment of Inherited disorders of Metabolism), (Fowler et al. 2008), EMQN (European Molecular Quality Network), CFnetwork, and CEQA (Cytogenetic EQA) measures for the harmonization of the different schemes were agreed and deadlines for their ISO accreditation were fixed. In addition, several meetings took place between the European EQA Schemes (EMQN or CEQA) and the National EQA providers to ascertain the degree of similarity and assess a suitable approach for further harmonization or co-operation between the EQA schemes. As a consequence of these meetings e.g. the GfH Molecular Genetic EQA schemes organization in Germany merged with EMQN. The Cytogenetic EQA scheme, CEQA, set up by the NoE (Hastings et al. 2007, 2008), is unique in that its assessors include the National Cytogenetic Scheme Organizers. The format of CEQA is now being incorporated into some of the national schemes. CEQA, EMQN and the two UKNEQAS (UK EQA organization) schemes for Cytogenetics and Molecular Genetics utilize the same EQA Manager software. Finally, there was a meeting between the three disciplines and national accreditation bodies to identify common needs. The SAS (Swiss Accreditation Service) Standard checklist for accreditation of quality assurance agencies has been translated into English and a generic National Representatives Job Description was agreed. All three European schemes have also expanded their laboratory participation and the repertoire of EQAs offered to participating laboratories increased.

Best Practice meetings for Molecular Genetics, biochemical genetics and cytogenetics were organized and a list of all the existing guidelines (e.g. Dequeker et al. 2009; Ellard et al. 2008) is available on the EuroGentest website.

In order to develop governance structures and to promote sustainability, the three disciplines have created an “umbrella” organization in the ESHG as “Genetic Service Quality Committee” whose remit includes oversight for the European EQA schemes.

Reference Materials

To identify the present and future needs for Reference Materials (RM) for genetic testing, to set priorities for the development of new RM and to support development of RM in this field a series of initiatives were taken (Gancberg et al. 2008). A field study of synthetic CF control material was performed and a WHO panel for PWS/AS is being finalized.

The IVD (In Vitro Diagnostics) Directive of the EU has a clear impact on genetic testing. Participants of the NoE have formulated a series of recommendations to require information on the clinical validity of new diagnostic kits or tools before they are allowed on the market.

Validation of Methods and Technologies

To establish and produce guidelines/SOPs for validation of diagnostic commercial kits an international drafting committee including members from the US is finalizing consensus guidelines on the procedures to validate new methods in the laboratory.

Training in QuA

In order to support the labs in obtaining accreditation under the ISO norm 15,189 workshops and round table discussions on aspects of quality management were regularly held in different locations in the EU in collaboration with the SME, MCR. The availability of these workshops, which are in high demand, has been increased by training additional trainers. A summary report of the outcome of the workshops is used as a reference document for laboratories preparing for accreditation.

Genetic Counseling

Since the genetic clinic is an integral part of the genetic services provided to the population, it was considered that quality issues are as important for the clinic as they are for the laboratories. Nevertheless, the organization of EQAs for clinical services in the different EU countries would be difficult in view of the different organizations in which these facilities operate and the different languages spoken in the different countries or regions. The NoE nevertheless estimated that in time accreditation under an ISO norm e.g. 9000–2001, would become unavoidable. As a first approach therefore a self assessment tool for the counselors was developed, freely available for the clinical geneticists and further steps towards introducing quality management in the clinics, e.g. by training, are being prepared.

Databases

A QAu Database

Although a number of public websites provide lists of medical genetic testing laboratories and of tests that are available, public information about QAu is sparse or even intentionally absent. To remedy this, EuroGentest, in collaboration with Orphanet, has performed a survey on QAu in European genetics laboratories. Over 1,000 laboratories in Europe offering human genetic testing were identified and received an online QAu survey. To ensure the highest possible accuracy of information, replies were peer-reviewed and verified with data from the EQA providers and national accreditation bodies.

The database has already collected and validated data from more than 300 laboratories. The QAu database, containing information on the lab director, quality manager, address, which diseases are tested, as well as information on QAu of the lab – participation in EQA and accreditation status – has been integrated in the Orphanet database where it is freely available for consultation.

Orphanet (www.Orpha.net)

Orphanet, the well established database for rare disease is a full participant in the NoE. It has continued to work on the geographical expansion of its data collection. Data collection is now on- going in 29 countries and contains information on 1,233 laboratories providing a test for 1,504 different genetic diseases.

In the mean time Orphanet has also linked to the dataset of Genatlas and of SwissProt, the international database of proteins. Currently, 1,298 diseases, linked to 1,594 genes, are common to both datasets. It also developed a new hierarchical system for disease nomenclature, which allows one to easily find information on diseases and their different subtypes.

Clinical Genetics, Community Genetics and Public Health

The participants in these activities have moved gradually, based on reviewing published information and on surveys of European geneticists, to drafting consensus expert advices (Rantanen et al. 2008). They have generated a good overview of the practice of clinical genetics in Europe and are paving the way for harmonization and improvement of the practice.

A summary of the International guidelines for genetic counseling and regulations and practices related to genetic counseling in 38 European countries was published as well as the list of the national regulations/laws on counseling. Recommendations for genetic counseling were drafted by a group of experts, which since have been endorsed by the ESHG. To sensitize clinical geneticists for quality issues, the self-assessment tool mentioned earlier was developed and a manuscript reviewing 102 publications on patient perspectives of genetic counseling was drafted.

Information about access to genetic testing and test utilization for single-gene, mostly rare disorders, in European countries has been collected. A background paper on prioritization issues in genetic counseling, resulting from a workshop held on this topic is being prepared. A critical assessment of systematic approaches to define and evaluate the clinical validity and utility of genetic tests, in particular the ACCE model: “A Model Process for Evaluating Data on Emerging Genetic Tests” has been drafted and a decision tree and “Points to Consider Regarding Clinical Utility of Genetic Testing”, a framework for disease-specific guidelines is being published www.EuroGentest.org.

Finally, Clinical utility Gene cards for the first 32 Mendelian diseases, prepared by the German Society for Human Genetics, have been translated in English and are now freely available on the website.

The *CAPABILITY* project, which receives separate financial support from the EU, focuses on genetic testing in developing countries and as such has strong links to EuroGentest. It is developing an international survey of facilities in many developing countries, in collaboration with the Institute for Prospective Technological studies (IPTS) from Sevilla.

At the request of the EU commission, a context-dependent definition of genetic testing, based on an extensive survey of the literature, surveys of geneticists and on

expert advice, is being finalized. This definition will become extremely important for the harmonization of the use of the term "genetic testing" in legal, ethical and other official documents.

Research and Emerging Technologies

A series of laboratories have joint in an effort to create a unique European platform for the evaluation of new technologies before they are offered to the diagnostic labs.

This initiative was welcomed by the diagnostic manufacturers, who found in this platform an independent and qualified forum for the validation of their products or technologies. In a number of cases, it also led to the identification of some shortcomings, which could then be overcome successfully by the companies. Recently, a number of participants joined in the FP7 funded research project TECHGENE, aimed at improving high throughput diagnostic technologies.

A few examples of technologies already evaluated: DNA extraction by use of the Chemagen Extractor; MLPA for BRCA; the high resolution melting curve analysis (HR-MCA) on three different instruments each with its specific chemicals; Conformation Sensitive Capillary Electrophoresis (CSCE); PAP (Pyrophosphorolysis Activated Polymerization) for mutations in mixtures from different individuals. The evaluations should also result in the drafting of generic SOPs available to all labs intending to use these technologies.

Sequencing software and tools for mutation nomenclature (Mutalyzer) and interpretation. (Interactive Biosoftware, Alamut) is under evaluation and a wiki format is available for the presentation of quality information. Work to establish data for sensitivity of single versus double strand sequencing was undertaken. A potentially suitable standard for data exchange was identified and proof of concept undertaken.

Patent Search and Evaluation

Awareness was raised about the importance of IPR (Intellectual Property Rights) within the Network. EuroGentest participants contributed to the "Background Document" and "Recommendations on gene patenting and licensing" of the European Society of Human Genetics (ESHG). A database of European diagnostic gene patents was established of top-20 diagnostic gene patents.

Patient and Professional Issues: Education, Ethics and Patient Rights

Geneticists are very well aware of the fact that representatives of patient organizations are their natural allies and can bring a unique expertise on how to improve the services. Moreover, in view of the role still played by the Member States in regulating the provision of health services it was important to examine to what extent the different MS had specific legislation or regulations pertaining to patients rights.